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RESEARCH ARTICLE

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The relation of telomere length at midlife to subsequent 20-year depression trajectories among women

Jennifer Cai Gillis[1,2] | Shun-Chiao Chang[2] | Wei Wang[2] | Naomi M. Simon[3,4] | Sharon-Lise Normand[1,5] | Bernard A. Rosner[1,2] | Deborah Blacker[1] | Immaculata DeVivo[1] | Olivia I. Okereke[1,2,3]

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

[2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

[3]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

[4]Department of Psychiatry, NYU School of Medicine, New York, New York

[5]Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts

Correspondence
Olivia I. Okereke, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA, 02114.
Email: ookereke@partners.org

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Abstract

Background: Telomeres cap and protect DNA but shorten with each somatic cell division. Aging and environmental and lifestyle factors contribute to the speed of telomere attrition. Current evidence suggests a link between relative telomere length (RTL) and depression but the directionality of the relationship remains unclear. We prospectively examined associations between RTL and subsequent depressive symptom trajectories.

Methods: Among 8,801 women of the Nurses' Health Study, depressive symptoms were measured every 4 years from 1992 to 2012; group-based trajectories of symptoms were identified using latent class growth-curve analysis. Multinomial logistic models were used to relate midlife RTLs to the probabilities of assignment to subsequent depressive symptom trajectory groups.

Results: We identified four depressive symptom trajectory groups: minimal depressive symptoms (62%), worsening depressive symptoms (14%), improving depressive symptoms (19%), and persistent-severe depressive symptoms (5%). Longer midlife RTLs were related to significantly lower odds of being in the worsening symptoms trajectory versus minimal trajectory but not to other trajectories. In comparison with being in the minimal symptoms group, the multivariable-adjusted odds ratio of being in the worsening depressive symptoms group was 0.78 (95% confidence interval, 0.62–0.97; $p = 0.02$), for every standard deviation increase in baseline RTL.

Conclusions: In this large prospective study of generally healthy women, longer telomeres at midlife were associated with significantly lower risk of a subsequent trajectory of worsening mood symptoms over 20 years. The results raise the possibility of telomere shortening as a novel contributing factor to late-life depression.

KEYWORDS
depression, depressive symptoms, late-life, telomeres, trajectories

1 | INTRODUCTION

Telomere length (TL) is thought to be a marker of biological aging. Telomere attrition occurs with each somatic cell division and may be accelerated by oxidative stress and inflammation, both often elevated among individuals with depression (Black, Bot, Scheffer, Cuijpers, & Penninx, 2015; Correia-Melo, Hewitt, & Passos, 2014; Setiawan et al., 2015). Prior studies have noted that persons with a history of depression have shorter TL than those without such history (Ridout, Ridout, Price, Sen, & Tyrka, 2016; Schutte & Malouff, 2015; Solomon et al., 2017; Starnino, Busque, Tardif, & D'Antono, 2016). Once telomeres reach a critical length, apoptosis, mitochondrial damage, and genomic-instability may occur (Blackburn, 2005; Sahin et al., 2011).

Whereas oxidative stress may result in telomere attrition and dysfunction, emerging data suggest that telomere shortening could itself trigger cascades of cell dysfunction and death (Hovatta, 2015; Sahin & Depinho, 2010; Verhoeven, Revesz, Wolkowitz, & Penninx, 2014). Specifically, telomere shortening and dysfunction may further increase the production of reactive oxygen species (ROS)—contributing to mitochondrial and metabolic dysfunction (Sahin & Depinho, 2010). High energy-demand organs such as the heart and brain are particularly sensitive to damage from ROS (Magistretti & Allaman, 2015). Thus, associations between depression and TL may be bidirectional: depression may adversely affect telomeres, and telomere dysfunction may predispose to future depressive symptomatology—particularly in later-life when accumulated damage from ROS may be most prominent. As brain regions (e.g., hippocampus), central to mood health are damaged over time by ROS insults, depressive symptoms may emerge or worsen (MacQueen et al., 2003).

Yet, associations of TL with future depressive symptoms have been inadequately explored. Therefore, we examined how midlife TL related to subsequent 20-year trajectories of mood symptoms among 8,801 women in the Nurses' Health Study (NHS).

2 | MATERIALS AND METHODS

2.1 | Study sample

The NHS enrolled 121,700 female nurses, aged 30–55 years, in 1976 from 11 U.S. states. Participants have since completed biannual mailed questionnaires. Study retention has remained at ~90%. In 1989–1990, a subset of 32,826 NHS participants supplied blood samples; the sample for analysis was derived from these blood subcohort participants (Hankinson et al., 1995). Out of $n = 32{,}826$, four were excluded for missing date-of-birth, two for missing disease case status information (later used to select participants for telomere assays); 205 died before returning any depression questionnaire data (depressive symptoms were assessed using validated surveys beginning in 1992). An additional 3,215 were excluded for having less than three depression measures over follow-up. Those excluded for insufficient depression measures had: older age; higher depression scores; lower physical activity; higher medical comorbidity; heavier smoking.

A total of 29,400 women remained after the above exclusions. Additional exclusions were then made, as our analytic sample consisted of NHS blood subcohort participants with relative telomere length (RTL) data. RTL was measured in over a dozen NHS nested case-control studies of different diseases (De Vivo et al., 2009; Devore, Prescott, De Vivo, & Grodstein, 2011; Han et al., 2009; Page et al., 2008; Prescott, McGrath, Lee, Buring, & De Vivo, 2010). After exclusion of 20,599 women not included in these prior case-control studies and thus lacking RTL measures, the final sample included 8,801 (Figure 1). There were 3,029 cases (i.e., from nested case-control studies) and 5,772 controls (matching healthy participants in the case-control studies).

The study was approved by the institutional review board of Brigham and Women's Hospital.

2.2 | Depressive symptoms

Depressive symptoms were assessed on NHS questionnaires at 4-year intervals from 1992 to 2012. During this period, three different measures were utilized: the five-item Mental Health Inventory (MHI-5) from the Medical Outcomes Study Short Form-36 (1992, 1996, and 2000; Ware & Sherbourne, 1992); the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10; 2004); and the 15-item Geriatric Depression Scale (GDS-15; 2008, 2012). To model depressive symptom trajectories, we first harmonized and placed these three different measures on the same numerical scale, using an equipercentile equating method, described in detail elsewhere (Chang et al., 2016). The harmonized scale expressed the CES-D-10 and GDS-15 on the MHI-5 scale; original (1992/1996/2000) and estimated (2004/2008/2012) MHI-5 scores were then used to model trajectories. Prior work indicates excellent performance for identifying major depression and high concordance between estimated (using the equating method) and actual scores within a validation subset (Chang et al., 2016).

2.3 | Relative telomere length

RTL was obtained as the ratio of telomere repeat copy number to single gene copy number (T/S) and determined by real-time quantitative polymerase chain reaction assay. Assays were conducted with genomic DNA extracted from peripheral blood leukocytes from the 1989 to 1990 blood samples. Details regarding these procedures have been described elsewhere (Crous-Bou et al., 2014; De Vivo et al., 2009; Han et al., 2009; Hankinson et al., 1995). Because the RTL measures were pooled across various case-control studies, we adjusted for batch variation within the T/S ratio estimates using methods described by Rosner, Cook, Portman, Daniels, and Falkner (2008) We derived z-scores of log-transformed batch-adjusted T/S ratios; this was the RTL exposure of interest. The average coefficient of variation for the exponentiated T/S ratio was 9.6%.

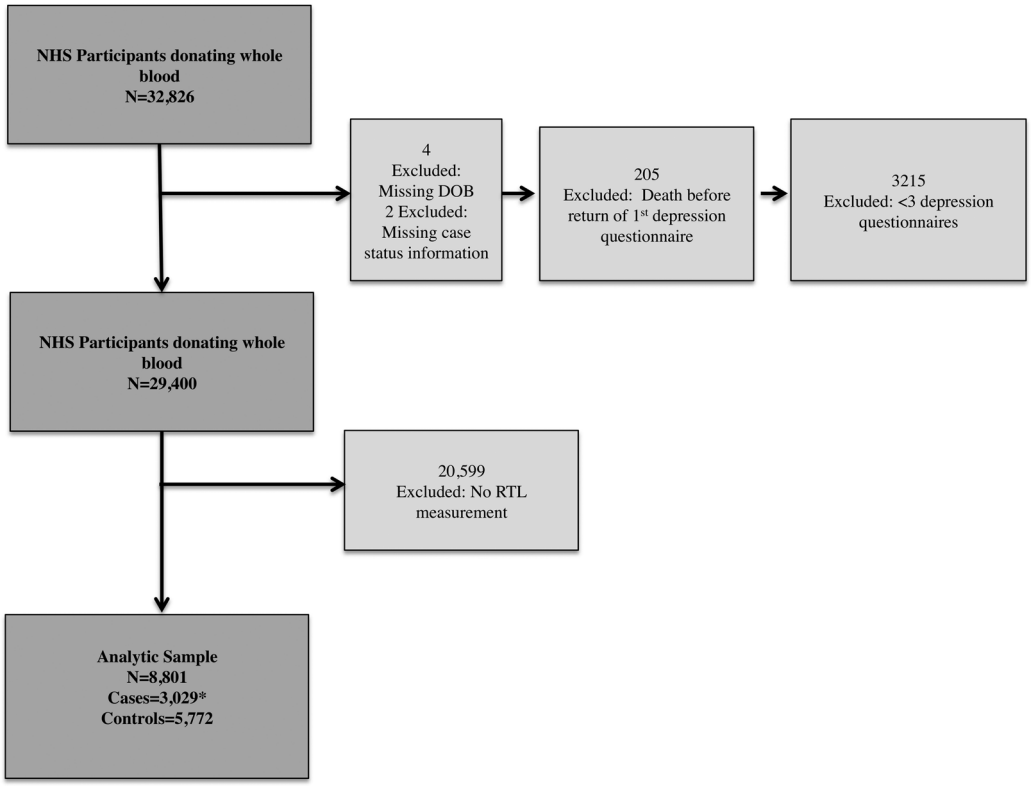

FIGURE 1 Study population exclusions. DOB: date of birth; NHS: Nurses' Health Study; RTL: relative telomere length

2.4 | Statistical analysis

Our statistical analyses proceeded in two stages of group-based trajectory modeling, as implemented using the Trajectory (TRAJ) procedure (Proc Traj) for SAS 9.3 (Jones, Nagin, & Roeder, 2001). First, we estimated the number of latent groups; then we explored the optimal polynomial shape for each group-based trajectory using standard approaches (Byers, Vittinghoff, & Lui, 2012; Chang et al., 2016; Jones et al., 2001). We considered models of 2–7 groups; scaled-age ([age at measurement–age at baseline]/10) was the time variable. We used scaled-age rather than raw age, as other work indicates that scaling may yield a better approximation of group trajectories (Chang et al., 2016; Jones et al., 2001). We compared the performance of both forms of age and confirmed that scaled-age better approximated actual group trajectories. To select the number of groups, we used standard practices of examining the Bayesian Information Criteria (BIC), the average posterior probability of group membership, parsimony, and clinical relevance of the groups. After selecting the number of groups, the optimal shape of each group's mean trajectory was examined iteratively. For each group, we considered polynomial shapes of linear through quintic. All eligible participants donating blood (n = 29,400) were included in the sample for the first stage.

In the second stage, we examined the association between baseline RTL and depressive symptom trajectories in the final analytic sample of n = 8,801. We modeled the odds of group-based trajectory membership associated with each standard deviation (*SD*) increase in RTL using multinomial logit models implemented in Proc Traj (Jones et al., 2001). Basic models were unadjusted for covariates, but age was controlled for as it served as the method for relating depression symptoms to time. Multivariable-adjusted models included: smoking (pack-years); body mass index (kg/m^2); alcohol consumption (g/day); physical activity (metabolic equivalent, hrs/week); Charlson comorbidity index (Charlson, Pompei, Ales, & MacKenzie, 1987); paternal age-at-birth (years), antidepressant use (yes/no); menopausal/hormone therapy status (premenopausal, postmenopausal, and currently on hormones, postmenopausal and not currently on hormones); case/control status. Covariates were selected based on prior literature regarding likely confounders of TL and depression. Covariates were ascertained from questionnaires returned just before or at time-of-blood draw.

2.5 | Secondary analyses

Secondarily, we examined RTL and depression incidence using Cox proportional hazards models. Individuals were classified as having

incident depression based on the first occurrence of (a) symptom score beyond validated cut-off for major depressive disorder (MDD; i.e., MHI-5 ≤ 52; CES-D-10 ≥ 10; GDS-15 ≥ 6), (b) self-reported regular antidepressant use, or (c) self-reported physician/clinician-diagnosed depression. We also examined models where depression cases were classified by symptom scores only. Person-time was contributed from the return of the baseline questionnaire until the occurrence of depression, death, loss to follow-up, or end of follow-up period, whichever came first.

Finally, we explored how 10-year change in RTL was prospectively associated with incident depression between 2000 and 2012. This analysis included a limited subset (n = 1,039) of women who were part of a second NHS blood collection in 2000/2001, had available RTL data at both blood collections and were alive as of the 2000 questionnaire cycle, as described elsewhere (Chang et al., 2018).

3 | RESULTS

3.1 | Participant characteristics

Table 1 displays the baseline characteristics of the analytic sample (n = 8,801) by RTL z-score quartile. Those in the lowest quartile were older and had higher pack-years of smoking; other characteristics did not meaningfully differ across quartiles.

3.2 | Depression trajectories

We examined models of between 2 and 7 groups and selected a four-group model (Figure 2a,b) based on the optimal combination of BIC, average posterior probabilities, and clinical interpretability. There were four depressive symptom trajectory types (label hereafter, prevalence): minimal symptoms ("minimal," 61%), improving symptoms ("improving," 20%), worsening symptoms ("worsening," 13%), and persistent-severe symptoms ("persistent-severe," 6%). The worsening group initially showed similar levels of symptoms to that of the minimal group; however, over follow-up symptoms increased from a euthymic range to that consistent with clinical depression. The improving and persistent-severe group trajectories both began with clinical-range symptoms, although initial symptom levels were slightly less severe for the improving group. Over the 20-year follow-up, however, the improving group showed symptom reduction—ultimately approaching symptom levels similar to those of the minimal group. Baseline characteristics by depressive symptom trajectory group are provided in Table S1.

TABLE 1 Baseline participant characteristics by relative telomere length quartile at blood draw in 1989/1990

	1st Quartile (n = 2,200)	2nd Quartile (n = 2,200)	3rd Quartile (n = 2,201)	4th Quartile (n = 2,200)
Age, (*SD*)*,[a]	59.1 (6.2)	58.6 (6.5)	58.0 (6.4)	57.5 (6.6)
MHI-5 score (*SD*)[b]	78.0 (13.8)	78.9 (13.4)	77.7 (14.4)	78.4 (13.4)
Case status, %[c]	35	35	34	35
Pack-years of smoking, (*SD*)	12.5 (18.1)	12.1 (17.7)	12.0 (17.9)	11.8 (18.0)
Body mass index, (*SD*)	25.2 (4.8)	25.4 (4.8)	25.2 (4.7)	25.2 (4.6)
Antidepressant use, %	5	4	4	4
Alcohol intake, g/week (*SD*)	5.6 (9.7)	5.5 (9.6)	5.6 (9.9)	5.2 (8.8)
Physical activity, MET hrs/week (*SD*)	16.9 (23.6)	16.9 (21.8)	17.1 (25.8)	16.1 (17.7)
Education: BA, %	20	21	19	22
Education: MA or Dr, %	11	10	10	10
Premenopausal, %	14	14	14	13
Postmenopausal & currently on HRT, %	35	35	36	35
Paternal age-at-birth, (*SD*)	31.0 (6.9)	31.7 (7.2)	31.6 (7.1)	31.7 (6.9)
Hypertension, %	29	30	29	30
High cholesterol, %	42	43	44	44
CVD (MI, stroke, CABG), %	7	5	6	5
Diabetes, %	4	5	4	4
Respiratory disease, %	9	9	8	7
Charlson Index, (*SD*)[d]	0.2 (0.6)	0.2 (0.6)	0.2 (0.5)	0.2 (0.5)

Values are means (*SD*) or percentages and are standardized to the age distribution of the study population. CABG: coronary artery bypass grafting; CVD: cardiovascular disease; HRT: hormone replacement therapy; MET: metabolic equivalent; MHI-5: Mental Health Inventory-5; MI: myocardial infarction; *SD*: standard deviation.

[a]Value is not age- adjusted.

[b]Mental Health Inventory-5.

[c]Classified as a "case" in the nested case-control studies of various diseases used to form analytic sample.

[d]All comorbidities are from self-reports of diagnosis by a healthcare professional Charlson Comorbidity Index (Charlson et al., 1987).

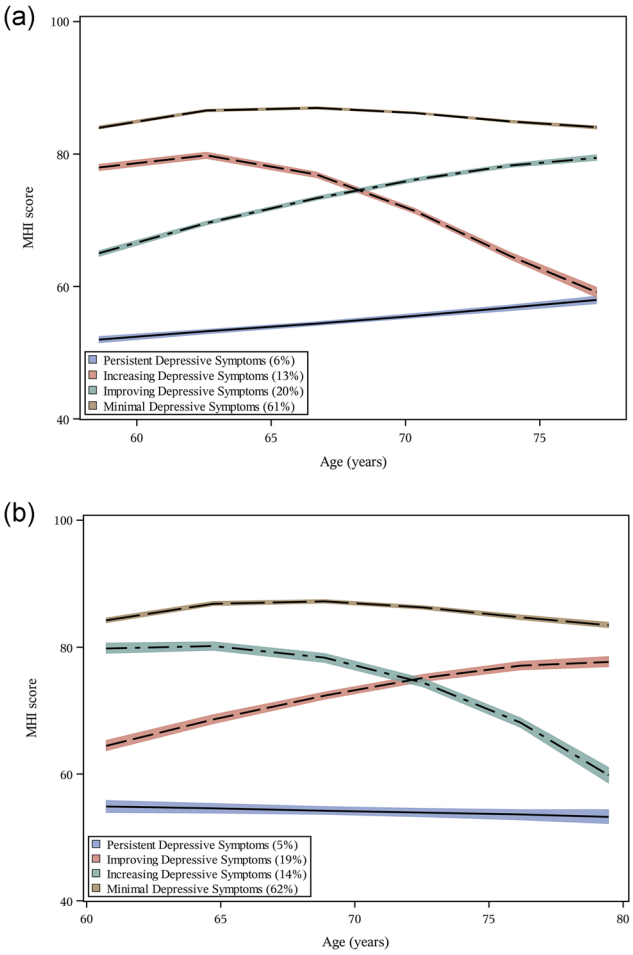

FIGURE 2 (a) Twenty-year mean unadjusted MHI* depressive symptom trajectories** (lower scores indicate more depressive symptoms) by age among women in the Nurses Health Study (N = 29,400 in full blood cohort). (b) Twenty-year multivariable-adjusted*** MHI* depressive symptom trajectories** (lower scores indicate more depressive symptoms; (N = 8,801 in the analytic sample). MET: metabolic equivalent; MHI: Mental Health Inventory

* Mental Health Inventory 5
** The figures illustrate group-based trajectories and their 95% confidence bands (shaded). Trajectories are modeled as a function of age. Group membership for identified trajectories was assigned using the group to which each participant had the highest posterior probability of membership.
***Adjusted for case/control status, pack years of smoking, BMI, antidepressant use, alcohol consumption, physical activity (MET hours/week), menopausal & hormone replacement therapy status, Charlson Index score, and paternal age at birth

As a sensitivity analysis, we derived the trajectories within only the subset of 8,801 participants with RTL measures. The numbers of groups and shapes of trajectories were identical to those derived using data from the larger sample of blood study participants (data not shown).

3.3 | Multinomial model results

Table 2a displays results from the main analyses relating midlife RTL to group membership in subsequent 20-year trajectories of depressive symptoms. The largest group was the reference category (i.e., minimal group). In both age- and multivariable-adjusted models, there was no evidence of higher odds of membership in the improving or persistent-severe groups, compared with the minimal group, by RTL. However, midlife RTL was significantly associated with odds of being in the worsening versus minimal group, including after adjustment for multiple lifestyles and health confounders. Specifically, each *SD*-increase in RTLs was related to 22% lower odds of being in the worsening depressive symptoms group. Because we found a significant association among the groups with similar levels of low symptoms at baseline, we subsequently examined the association with RTL among groups with similar levels of high symptoms at baseline (persistent-severe vs. improving). We noted no significant association for this comparison, but groups were less similar in symptom levels than in our main analysis. The odds of being in the improving group versus persiste nt-severe group decreased by a nonsignificant 0.94 times for each RTL increase, p = 0.72 (data not shown in tables).

3.4 | Additional analyses

To address potential bias by including disease cases from the nested case-control studies, we repeated models with only the 5,772 healthy controls. Results from these analyses (Table 2b) were comparable to those observed in the main analyses.

We examined the association of RTL with depression incidence in Cox proportional hazards models. Whether TL was measured at the first (Table S2a) or second blood draw (Table S2b), there were no

TABLE 2a Odds of being in each trajectory group, compared with the odds of being in the minimal symptoms group (reference category), per standard deviation increase in relative telomere length (cases and controls, *n* = 8,801)NaN

Depressive symptom trajectory group	Age-only adjusted odds ratio	95% CI	*p* Values	Adjusted odds ratio*	95% CI	*p* Values
Minimal symptoms (*n* = 5,456)	Ref	Ref	Ref	Ref	Ref	Ref
Improving symptoms (n=1,672)	1.10	(0.91, 1.34)	0.32	1.10	(0.90,1.34)	0.36
Worsening symptoms (*n* = 1,232)	0.69	(0.55, 0.86)	0.001	0.78	(0.62, 0.97)	0.02
Persistent symptoms (*n* = 441)	0.95	(0.71, 1.27)	0.72	1.02	(0.76, 1.37)	0.89

Note. BMI: body mass index; CI: confidence interval; MET: metabolic equivalent.

[a]Adjusted for case/control status, pack-years of smoking, BMI, antidepressant use, alcohol consumption, physical activity (MET, hrs/week), menopausal & hormone replacement therapy status, Charlson Index score, and paternal age at birth. Cases and controls were from nested case-control studies of various diseases in the Nurses' Health Study blood cohort.

associations between RTL and depression incidence. Further, there was no significant relation of 10-year change in RTL to subsequent risk of depression among the subset of participants (*n* = 1,039) with RTL measures at both time points (Table S3). Finally, results were similar regardless of whether incident depression cases were classified by symptoms only or by self-reported diagnosis or antidepressant use.

4 | DISCUSSION

Among nearly 9,000 women followed over 20 years, we found significant relations of midlife TL to the subsequent trajectory of depressive symptoms into later-life. For each *SD* increment in RTL, the odds of being in the worsening symptoms group versus minimal symptoms group was 0.78 (95% confidence interval [CI], 0.62–0.97; *p* = 0.02)—or 22% lower. RTL was not associated with the likelihood of being in other trajectory groups. Our results suggest a novel potential link between telomeres lengths and the evolution of depressive symptoms between mid- and later-life.

Although RTL was associated with worsening depression among those with comparable symptom levels at baseline, it was not associated with being in the persistently high versus persistently low symptom group over time, and mean RTL did not differ at baseline between these groups. One potential explanation for this is the relatively small number of participants in the persistent-severe category (*n* = 441, or 5% of sample); there may not have been adequate power to detect a significant contrast between the persistently high and persistently low symptom groups, and thus caution is warranted in the interpretation. Alternatively, it is possible that the group that has persistently severe symptoms—where persistent depression is associated with a variety of adverse health consequences, including earlier mortality (Murphy et al., 2016)—and yet remains living and available for 20-year follow-up, may include older adults who are particularly resilient. For example, a speculative possibility is that genetic or other factors may be associated with both RTL and resilience to ill effects of depression; thus, observed estimates could have been influenced by a survivor effect among participants in that group. The members of these two groups were similar in RTL at baseline but may have been dissimilar in levels of resilience to oxidative stress or other factors that promote telomere attrition—as impacts of oxidative stress would be expected to be more pronounced in late-life when telomeres have shortened with age and with cumulative exposure to damaging environmental factors. Differences in survival may also explain some of the inconsistencies in findings noted between both cross-sectional and longitudinal studies of TL and depression.

Previous work has frequently, but not uniformly, indicated relations of depression to TLs in cross-sectional and longitudinal studies, where depression was examined as an exposure.(Garcia-Rizo et al., 2013; Georgin-Lavialle et al., 2014; Hartmann, Boehner, Groenen, & Kalb, 2010; Hassett et al., 2012; Hoen et al., 2011, 2013; Huzen et al., 2010; Karabatsiakis, Kolassa, Kolassa, Rudolph, & Dietrich, 2014; Ladwig et al., 2013; Liu, Zhang, Yan, Wang, & Li, 2014; Lung, Chen, & Shu, 2007; Needham et al., 2015; Phillips et al., 2013; Ridout et al., 2016; Rius-Ottenheim et al., 2012; Schaakxs,

TABLE 2b Odds of being in each trajectory group, compared with the odds of being in the minimal symptoms group (reference category), per standard deviation increase in relative telomere length (controls only, *n* = 5,772)NaN

Depressive symptom trajectory group	Age-only adjusted odds ratio	95% CI	*p* Values	Adjusted odds ratio**	95% CI	*p* Values
Minimal symptoms (*n* = 3,536)	Ref	Ref	Ref	Ref	Ref	Ref
Improving symptoms (*n* = 993)	1.22	(0.95, 1.57)	0.13	1.19	(0.92, 1.54)	0.19
Worsening symptoms (*n* = 916)	0.68	(0.52, 0.89)	0.005	0.76	(0.58, 1.00)	0.05
Persistent symptoms (*n* = 327)	0.94	(0.66, 1.34)	0.72	1.07	(0.74,1.53)	0.73

Note. BMI: body mass index; CI: confidence interval; MET: metabolic equivalent.

[a]Adjusted for pack-years of smoking, BMI, antidepressant use, alcohol consumption, physical activity (MET, hrs/week), menopausal & hormone replacement therapy status, Charlson Index score, and paternal age at birth. Controls were from nested case-control studies of various diseases in the Nurses' Health Study blood cohort.

Verhoeven, Oude Voshaar, Comijs, & Penninx, 2015; Schutte & Malouff, 2015; Shaffer et al., 2012; Shalev et al., 2014; Simon et al., 2015; Solomon et al., 2017; Starnino et al., 2016; Surtees et al., 2011; Teyssier, Chauvet-Gelinier, Ragot, & Bonin, 2012; Verhoeven et al., 2018; Verhoeven, van Oppen, Revesz, Wolkowitz, & Penninx, 2016; Wikgren et al., 2012) Most studies, so far, have been cross-sectional. Some cross-sectional studies among adults reported significant associations between depression and shorter TL (Garcia-Rizo et al., 2013; Hartmann et al., 2010; Hassett et al., 2012; Hoen et al., 2011; Karabatsiakis et al., 2014; Needham et al., 2015; Starnino et al., 2016; Teyssier et al., 2012; Verhoeven et al., 2016; Wikgren et al., 2012); others showed null associations (Georgin-Lavialle et al., 2014; Hoen et al., 2011, 2013; Huzen et al., 2010; Ladwig et al., 2013; Schaakxs et al., 2015; Shaffer et al., 2012; Simon et al., 2015; Surtees et al., 2011). Relatively fewer studies have examined how depression related to TL over time; these longitudinal studies show mixed findings (Liu et al., 2014; Lung et al., 2007; Phillips et al., 2013; Rius-Ottenheim et al., 2012; Schutte & Malouff, 2015; Shalev et al., 2014; Vance et al., 2018; Verhoeven et al., 2016; Verhoeven et al., 2018). A recent meta-analysis of longitudinal and cross-sectional studies examining the association of depression with TL, found no association for the pooled longitudinal result ($R = -0.001$; 95% CI, −0.08; 0.08; $p = 0.98$; Schutte & Malouff, 2015) a significant association was indicated for the pooled cross-sectional studies (Schutte & Malouff, 2015). In the last year, our group also examined relations of depression to prospective change in RTL in a subset of $n = 1{,}250$ NHS participants; Chang et al. (2018) similarly observed no significant association between baseline depression and 11-year telomere attrition, although point estimates and statistical trends were consistently in the direction of worse telomere attrition among those with versus without depression. Overall, longitudinal evidence remains relatively sparse. Indeed, the meta-analysis by Schutte and Malouff (2015) was more limited for the pooled longitudinal studies: only five studies met inclusion criteria, compared with the 25 studies included in the cross-sectional analysis (Schutte & Malouff, 2015). Also, it is possible that the inconsistencies in findings may relate to the extent of survivor effects present in the different cohorts under examination, where greater influences of survival would be expected with older cohorts.

Whereas prior studies have examined prospective relations of depression to TL, similar attention has not focused on the association of TL with subsequent depression. The possibility of this temporal direction has been raised by earlier studies among children and adolescents (Gotlib et al., 2015; Rackley et al., 2012; Wojcicki et al., 2015). For example, individuals born with dyskeratosis congenita, a disorder impeding normal telomerase activity and rapidly accelerating telomere attrition, show an increased risk of psychiatric disorders when compared with individuals suffering from other chronic illnesses (Rackley et al., 2012). However, the relevance of these findings to older adults is not clear: the biological relationships between depression and RTL may differ among these groups, and other confounders and factors associated with disorders of aging may play a role. Similarly, a temporal association between TL and subsequent depression outcomes was also suggested by data from a more recent preliminary study. Hough et al. (2016) examined antidepressant response in relation to baseline TL among adults 20–65 years ($n = 27$; mean age = 38 years) diagnosed with MDD; shorter TL was associated with worse antidepressant response and with more negative affect over an 8-week period.

When results from the current study are considered alongside the above-mentioned reports, an intriguing possibility is raised that having shorter telomeres may predispose to development of worse psychiatric symptoms among adults. Indeed, in a separate NHS cohort analysis using a latent class (finite mixture modeling) approach to identify phobic anxiety symptom groups; Ramin et al. (2015) reported a nonstatistically significant trend (multivariable-adjusted, $p = 0.09$) for midlife RTLs and risk of late-life anxiety. Among $n = 3{,}194$ women with no or minimal phobic anxiety symptoms at baseline, those with shorter compared with the longest telomeres at midlife had nearly two-fold higher odds of severe phobic anxiety 16 years later. Nonetheless, an alternative explanation for those preliminary findings is that short TLs may be peripheral biomarkers for other biological processes that impact subsequent affective outcomes more directly.

The potential for a bidirectional association between telomeres and psychopathology has a plausible biologic basis. Whereas depression and oxidative stress have been associated with shorter telomeres, it is also possible that telomere shortening may itself potentiate oxidative stress (Liu et al., 2014). One mechanism may involve the release of ROS and subsequent cellular stress cascades.(Cai et al., 2015; Karabatsiakis et al., 2014; Sahin & Depinho, 2010; Savitz & Drevets, 2009; Szebeni et al., 2014) Depression and other forms of psychological stress may increase ROS, resulting in damage to DNA and other cellular components (Karabatsiakis et al., 2014; Teyssier et al., 2012; Tyrka et al., 2015; Verhoeven et al., 2014; Wei, Backlund, Wegener, Mathe, & Lavebratt, 2015). This damage may impede normal cell and antioxidant defenses and result in apoptosis or accelerated telomere attrition. Yet, as noted by Sahin & Depinho (2010), dysfunctional telomeres can activate their own cascade of DNA damage, oxidative stress, and mitochondrial dysfunction via a p53-mediated process; this may lead to further downstream mitochondrial and metabolic dysfunction, including among postmitotic cells that are energy demand-sensitive (Hovatta, 2015; Sahin et al., 2011; Verhoeven et al., 2014; Wolkowitz et al., 2015). Indeed, as the brain has the highest demand for mitochondrial energy of any organ, neurons are particularly vulnerable to deficiencies in energy production (Pei & Wallace, 2018; Wallace, 2017). Indeed, such processes may result in loss of susceptible neurons in key regions for mood maintenance and neurogenesis, such as the hippocampus (which has the highest telomerase activity of any brain region). For example, mice with critically short telomeres show reduced neurogenesis and neural differentiation—suggesting that telomere dysfunction could reduce neuroplasticity with age (Ferron et al., 2009). Thus, a cascade of telomere attrition and downstream consequences may be particularly relevant for older adults with respect to potential for disruptions of homeostatic mechanisms

within the brain (Duman, Malberg, Nakagawa, & D'Sa, 2000; Szebeni et al., 2014) Nonetheless, whereas these potential mechanisms relating telomere shortening and dysfunction to brain outcomes are compelling, we were not able to observe such processes directly in the present study.

This study features important strengths, including a large cohort of participants followed over decades for depressive symptoms and potential confounders that were measured repeatedly using validated questionnaires. In addition, this study makes a novel contribution by applying group-based trajectory modeling to explore the relationship between TL and subsequent depressive symptoms. The ability to examine mood trajectories over 20 years in a large, well-characterized sample afforded finer discrimination of depression outcomes and their relations to antecedent TL. When we explored, as a sensitivity analysis, this association using a simple case classification of depression in survival models, TL was not significantly related to incident depression. These differences may reflect that a more nuanced understanding of the data might be achieved in this context when depression is treated as a continuous, dimensional outcome in group-based trajectory models versus as a dichotomous, case endpoint in traditional survival models. Specifically, survival analyses are based on reaching a threshold of caseness; once classified as a case, an individual contributes no further information. Participants may also experience the competing risk of death before ever being counted as a case. By contrast, the group-based trajectory modeling approach allowed information at all available time points to be included in analyses.

Limitations should also be considered. First, depressive symptoms were only assessed at 4-year intervals; thus, interim fluctuations in symptoms could be missed. Shorter intervals between evaluations would have provided finer granularity of trajectories. However, we used data from six-time points over 20 years and provided sufficient information regarding symptoms over time such that latent groups could be identified. Second, the study cohort consisted of women who were mostly nonLatina white (95%), had access to healthcare resources, and had relatively high education levels (associate degree and above). Although there is not presently a strong biological rationale to suggest that the association between TL and depressive trajectories would differ by sex, education or race/ethnicity, the limited generalizability of the sample indicates that results should be interpreted with caution. Third, RTL is a biological measure with potential sources of error in both the telomere and single gene assays. Random measurement error would likely be nondifferential and could result in bias in estimates toward the null.

In summary, results from this study indicated that midlife women with longer telomeres at baseline were less likely to experience worsening depressive symptoms over the subsequent 20 years. Findings suggest that mechanisms involved in telomere shortening could be relevant to the evolution of depressive symptoms during aging. As data are minimal regarding the potential for a bidirectional relationship between depressive symptoms and telomere attrition, novel findings from this study make a notable contribution to the evidence base on telomeres and psychiatry.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

ORCID

Jennifer Cai Gillis http://orcid.org/0000-0002-7431-0613
Shun-Chiao Chang http://orcid.org/0000-0002-1649-3191
Naomi M. Simon http://orcid.org/0000-0002-8867-889X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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