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The Relation of Optimism to Relative Telomere Length in Older Men and Women

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Abstract

Objective: Mounting evidence suggests that higher optimism is associated with reduced risk of age-related morbidities and premature mortality. Yet, possible biological mechanisms underlying

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these associations remain understudied. One hypothesized mechanism is a slower rate of cellular aging, which in turn delays age-related declines in health.

Methods: We used data from two large cohort studies to test the hypothesis that higher optimism is associated with longer leukocyte telomere length. Using cross-sectional data from the Health and Retirement Study (HRS; N=6,417; mean age=70 years) and the Women's Health Initiative (WHI; N=3,582; mean age=63 years), we used linear regression models to examine the association of optimism with relative telomere length (assessed in leukocytes from saliva [HRS] or plasma [WHI]). Models adjusted for sociodemographics, depression, health status, and health behaviors.

Results: Considering both optimism and telomere length as continuous variables, we found consistently null associations in both cohorts, regardless of which covariates were included in the models. In models adjusting for demographics, depression, co-morbidities, and health behaviors, optimism was not associated with mean relative telomere length (HRS: β=−0.002; 95% CI:−0.014, 0.011; WHI: β=−0.004; 95% CI:−0.017, 0.009).

Conclusions: Findings do not support mean telomere length as a mechanism that explains observed relations of optimism with reduced risk of chronic disease in older adults. Future research is needed to evaluate other potential biological markers and pathways.

Keywords

optimism; psychological well-being; telomere length; aging

The population aged >65 years in the United States is projected to increase by nearly 60% in the next 20 years (1). Thus, promoting healthy physical and cognitive aging is a critical public health priority. A substantial body of research has linked specific facets of psychological well-being with lower risk of mortality and morbidity (2). Specifically, dispositional optimism—a psychological trait characterized by the generalized expectation of a positive future—has been consistently associated with reduced risk of premature mortality and of age-related chronic conditions such as heart disease and cognitive impairment (2–6). Both biologic (e.g. buffering toxic cellular effects of stress-related neuroendocrine activation) and behavioral (e.g. increased likelihood of engaging in healthy behaviors) mechanisms may explain the association between optimism and healthy aging (2,7–9). Yet limited research has addressed whether optimism may be associated with a slower rate of cellular aging.

Telomeres are repetitive sequences of DNA at the ends of chromosomes that protect DNA. They shorten with each cell division until they trigger cell death or senescence (10). While telomere dynamics are regulated and modified by numerous processes, shorter telomere length has been identified as a marker of cellular aging (10). However, previous studies evaluating the association between relative telomere length in relation to either chronic diseases or psychosocial factors have reported mixed findings. In some studies, shorter relative telomere length has been linked with increased risk of myocardial infarction and mortality due to heart disease and some cancers (11,12); findings, however, have not been consistent in all studies nor have associations been evident with other conditions, such as cerebrovascular disease and cognitive decline (11,13). Prior work has also linked shorter telomere length to higher levels of chronic stress as measured by poverty, exposure to

violence, stress of being a family caregiver, and to higher psychological distress (10). Yet, other research has found null associations between relative telomere length and psychosocial factors (e.g., depression, anxiety) (14). Such inconsistencies in the literature could be partly explained by the fact that psychosocial factors are not uniform in their behavioral or biological sequelae. Thus, it is critical to directly evaluate if optimism is related to telomere length.

A handful of studies previously evaluated the association between optimism (or its counterpart, pessimism) with telomere length (15–19). Four of five studies reported that lower optimism was related to shorter relative telomere length (15–18), although findings are not entirely consistent. Several of these studies considered positively and negatively worded items from a questionnaire-based measure of optimism separately, as capturing either a pessimistic or optimistic orientation, and found associations with negatively, but not positively worded items (17,18). One study among men only found an association of having a pessimistic orientation with repeated measures of telomere length pooled across time (18). However, generally sample sizes were small (between 36 and 490), limiting the ability to adjust for confounders and accurately evaluate effect estimates. In a recent study evaluating optimism in relation to other markers of cellular aging, optimism was not associated with two measures of DNA methylation aging (i.e., epigenetic clocks) in two different samples of men (Normative Aging Study) and women (Women's Health Initiative) (20).

Thus, we used data from two large cohorts, the Health and Retirement Study (HRS) and the Women's Health Initiative (WHI), to further test the hypothesis that higher optimism is associated with longer relative leukocyte telomere length (LTL). We considered relevant covariates identified from prior research, including sociodemographics, health status, depression, and health-related behaviors (10).

Methods

Study Populations

The Health and Retirement Study (HRS) is a nationally representative study of US adults aged >50 years. In 2008, a random 50% of HRS participants was selected for an enhanced face-to-face (EFTF) interview. After the interview, respondents were given a psychosocial questionnaire to be returned by mail (response rate=84%); they were also invited to provide a saliva sample (85% consented). This is the only wave when telomere length was assayed (21). Respondents who consented to provide saliva samples, compared to those who did not, did not differ across age, sex, or socioeconomic indicators (21). Among eligible respondents who provided saliva samples and completed the psychosocial questionnaire (n=6,541), we excluded 124 with missing data on optimism (described below), yielding an analytic sample of 6,417.

We also used data from the Women's Health Initiative (WHI), a long-term study of initially healthy postmenopausal women. Starting in 1993, women aged 50-79 years were recruited throughout the U.S. and entered a clinical trial (WHI-CT) or an observational study (WHI-OS). At baseline, women completed self-administered questionnaires including information about sociodemographics, psychosocial characteristics, health-related behaviors, and health

conditions. Telomere data were available from a nested case-control study of diabetes in WHI-OS (22), with 1,584 cases of diabetes and 2,198 controls (with neither diabetes nor cardiovascular disease), using stored blood collected at baseline when all women were diabetes-free. Among those who provided demographic, clinical, and behavioral data at baseline (n=3,713), we excluded 131 with missing data on optimism, resulting in an analytic sample of 3,582 women.

Institutional review board approval was obtained for each study. Extensive documentation is available for HRS (http://hrsonline.isr.umich.edu/) and WHI (www.whi.org/).

Measures

Optimism—In HRS and WHI, optimism was assessed using the Life Orientation Test-Revised (LOT-R) questionnaire. The measure has good discriminant and convergent validity, and good reliability (23). Using a 6-point Likert scale, participants were asked the degree to which they agreed with 6 statements such as, “In uncertain times, I usually expect the best.” After reverse coding negatively-worded items, all items were summed to create a composite score, with higher scores indicating higher optimism; to facilitate comparisons across studies, we standardized optimism scores (M=0, SD=1). Because optimism is best characterized by both endorsing the positively-worded items and rejecting negatively-worded items (24), we followed recent recommendations to use the 6-item composite rather than 3-item subscales that are sometimes used (25). To assess discontinuous or threshold effects, we created quartiles of optimism based on the distribution of scores in each sample. In secondary analyses, because other studies sometimes present findings with only the negatively oriented items, we evaluated the 3-item pessimism subscale. Optimism appears to be moderately stable in adulthood (4-year correlation=0.61 in the HRS).

Telomere Length Measurement

HRS: In 2008, saliva samples were obtained using Oragene Collection Kits and sent to a central laboratory for DNA extraction. DNA was sent to Telome Health, where relative average telomere length was measured using quantitative PCR (21). Relative average telomere length expressed as a T/S ratio was established by measuring the number of telomere repeats (T) relative to the amount of a single-copy gene copy number (S). Each DNA sample was assayed as duplicates or triplicates. The coefficient of variation (CV) for each sample was calculated based on the number of runs each sample was assayed. Samples <12.5% CV passed, while samples with >12.5% CV were re-assayed. Genomic DNA from cancer cell lines was included to evaluate performance of each PCR run, and CV’s were 3.5%, 5.6%, and 6.3% across the three cell lines (21).

WHI: Measurement of telomere length was collected at the baseline examination (between September 1994 and December 1998), and has been described elsewhere (26). Briefly, the high-throughput method proposed by O’Callaghan et al. was used (27). Mean telomere length per chromosome was calculated using the following formula: (TL/copies of diploid genome)/(23×2). As part of quality control, 10% of the samples were blinded reproducibility samples. The overall intraplate CV was 0.8%, and the interplate CV was 5.7% (26).

Missing telomere length data was imputed in both datasets, although there were few participants missing data generally. We imputed missing data using an imputation by chained equations procedure by generating 30 datasets, because it provides a more accurate estimate of association than other methods of handling missing data (28).

Covariates—All covariates were reported at baseline in WHI (1993) and during the 2008 wave of HRS; unless noted, they were assessed and coded in the same way. Sociodemographic factors included age (continuous), sex (male/female; only in HRS), race/ethnicity (White, African-American, Hispanic, Other), educational attainment (no high school degree, GED or high school diploma, some college or higher), and total income (in WHI; <$20,000, $20,000-$49,999, $50,000-$74,999, $75K) or total wealth (in HRS; quartiles of the score distribution). Baseline health status, assessed via participants' report of doctor's diagnosis or taking medication, included: hypertension (yes/no), high cholesterol (yes/no), diabetes (yes/no), and obesity (yes/no; assessed by self-report in HRS and measured by trained staff in WHI; body mass index [BMI]≥30kg/m^2). In WHI, depression (yes/no) was assessed using the Burnam Screening Algorithm questionnaire that includes six items from the CES-D and two from the Diagnostic Interview Scale (DIS) (29,30), with a cutoff of ≥0.06 indicating depression. In HRS, depression status (yes/no) was assessed using the eight-item Center for Epidemiologic Studies Depression Scale (CES-D) and defined as a score of ≥4 (30). Health behaviors included smoking status (current, former, never), alcohol consumption (HRS: current drinker (yes/no); WHI: current, any former use, never), and physical activity (HRS: never, 1-3x/month, 1x/week, >1/week, everyday; WHI: total metabolic equivalent task-hours [MET-hours]/week).

Statistical Analysis

All ordinary least square regression models were run separately within each cohort and three sets of models were created. The first model adjusted for age. The second model added potential confounders including sex (only in HRS), race/ethnicity, education, income (in WHI) or total wealth (in HRS), baseline health, and depression. A third model added health-related behaviors, including smoking, alcohol consumption, and physical activity. Further, telomere length was transformed with the natural logarithm in all models.

We conducted several additional analyses. To test potential effect modification by sex, race/ethnicity, depression, or baseline health (defined as two categories: having hypertension, high cholesterol, diabetes and/or obesity versus having none of these conditions)—we conducted separate analyses stratified by each factor, and also evaluated an interaction term of optimism with each factor in separate models. We also considered the pessimism subscale in relation to telomere length. Further, the use of a diabetes case-control cohort in WHI may have implications for our findings given an observed link between optimism and risk of diabetes (31,32). While telomere measures were obtained at baseline before participants developed diabetes, to fully consider this issue, we conducted analyses excluding cases who developed diabetes after baseline in WHI. Since HRS included diabetes cases at baseline, we conducted alternate analyses excluding those with diabetes at baseline in HRS. Additionally, to evaluate potential bias introduced by multiple imputation for covariates and outcomes, we

also performed a sensitivity analysis with participants who had only complete data (n=4,231 in HRS and n=3,461 in WHI).

All analyses were conducted in Stata (version 15.0) or SAS (version 9.4).

Results

Descriptive Statistics

In HRS, participants identified as White (76%), Black, (13%), Hispanic (9%) or other (3%). At study baseline, respondents had a mean age of 70 years (SD = 10), and the highest proportion were women (58%) and high school educated (54%). In WHI, women identified as White (53%), Black, (30%), Hispanic (11%) or other (7%). At study baseline respondents had a mean age of 63 years, (SD = 7) and most had >high school education (75%). Table 1 provides additional details about participants. In both cohorts, distributions of some sociodemographics, health behaviors, and health conditions were similar across optimism quartiles, but more optimistic participants generally reported more education, income/wealth, and physical activity, as well as lower prevalence of obesity, hypertension, cholesterol, diabetes, and depression.

Optimism and Relative Telomere Length

In both the HRS and WHI cohorts, associations between optimism as a continuous variable and telomere length were null in age-adjusted models (Table 2). In subsequent models that adjusted for additional covariates, associations did not meaningfully change and remained null across both samples (e.g., fully-adjusted models HRS (β=−0.002; 95% CI: −0.014, 0.011); WHI (β=−0.004; 95% CI: −0.017, 0.009)).

Likewise, in analyses evaluating quartiles of optimism in relation to telomere length, the associations were null in both cohorts and across all models (Table 2). For example, comparing the highest to lowest optimism quartile, adjusting for age and other covariates, no association was evident in HRS (β=0.000; 95% CI: −0.032, 0.032) or WHI (β=−0.012; 95% CI: −0.047, 0.024).

There was no interaction in HRS between optimism and sex (*p*-interaction = 0.9), or in either cohort by depression (*p's*-interaction 0.2-0.8), race/ethnicity (*p's*-interaction 0.5-0.9), or baseline health status (*p's*-interaction 0.5-0.9) in fully-adjusted models. Associations were also null in models that stratified by all these factors in both cohorts (results not shown). Further, when evaluating a pessimistic orientation in relation to telomere length, associations remained null (e.g., fully-adjusted models in HRS, β=−0.002; 95% CI: −0.014, 0.011; WHI, β=−0.002; 95% CI: −0.015, 0.011). We also conducted analyses excluding those with diabetes at baseline in HRS or people who went on to develop diabetes after baseline in the nested case-control study in WHI. In demographic-adjusted models, the parameter estimates were null in both HRS (β=−0.001; 95% CI: −0.013, 0.010) and WHI (β=−0.007; 95% CI: −0.024, 0.009), and remained null in all covariate models. In analyses that evaluated only participants with complete data (Table S1), effect estimates were similar to those derived with multiply-imputed datasets for both HRS and WHI.

Discussion

In two large, ethnically diverse, well-characterized cohorts, we observed consistently null cross-sectional associations between optimism and leukocyte telomere length. These findings suggest that slower cellular aging, as indicated by telomere length at a single point in time, may not represent a biological pathway through which optimism operates to reduce risk of age-related chronic diseases and mortality. There was no evidence of effect modification by sex, depression, race/ethnicity, or baseline health in either cohort. Associations were also null when evaluating the pessimism subscale in relation to relative telomere length. Given the large sample sizes, use of an identical validated measure of optimism, and replication of findings across potential effect modifiers in two cohorts, these null results are informative.

Our findings differ from past research which has found positive associations between optimism and telomere length (15–18). A possible reason is that our sample size was larger than in previous studies, and thus provided more accurate effect estimates. Additionally, past longitudinal studies have shown that over time adults typically maintain their rank ordering of telomere length when compared to peers (33,34), even after accounting for variation in telomere length shortening that occurs across individuals. As a result, links between psychosocial factors and telomere length may be more difficult to detect in analyses utilizing measures taken from a single time point; it also may be easier to detect associations with repeated measures of the same biomarker because of decreased measurement error (15,17–19). Strong associations with pessimistic orientation were reported in the only study that evaluated relations with measures of telomeres taken at multiple time points (18).

Interestingly, other research on the relationship between psychosocial factors and telomere length has suggested that associations may be evident only among healthy individuals. A meta-analysis of 41 studies evaluating associations between childhood adversity and telomere length found that relations were substantially weaker among those with existing medical conditions or psychiatric disorders, and among participants who took medications or smoked (35). Studies evaluating various forms of psychological distress (e.g., depression) in relation to telomere length have also more consistently found evidence of associations among younger (e.g., healthier) versus older adults. In aggregate, these studies suggest that specific relations between psychological factors and telomere length could be harder to detect at older ages due to an array of other factors that accumulate to impact telomere length in later life.

Our measure of telomere length assessed one aspect of telomere dynamics, and other aspects may differently reflect potential underlying biological processes. For example, some previous work has measured telomerase (16), a cellular enzyme that adds telomeric repeat sequences to the telomere at the end of its eukaryotic chromosomes and helps maintain healthy cell function. Additionally, assessing *mean* telomere length does not capture other potentially important telomere length dynamics. For example, even if one telomere is short, out of 92 in one cell, it can trigger cell senescence; some studies suggest that the shortest telomeres, but not mean telomere length, are associated with senescence or disease. Future

research might evaluate the association between optimism and cellular aging by using other parameters to capture a more dynamic process.

The current study has both limitations and strengths. As noted above, among the limitations are a cross-sectional study design and possible measurement error. In addition, HRS and WHI measured relative telomere length using somewhat different approaches (i.e., saliva samples and blood samples, respectively). Nonetheless, important strengths include the large sample sizes, which facilitate detection of small effect sizes. Moreover, we replicated results in two different cohorts using the same measure of optimism, adjusted for a range of relevant covariates, and tested for effect modification among important candidate factors.

In conclusion, in two large cohorts of racially and ethnically diverse older adults, we found no evidence of a cross-sectional association between optimism and leukocyte telomere length. These findings suggest that cellular aging, as represented by mean relative telomere length, may not be a mechanism explaining associations between optimism and health outcomes in older adults. Given the growing body of research showing associations between higher optimism and reduced risk of age-related morbidity and mortality, research exploring other possible biological mechanisms underlying this association is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms

HRS	Health and Retirement Study
SD	Standard Deviation
GED	General Educational Development
EFTF	Enhanced Face-to-Face
IRB	Institutional Review Board
LTL	Leukocyte telomere length
WHI	Women's Health Initiative
WHI-CT	Women's Health Initiative Clinical Trial
WHI-OS	Women's Health Initiative Observational Study
LOT-R	Life Orientation Test-Revised
CV	Coefficient of variation

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Table 1.

Baseline Characteristics of Study Participants

	Health and Retirement Study (n=6,417)		Women's Health Initiative (n=3,582)	
	Optimism Levels		Optimism Levels	
Characteristics	**1st Quartile (n=1,715)**	**4th Quartile (n=1,621)**	**1st Quartile (n=834)**	**4th Quartile (n=1,173)**
Sociodemographic Factors				
Mean Age (SD)	69 (10)	69 (9)	63 (7)	63 (7)
Female (%)	56	63	100	100
Race/Ethnicity (%)				
White	73	82	45	55
African-American	12	12	28	33
Hispanic	11	5	17	7
Other	4	2	11	5
Education				
<High School	31	10	18	5
High School	55	54	23	11
Some College or higher	14	37	59	84
Total Wealth or Income				
HRS				
1st Quartile	32	17		
2nd Quartile	28	17		
3rd Quartile	24	30		
4th Quartile	15	37		
WHI				
<$20,000			31	13
$20,000-$40,000			41	41
$50,000-$79,999			13	23
≥$75,000			9	20
Unknown			5	3
Baseline Health				

	Health and Retirement Study (n=6,417)		Women's Health Initiative (n=3,582)	
	Optimism Levels		Optimism Levels	
Characteristics	**1st Quartile (n=1,715)**	**4th Quartile (n=1,621)**	**1st Quartile (n=834)**	**4th Quartile (n=1,173)**
History of Hypertension (%)	52	42	44	39
High Cholesterol (%)				
HRS	51	43		
Cholesterol Meds				
WHI				
History of High Cholesterol (%)			17	14
Type 2 Diabetes (%)	19	10	9	6
Obesity (BMI≥30kg/m^2)	31	26	45	35
Depression (%)	24	2	25	5
Health Behaviors				
Smoking (%)				
Current	17	11	8	7
Former	41	43	36	42
Never	42	46	55	51
Alcohol (%)				
HRS				
Current	42	57		
WHI				
Current			52	64
Former			27	22
Never			21	14
Physical activity				
HRS (%)				
Never	26	13		
1-3x/month	11	7		
1x/week	13	10		
>1/week	37	55		
Everyday	37	14		

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	Health and Retirement Study (n=6,417)		Women's Health Initiative (n=3,582)	
	Optimism Levels		Optimism Levels	
Characteristics	1st Quartile (n=1,715)	4th Quartile (n=1,621)	1st Quartile (n=834)	4th Quartile (n=1,173)
WHI				
Mean METs/week (SD)			9.6 (12.9)	13.7 (14.9)

Table 2.

Linear Regression Coefficients for the Association Between Optimism and Leukocyte Telomere Length

	Optimism Levels				
Health and Retirement Study	**Continuous Optimism Score[a]**	**Quartile 1 (n = 1,715)**	**Quartile 2 (n = 1,495)**	**Quartile 3 (n = 1,586)**	**Quartile 4 (n = 1,621)**
	Mean Difference ß (95% CI)		Mean Difference ß (95% CI)	Mean Difference ß (95% CI)	Mean Difference ß (95% CI)
Age Adjusted Model	−0.001 (−0.012, 0.011)	Ref.	0.007 (−0.022, 0.036)	0.008 (−0.022, 0.037)	0.002 (−0.028, 0.032)
Basic Confounders Model[b]	−0.002 (−0.014, 0.011)	Ref.	0.003 (−0.026, 0.031)	0.005 (−0.025, 0.036)	0.000 (−0.032, 0.032)
All Covariates Model[c]	−0.002 (−0.014, 0.011)	Ref.	0.003 (−0.026, 0.032)	0.007 (−0.023, 0.037)	0.000 (−0.032, 0.032)
Women's Health Initiative	**Continuous Optimism Score[a]**	**Quartile 1 (n = 834)**	**Quartile 2 (n = 681)**	**Quartile 3 (n = 894)**	**Quartile 4 (n = 1,173)**
Age-Adjusted Model	−0.005 (−0.017, 0.007)	Ref.	−0.042 (−0.079, 0.004)	−0.0004 (−0.036, 0.035)	−0.017 (−0.050, 0.016)
Basic Confounders Model[b]	−0.004 (−0.017, 0.009)	Ref.	−0.037 (−0.075, 0.002)	0.008 (−0.02, 0.045)	−0.011 (−0.046, 0.025)
All Covariates Model[c]	−0.004 (−0.017, 0.009)	Ref.	−0.038 (−0.076, 0.003)	0.007 (−0.029, 0.044)	−0.012 (−0.047, 0.024)

[a] per 1 SD increase in LOT-R score

[b] Basic confounders model: age, race/ethnicity, education, income (in WHI) or total wealth (in HRS), hypertension, high cholesterol (in WHI) or high cholesterol medication (in HRS), diabetes, obesity, depression

[c] All covariates model additionally adjusts for: smoking, alcohol consumption, physical activity