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Original Article

Does Telomere Length Indicate Biological, Physical, and Cognitive Health Among Older Adults? Evidence from the Health and Retirement Study

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Abstract

Telomere length (TL) has been suggested as a biomarker that can indicate individual variability in the rate of aging. Yet, it remains unclear whether TL is related to recognized indicators of health in an aging, older nationally representative sample. We examine whether TL is associated with 15 biological, physical, and cognitive markers of health among older adults ages 54+. TL was assayed from saliva using quantitative polymerase chain reaction (T/S ratio) in the 2008 Health and Retirement Study (n = 4,074). We estimated probability of high-risk levels across indictors of health by TL and age—singly and jointly. TL was associated with seven indicators of poor functioning: high-density lipoprotein and total cholesterol, cystatin C, pulse pressure, body mass index, lung function, and walking speed. However, after adjusting for age, associations were substantially attenuated; only associations with cholesterol and lung function remained significant. Additionally, findings show TL did not add to the predictive power of chronological age in predicting poor functioning. While TL may not be a useful clinical marker of functional aging in an older adult population, it may still play an important role in longitudinal studies in young and middle aged populations that attempt to understand aging.

Keywords: Biomarkers, Biology of Aging, Population Health, Telomeres

Telomere shortening is recognized as fundamental to the human aging process and telomere length (TL) is hypothesized to be a biomarker of aging. Telomeres are repeating DNA sequences that cap the ends of chromosomes and gradually shorten with age. This shortening has been linked to physiological and genetic mechanisms of aging including oxidative stress, inflammation, chronic disease, cellular senescence, and mortality (1–8), as well as social factors of aging including race/ethnicity, low socioeconomic status (SES), gender, stress, and smoking (7,9–12). Prior research has also suggested TL is a measure of cumulative biological weathering and accelerated aging (8,13,14), situating TL as a candidate biomarker of aging or a stand-alone measure of age related declines across all systems. This distinguishes TL from other biomarkers that often are included in composite measures since they only reflect age related declines of a single health outcome or system. However, the utility of TL as a biomarker of aging is uncertain because some studies find no association between TL and mortality (15), social factors (16), and other age related health outcomes of interest (17).

If TL reflects biological age, it should be associated with biological, physical, and cognitive function among older adults. Several prior studies have found associations between shortened TL and worse cognitive performance (18,19), increased levels of the inflammatory markers C-reactive protein (CRP) and interleukin 6 (IL-6) (20) and poor cardiovascular functioning as measured by elevated pulse pressure (21) and blood pressure (22), but the results have been inconsistent. Only a few studies have linked TL to markers of physical function, such as lung function and handgrip strength, with most studies finding no association (23–25). Inconsistency of findings in prior research may be largely attributed to methodological differences between studies—differences in sample sizes, age ranges, and

TL quantification techniques. Nearly all the prior studies use select, homogenous, or younger adult populations that may not reflect the diversity and variability present in the broader U.S. older adult population (26). Prior work has also been limited in the availability of objective health measures, with most studies linking TL to one system or indicator of health. The methodological differences between studies and a lack of nationally representative samples with objective measures of biological, physical, and cognitive health does not allow for clear conclusions about TL and health among older adults (17).

Given the equivocal findings of TL with indicators of health, it may be important to consider whether the investment in TL in large population-based studies of older adults is warranted. One proposed condition in evaluating the utility of TL as a biomarker of aging is that it should have explanatory power in predicting health outcomes beyond that of chronological age (27). The aim of this study is to determine if TL is a useful biomarker of aging for population-based research in predicting established markers of health among older adults. We evaluate the predictive power of TL by examining whether it predicts high risk on a variety of indicators of biological, physical, and cognitive functional status in a diverse, nationally representative sample of older adults. TL is assessed for its predictive capacity alone in addition to that of age on high-risk indicators of health.

Methods

Sample

Data for this study come from the Health and Retirement Study (HRS), an ongoing nationally representative panel survey of adults older than age 50 in the United States. The HRS, which began in 1992, conducts interviews every 2 years using a combination of telephone and face-to-face interviews. In 2006, a random one half of the sample was selected for an enhanced face-to-face interview, which included collection of physical measures and biomarkers. The other half of the sample received the enhanced face-to-face interview in 2008. We use data from the half sample collected in 2008 since that was when TL was assayed, combining the 2008 TL data with the 2008 biomarker subsample and physical assessment measures. Respondents were not eligible to complete the physical measures and biomarkers if they resided in a nursing home, were interviewed by a proxy, or were interviewed by telephone. We restrict our analyses to 5,392 age-eligible respondents who had TL assays completed in 2008. We excluded 112 respondents with TL values greater than four standard deviations from the mean or who did not identify as white, black, or Hispanic. We imputed values on all other covariates with missing data using *mi impute* with chained equations in Stata 14. The final analytic sample consisted of 5,280 community-dwelling adults ages 54 and older.

Measures

TL

TL is measured from saliva, which is highly correlated with blood leukocyte TL (r = .72), a measurement of TL that is frequently used in other studies (28). The saliva consent rate was 85% and the completion rate, conditional on consent, was 99%, for an overall completion rate of 84%. Survey interviewers obtained saliva samples from respondents using an Oragene Collection Kit and immediately sent the samples to a central laboratory for processing. DNA was extracted and all samples were stored in their original plates at –80°C. TL assays were performed by Telome Health (29–31) using quantitative polymerase chain reaction, a well-validated and now widely accepted technique to measure TL, by comparing telomere sequence copy number in each respondent's sample (T) to a single-copy gene copy number (S), resulting in a T/S ratio (30,32). DNA samples were assayed in 96 well plates. The HRS took effort to minimize experimental variability by testing coefficient of variation (CV) for each sample based on three runs (three pairs of T and S runs) for plates 2–9, 11, and 13 and based on two runs for plates 1, 10, and 13–64. Samples that had smaller than 12.5% CV were considered as pass and samples with greater than 12.5% CV were reassayed (overall pass rate > 98%). Additionally, the HRS provides plate numbers in order to account for this variation in plate assay and dilution methods (33).

Biomarkers

Biomarker measurements were obtained from physical assessments and dried blood spot collection (34,35). Biomarkers of cardiovascular function, metabolic processes, inflammatory response, and organ function are included. We use definitions of risk based on clinical practice guidelines for biomarkers (34). The biomarker measures, means and ranges, definitions for high risk, and at-risk percentage are shown in Table 1.

Cardiovascular function is measured with systolic and diastolic blood pressure, pulse pressure, and heart rate. Systolic and diastolic blood pressure and heart rate was measured using an automated blood pressure monitor with an inflated blood pressure cuff. Three measurements were taken, and values were averaged to create a mean score. Pulse pressure is the difference between average systolic and diastolic blood pressure. Based on clinical guidelines, we defined high risk as values above 140 mmHg on systolic blood pressure, values above 90 mmHg on diastolic blood pressure, values above or equal to 60 mmHg on pulse pressure, and heart rate of 90 beats per minute or faster.

Dried blood spots were assayed for five analytes, which are markers of metabolic function, inflammatory response, and organ function. Indicators of metabolic processes include total cholesterol, high-density lipoprotein (HDL) cholesterol, and HbA1c. We consider individuals to be high risk if their values were less than or equal to 40 mg/dL on HDL cholesterol and greater than or equal to 240 mg/dL on total cholesterol. We considered individuals high risk on HbA1c if their values are greater than or equal to 6.6%. Levels of general systemic inflammation are measured with CRP. Those with CRP values greater than or equal to 3.0 mg/L are considered to be high risk. Cystatin C is an indicator of kidney function, and individuals are considered high risk with values greater than or equal to 1.55 mg/L.

Obesity is a dichotomous indicator comparing those with body mass index (BMI) of 30 kg/m^2 and above to those with BMI less than 30 kg/m^2.

Physical performance

Indicators of physical performance include lung function, walking speed, balance, and grip strength. Detailed information on the protocols used to assess physical performance is available from the HRS (34). The physical performance measures, their means and ranges, definitions for high risk, and at-risk percentage are shown in Table 1.

Lung function was assessed using peak flow. Three measurements of peak expiratory flow were taken 30 seconds apart using the Mini-Wright peak flow meter. Values were averaged for a mean lung function score. We consider men to be high risk if their peak flow values are greater than or equal to 550 L/min and greater than or equal to 400 L/min for women (34).

Table 1. Descriptive Statistics for Telomere Length, Biomarker Measures, and Physical Performance, Health and Retirement Study ($n = 5,280$)

				High Risk	
	Mean	Min	Max	%	Cut Points
Telomere Length (T/S ratio)	1.3	0.2	4.3	–	–
Biomarkers					
HDL Cholesterol (mg/dL)	54.9	12.1	130.0	35.6	≤40[a]
Total Cholesterol (mg/dL)	202.4	89.0	392.6	18.9	≥240[a]
HbA1c	5.9	3.6	14.8	13.4	≥6.5[a]
CRP (mg/L)	4.5	0.0	158.2	38.4	≥3.0[a]
Cystatin C (mg/L)	1.1	0.4	10.2	8.6	>1.55[a]
Systolic BP (mmHg)	132.9	72.0	218.3	31.3	≥140[a]
Diastolic BP(mmHg)	79.6	43.7	145.0	17.9	≥90[a]
Heart Rate (bpm)	70.0	36.3	141.0	5.7	≥90[a]
Pulse Pressure (mmHg)	53.3	19.0	117.3	24.0	≥60[a]
BMI- Obese (kg/m^2)	28.1	10.6	67.8	32.6	≥30[a]
Physical Performance					
Lung Function (L/min)	356.7	60.0	900.0	22.7	≥400 (women); ≥550 (men)[a]
Walking Speed (m/s)[a]	1.0	0.1	125.0	13.0	<0.6[a]
Grip Strength (kg)	30.7	2.0	85.0	23.4	<20 (women); <33 (men)[b]
Balance Tandem Stand (30 s)	0.6	0.0	1.0	32.5	Incomplete side-by-side[a]
Cognition	15.2	0.0	27.0	17.6	<12[a]

Note: BMI = Body mass index; BP = Blood pressure; CRP = C-reactive protein; HDL = High-density lipoprotein; HbA1c = Glycosylated hemoglobin.
[a]Cut points for high risk are made according to clinical definitions or previous research. [b]Cut points for high risk are made empirically by taking either the lowest or highest quartile.

Walking speed was measured with a timed walk of 98.5 in. (2.5 m) in length in the respondent's home. Respondents were asked to complete the timed walk twice. The two timed walks were averaged for a mean walk time in seconds, which was then divided by 2.5 to create a measure of walking speed (m/s). Respondents could use walking aids (eg, walking sticks, canes, walkers) to complete their timed walk. We consider respondents whose average walking speed was less than 0.6 m/s to be at high risk, as has been done in other studies (36). Respondents who attempted but were unable to complete the timed walk, and therefore had no recorded walk time, were included in the high-risk category.

Balance was measured using the full tandem timed balance test. Respondents were first asked to hold a semitandem stance, which is a midlevel standing balance test, in which they stood with the side of the heel of one foot touching the side of the big toe of the other foot. Respondents who could hold this position for 10 seconds were then asked to complete a full-tandem balance test. The full-tandem stance is similar to the semitandem stance except that respondents were asked to stand with the heel of one foot in front of and touching the toes of the other foot for 30 seconds. For the purpose of analysis, those who were able to hold this stand for the full 30 seconds were considered to have completed the tandem balance test. We consider inability to perform the semitandem stance as high risk. Those who attempted but were unable to complete the semitandem balance test were also considered to be high risk on balance.

Grip strength was measured using a Smedley spring-type hand dynamometer with the respondent standing and holding the dynamometer at a 90° angle. Measures range from 0 kg to 100 kg. Two measurements were taken for each hand, alternating between the left and right hand. The maximum grip value from either hand was used in the analysis. Grip strength is substantially higher in men than women (37), and those in the lowest 25% of grip strength have worse outcomes (38). Therefore, we consider men and women to be high risk if they are in the lowest 25% of strength relative to other men and women, respectively. We also considered respondents to be high risk if they attempted but were unable to complete the grip strength assessment.

Cognition

Respondents' cognitive scores can range from 0 to 27 and are based on tests of immediate recall of 10 words, delayed recall of the same 10 words, 5 trials of Serial 7s, and Backward counting (score 0–2). We consider individuals as high risk if they scored less than 12 (39).

Model covariates include age, gender, race/ethnicity, and a count of chronic conditions. Age was measured in years. Gender is a dichotomous variable with males treated as the reference. Race/ethnicity is a three category variable representing non-Hispanic whites, non-Hispanic blacks, and Hispanics. The summary measure of chronic disease burden (range 0–5) sums the number of doctor diagnosed self-reports of five major chronic conditions and diseases that have been associated with TL—heart disease (40), cancer (41), stroke (42), diabetes (43), and lung disease (44)—that may confound the association between TL and indicators of biological, physical, and cognitive functional status.

Data Analysis

Logistic regression models were used to examine associations of TL and age with the odds of being high risk on indicators of biological, physical, and cognitive function. We also assessed our biomarker, physical and cognitive indicators as continuous outcomes, however findings are similar whether we use high-risk cutoffs or continuous measures. Therefore, we present our logistic regression models that use high-risk cutoffs since they adequately capture the associations with TL. First, we assess TL and age separately with our indicators of health and then jointly. We calculate the percent reduction using the change in the beta coefficient from singly assessed (just TL or just age) models to the jointly assessed models (TL and age together) for each outcome. All analyses were adjusted for gender, race/ethnicity, a summary measure of chronic disease burden, and the plate numbers

used to assay TL based on different dilution factors (33). Analyses were weighted to correct for differential probability of selection and nonresponse. Analyses were performed using Stata version 14. Estimates from multiply imputed data were combined based on Rubin's rule (45).

Results

Table 1 describes the distribution of TL and high-risk categorization of biomarkers, physical performance measures, and cognition for the full sample. Mean TL for the full sample was 1.3. Approximately 36% of the sample was considered high risk on HDL cholesterol while around 19% were high risk for total cholesterol. About 13% of the sample was measured high on HbA1c. Thirty eight percent of the sample had high levels of inflammation measured by CRP. Nine percent measured high on Cystatin C, a measure of kidney function. Nearly 31% measured high on systolic blood pressure and 18% on diastolic blood pressure. Six percent were high risk on heart rate and 24% on pulse pressure. Approximately 33% of the sample was classified as obese and were high risk on balance. Twenty-three percent of the sample had poor lung function and grip strength while 13% were high risk on walking speed. Eighteen percent were considered high risk on cognitive function.

Table 2 shows the results of regressing TL and age on each high-risk marker of biological functioning and health. Panel A shows the association between TL and each outcome first without age (Model 1) and then with age (Model 2). Model 1 shows, before adjusting for age, longer TL is associated with lower odds of being in the high-risk category for total cholesterol (β = −0.37, $p < .01$), cystatin C (β= −0.36, $p < .05$), pulse pressure (β = −0.23, $p < .05$), and walking speed (β = −0.31, $p < .05$). Yet, longer TL is also significantly associated with high-risk HDL cholesterol (β = 0.19, $p < .10$), BMI (β = 0.21, $p < .05$) and lung function (β = 0.36, $p < .001$).

Table 2. Results of Logistic Regression Models of Telomere Length and Age on Indicators of High-Risk Health and Functioning (n = 5,280)

	Model 1			Model 2			
	Assessed Singly			Assessed Jointly			
Outcome (DV)	β	*SE*		β	*SE*		% reduction
(a) TL (IV)							
Biomarkers							
HDL Cholesterol	0.19	0.10	+	0.19	0.10	*	0%
Total Cholesterol	-0.37	0.13	**	-0.45	0.14	**	-22%
HbA1c	0.17	0.12		0.17	0.12		0%
CRP	0.07	0.09		0.04	0.09		43%
Cystatin C	-0.36	0.18	*	-0.12	0.16		67%
Systolic BP	-0.01	0.09		0.08	0.09		900%
Diastolic BP	0.06	0.11		0.02	0.11		67%
Heart Rate	-0.09	0.18		-0.18	0.19		-100%
Pulse Pressure	-0.23	0.10	*	-0.05	0.09		78%
BMI- Obese	0.18	0.09	*	0.09	0.09		50%
Physical Performance							
Lung Function	0.36	0.10	***	0.23	0.11	*	36%
Walking Speed	-0.31	0.15	*	0.02	0.14		106%
Grip Strength	-0.16	0.11		0.09	0.11		156%
Balance Tandem Stand	-0.09	0.09		0.10	0.10		211%
Cognition	-0.08	0.12		0.10	0.11		225%
(b) Age (IV)							
Biomarkers							
HDL Cholesterol	0.00	0.00		0.00	0.00		0%
Total Cholesterol	-0.02	0.00	***	-0.03	0.00	***	-50%
HbA1c	0.00	0.01		0.00	0.01		0%
CRP	-0.01	0.00	***	-0.01	0.00	***	0%
Cystatin C	0.09	0.01	***	0.09	0.01	***	0%
Systolic BP	0.04	0.00	***	0.04	0.00	***	0%
Diastolic BP	-0.02	0.00	**	-0.02	0.00	**	0%
Heart Rate	-0.04	0.01	***	-0.04	0.01	***	-5%
Pulse Pressure	0.07	0.00	***	0.07	0.00	***	0%
BMI- Obese	-0.05	0.00	***	-0.05	0.00	***	0%
Physical Performance							
Lung Function	-0.09	0.01	***	-0.09	0.01	***	0%
Walking Speed	0.15	0.01	***	0.15	0.01	***	0%
Grip Strength	0.10	0.00	***	0.11	0.00	***	-10%
Balance Tandem Stand	0.08	0.00	***	0.08	0.00	***	0%
Cognition	0.07	0.00	***	0.07	0.01	***	0%

Note: All models adjust for gender, race/ethnicity, number of chronic conditions and telomere assay plate.
BMI = Body mass index; BP = Blood pressure; CRP = C-reactive protein; HDL = High-density lipoprotein; HbA1c = Glycosylated hemoglobin.
+$p < .10$; *$p < .05$; **$p < .01$; ***$p < .001$.

Associations between TL and high-risk health indicators are reduced after including age in Model 2. Most associations observed in Model 1 are reduced by more than 35% with the inclusion of age and the only remaining statistically significant associations with TL are high-risk HDL ($\beta = 0.19$, $p < .05$) and total cholesterol ($\beta = -0.45$, $p < .01$) and lung function ($\beta = 0.23$, $p < .05$). TL and age are only weakly correlated ($r = -.11$) so these changes are unlikely due to multicollinearity between TL and age.

The results for age (panel b) assessed singly show increasing age is significantly related to each of the outcomes except HDL cholesterol and HbA1c. These associations remain largely unchanged after adjusting for TL in Model 2. The only exceptions were total cholesterol, heart rate, and grip strength, which show small increases with the addition of TL to the model. On the whole, however, TL does not appear to have explanatory power beyond that of age.

Discussion

Our study, among a diverse group of older adults, found that TL did not predict the likelihood of being high risk on a number of measures of biological, physical, and cognitive functioning after adjusting for age. The marked attenuation after adjusting for age shows that the majority of the variance in health and functioning predicted by TL is shared with age. TL, however, did predict increased risk of poor high-risk HDL, total cholesterol and lung function after adjusting for age. Additionally, associations between age and health indicators remained the same after accounting for TL, suggesting TL does not explain any of the predictive power of age. Therefore, TL does not perform better than age in characterizing the variability in preclinical markers of health, physical assessment measures, and cognition in a diverse, nationally representative sample of older adults.

The evidence establishing a link between TL and indicators of poor health and age-related declines in physiological functioning has been inconsistent. Some studies have found shorter TL to be associated with higher levels of CRP (23), blood pressure (22), and pulse pressure (21). Additionally, studies using data from the National Health and Nutrition Examination Survey (NHANES) have found an inverse association between TL and cardiovascular disease (46–48). Several studies of older adults, however, have found no relationship between TL and health and functioning (24,25,49,50). TL may be a more robust predictor of health in younger adults than it is among older adults, for whom age is often the strongest predictor of health. For instance, the literature shows a consistent inverse association between TL and BMI among younger study populations (51, 52), but we find obese older adults have longer TL yet TL is not associated with obesity after adjusting for age. We did find TL to be associated with some of the health risk indicators, but in unexpected ways. We found a positive association between TL and high-risk HDL cholesterol and lung function, whereas the opposite association has been shown in studies of younger adults (47,53). Discrepant results between studies of primarily younger adults and those conducted in older populations suggest TL may not be as good an indicator of health at older ages as it is among young and middle-aged adults, for whom it can be used to understand early disease risk and onset.

The lack of associations between TL and high-risk indicators of biological, physical, and cognitive function suggests TL may not be a useful marker for predicting poor preclinical health outcomes among older adults. Our findings are consistent with another study using the HRS that has suggested TL is more likely a marker of disease rather than a cause. This study, which used a polygenic risk score of TL-associated genetic markers as an instrumental variable, found that shorter TL was weakly associated with an increased risk of heart disease but, surprisingly, was associated with a decreased risk of stroke (50). If TL is an indicator of disease, but not necessarily a cause, we wouldn't expect it to be associated with the biomarkers of physiological risk in the current study.

Although it is unclear whether TL is a useful clinical marker in cross sectional studies of functional aging among older adults, it may provide key insights into the aging process if assessed longitudinally. The rate of change (eg, telomere shortening) may be a more relevant indicator of the wear and tear that results in accelerated biological aging (54,55) than TL measured at one point in time. Longitudinal data are needed to determine whether this rate of change is a better predictor of preclinical markers of high-risk health. Additionally, some studies have suggested that TL may function better within a composite or multivariate measure rather than an isolated biomarker of aging (8,56). Future research should consider TL as one measure in a multifactorial biomarker measure or with genetic markers rather than a candidate biomarker of aging among older adults.

While there may be little evidence from this sample of older adults for the value of TL as a biomarker of aging, it has been shown to reflect other aspects of the aging experience. Prior research on TL in the HRS has found links with social relationship status (57), religious involvement (58), discrimination (59,60), depressive symptoms (61), life-span adversity (62), and marital disruption (63). These studies have shown that TL varies according to social experiences and mental health outcomes in expected ways, with shorter TL found among those with fewer social resources and greater adversity. Despite a clear connection between TL and social conditions in this older adult sample, no studies to date have linked shorter TL to worse preclinical health outcomes or disease states in the HRS.

This is the first study to examine TL as it relates to 15 high-risk indicators of biological, physical and cognitive function in a racially, ethnically and socioeconomically diverse sample of older U.S. adults, yet this study has some limitations. First, we used cross-sectional data and thus cannot disentangle whether the observed associations are attributable to differences in TL at birth or age-dependent TL shortening during adulthood or some combination of both. Longitudinal measures have the potential to measure intraindividual telomere shortening and may more accurately relate to age related declines in health. Additionally, TL may vary by cell type. Our TL data come from saliva which is a mixture of leukocyte and epithelial cells. TL from saliva has been shown to be highly correlated with blood leukocyte TL (28), however it is unclear whether TL assayed from saliva differentially predicts preclinical markers of health and disease (17). The measure of TL used in this study may be a relatively weaker measure of TL and this may explain the lack of associations with poor health risks. Finally, cross-sectional studies of older adults have shown reduced TL variability since these samples are likely comprised of survivors with relatively long telomeres (64,65).

Our findings indicate that TL is not a consistent measure of age related declines in preclinical markers of health, physical assessment measures, and cognition among a nationally representative sample of older adults. Importantly, our results here suggest that TL has relatively little to offer over and above chronological age. This may have practical and policy implications since TL tests are now available commercially and can be taken repeatedly with minimal harm. Physicians and researchers aiming to identify individuals at increased risk of disease, disability, and accelerated aging in late life may be better off using validated measures like grip strength, lung function, and blood pressure. These are all simple, cheap, and have established predictive capacity while TL assayed using quantitative polyemerase

chain reaction methods may not be appropriate for clinical diagnosis in diverse older adult populations. However, including biomarkers in studies of aging may still play an important role for advancing basic understanding of pathways and mechanisms, even if not appropriate or economical for clinical or individual use.

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Conflict of Interest

None reported.

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