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Association of leukocyte telomere length with perceived physical fatigability

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ABSTRACT

Background: Leukocyte telomere length (LTL) is a potential genomic marker of biological aging, but its relation to fatigability, a prognostic indicator of phenotypic aging (e.g., functional decline) is unknown. We hypothesized shorter LTL would predict greater perceived physical fatigability, but that this association would be attenuated by adjusting for chronological age.

Methods: Two generations of participants (N = 1997; 309 probands, 1688 offspring) were from the Long Life Family Study (age = 73.7 ± 10.4, range 60–108, 54.4 % women), a longitudinal cohort study of aging. LTL was assayed at baseline. Perceived physical fatigability was measured 8.0 ± 1.1 years later using the validated, self-administered 10-item Pittsburgh Fatigability Scale (PFS, 0–50, higher scores = greater fatigability). Generalized estimating equations were generated to model the association between LTL and PFS Physical scores.

Results: Prevalence of greater physical fatigability (PFS scores≥15) was 41.9 %. Using generalized estimating equations, a one kilobase pair shorter LTL was associated with higher PFS Physical scores ($\beta = 1.8$, $p < .0001$), accounting for family structure, and adjusting for field center, follow-up time, sex, and follow-up body mass index, physical activity, and chronic health conditions. When age was included as a covariate, the association was fully attenuated ($\beta = 0.1$, $p = .78$).

Conclusion: LTL may provide an alternative method for estimating an individual's lifetime exposure to chronic stressors, but does not appear to provide additional information not captured by chronological age. Further research is needed to characterize the interaction between age, LTL, and perceived fatigability, and develop a method of identifying individuals at risk for deleterious aging.

1. Introduction

Fatigability is highly prevalent among older adults and associated with important age-related outcomes including disability, loss of function, chronic disease, cognitive decline, and mortality (Schrack et al., 2020; Simonsick et al., 2018; Salerno et al., 2020; Glynn et al., 2022). Leukocyte telomere length (LTL) is a potential genomic marker of the cellular aging process and is known to decrease with age; however, the mechanistic relation between chronological age, LTL, and various age-related outcomes remains unclear. Shorter telomeres may simply be a biological marker that indicates advanced aging, or telomere attrition may be a cellular mechanism that is causally related to the progression of age-related chronic diseases (Zhan et al., 2018; Sanders and Newman, 2013). Like shorter LTL, increased physical fatigability is associated with older age and a variety of health conditions related to the aging process. Several covariates (including age, sex, body mass index [BMI], inflammation) are independently associated with both fatigability and LTL (Simonsick et al., 2018; Sanders and Newman, 2013; Cooper et al.,

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2019; LaSorda et al., 2020). The association between shorter LTL and higher levels of fatigue and fatigue-related outcomes has been reported (Bendix et al., 2014; Rajeevan et al., 2018); however, studies have not reported on the association of LTL and fatigability, a more sensitive measure of susceptibility to fatigue in older adults (Schrack et al., 2020; Simonsick et al., 2018; Simonsick et al., 2016).

Analyzing the association between LTL and physical fatigability will provide further insight into the role of LTL in the aging process. A deeper understanding of the cellular markers that are associated with aging will allow researchers and clinicians to assess aging on a cellular and biological level, leading to a more accurate characterization of the aging process, the identification of individuals at-risk for deleterious aging outcomes, and the development of targeted interventions.

Therefore, we examined whether shorter LTL predicts greater perceived physical fatigability. We hypothesized that individuals with shorter LTL would report greater perceived physical fatigability measured approximately 8 years later, after adjusting for sex, field center, chronic health conditions, BMI, and physical activity, and that this association would be attenuated by additionally adjusting for chronological age.

2. Material and methods

2.1. Study population

The Long Life Family Study (LLFS) is a longitudinal family study of aging and longevity in older adults with field centers in the United States and Denmark. Screening was performed to identify individuals from long-lived families using the family longevity selection score (FLoSS), which has been described previously (Sebastiani et al., 2009). In addition to genetic relatives of these individuals, spouses of genetically related family members were also enrolled to serve as controls. At baseline (2006–2009) a total of 4953 individuals from 539 families were recruited. In-person examinations were performed at baseline, followed by annual telephone follow-ups. In 2014–2017, a second round of in-person examinations was conducted for 2895 participants.

2.2. Outcome measure – perceived physical fatigability

The Pittsburgh Fatigability Scale (PFS), a validated measure of perceived fatigability (Glynn et al., 2015; Renner et al., 2021), was introduced during LLFS Visit 2 (2014–2017). Participants rated the physical fatigue they would expect or imagine they would feel for 10 different activities across a range of intensities on a 0 (“no fatigue”) to 5 (“extreme fatigue”) scale, resulting in scores ranging from 0 to 50 (higher scores indicating greater physical fatigability). For participants missing 1–3 items, scores were imputed (Wasson et al., 2019). A cut-point of $\geq$15 has been previously established to classify participants as having greater perceived physical fatigability (Schrack et al., 2020; Simonsick et al., 2018).

2.3. Independent variable – leukocyte telomere length

In LLFS, blood sample collection was performed by technicians trained and certified by study personnel according to a central protocol agreed upon by all field centers. After collection, samples were shipped to a central laboratory for DNA extraction (Newman et al., 2011). LTL was assayed at Columbia University by Dr. Honig’s laboratory, using real-time PCR with primers optimized for telomeres (T) and globin, a single copy reference gene (S). A linear regression formula was used to calculate LTL in base pairs from the T/S ratio (Lee et al., 2013; Honig et al., 2015).

2.4. Covariates

We verified age at baseline by matching participants to birth certificates, the Civil Registration System (Denmark) or other official documents such as a driver’s license. Demographic information including sex and race/ethnicity was also collected during Visit 1 (Newman et al., 2011). At Visit 2, height was measured to the nearest 0.1 cm using a Handi-stat set square (Perspective Enterprises, Portage, MI). Weight was measured to the nearest 0.1 kg using an electronic digital scale (SECA 841, Hanover, MD). We used these measurements to calculate body mass index (BMI) in kg/m^2.

We ascertained medical history and lifestyle information at baseline and updated during each annual follow-up and at Visit 2. Participants were asked to self-report (yes/no) a physician diagnosis of cancer (not including skin cancer), diabetes, hypertension, and arthritis. Self-reported history of hypertension and diabetes were confirmed by objective measures of blood pressure (systolic $\geq$130 mm Hg and/or diastolic $\geq$80 mmHg) and blood glucose (hemoglobin A1c $\geq$6.5 % or fasting glucose $\geq$126) performed by centrally trained research staff at Visit 2, and the use of relevant medications (LaSorda et al., 2020). The Framingham Physical Activity Index, which uses the time spent asleep, sedentary, and doing light/moderate/heavy physical activity on a typical day to calculate Metabolic Equivalent of Task (MET) h/day was used to ascertain physical activity levels (Kannel, 1979). Depressive symptomatology was measured using the 30-point Center for Epidemiologic Studies—Depression (CES-D) scale; scores $\geq$16 were defined as having clinically significant symptoms (Radloff, 1977).

2.5. Statistical analysis

At LLFS Visit 2, complete fatigability data was collected for 2564 participants, with fatigability scores imputed for 104 participants. This resulted in 2668 participants with perceived physical fatigability scores. The PFS has only been validated in adults 60 and older, so participants younger than 60 at Visit 2 (n = 293) were removed from the analysis, as were those missing baseline LTL data. This resulted in a sample of 2008 participants, of which 11 were excluded due to quality control issues relating to the physical activity measure, resulting in a final analytical sample of 1997 (Supplemental Fig. 1).

Descriptive statistics (means and standard deviations for continuous variables and frequencies and proportions for categorical variables) were generated overall and by splitting participants into LLFS generations. The statistical significance of the differences between generations was evaluated using two-sample *t*-tests for continuous variables and chi-squared tests for categorical variables.

Generalized estimating equations were generated with PFS Physical scores as outcomes to determine whether LTL was significantly associated with perceived physical fatigability. All models accounted for family structure using an exchangeable covariance matrix and were adjusted for field center. Based on our conceptual model (Supplemental Fig. 2) and evaluation of the Quasilikelihood under the Independence model Criterion (QICu) statistic (Pan, 2001), we developed a parsimonious fully-adjusted model with age, sex, and Visit 2 physical activity (continuous variable measured in MET-h/day), BMI, and chronic conditions (separate binary variables for non-skin cancer, diabetes, hypertension, and arthritis) to characterize the effect of these variables on the relation between LTL and fatigability. To evaluate whether there was a differential effect of LTL and perceived physical fatigability by generation, we first included an interaction between LTL and generation in the final parsimonious model, and then constructed models stratified by LLFS generation and five-year age cut-points.

3. Results

3.1. Descriptive characteristics

The age range for the final analytic sample was 60–108 years, mean 73.7 $\pm$ 10.4 years (Table 1). Mean follow-up time between Visit 1 and Visit 2 was 8.0 $\pm$ 1.1 years. The sample was 55.4 % women, 100 %

Table 1
Baseline characteristics of the Long Life Family Study (LLFS) sample by generation.

Variable	All (N = 1997)	Proband (n = 309)	Offspring (n = 1688)
LTL, base pairs	5347.7 ± 477.0	**5204.3 ± 407.1**	**5374.0 ± 484.3**
PFS Physical score, 0–50	14.3 ± 10.0	**26.3 ± 10.0**	**12.1 ± 8.3**
Greater physical fatigability[a], %	836 (41.9)	**263 (85.1)**	**573 (34.0)**
Age at Visit 2, years	73.7 ± 10.4	**92.8 ± 6.5**	**70.2 ± 6.4**
Body mass index, kg/m^2	27.3 ± 5.0	**25.9 ± 4.1**	**27.6 ± 5.1**
Women	1086 (54.4)	**188 (60.8)**	**898 (53.2)**
Physical activity[b], MET-h/day	36.5 ± 7.1	**30.4 ± 5.2**	**37.6 ± 6.8**
Diabetes[c]	213 (10.7)	42 (13.6)	171 (10.1)
Hypertension[d]	1203 (60.2)	**211 (68.3)**	**992 (58.8)**
Cancer[e]	661 (33.1)	**148 (47.9)**	**513 (30.4)**
Depressive symptomatology[f], ≥16	116 (5.8)	**27 (8.7)**	**89 (5.3)**
Arthritis[e]	915 (45.8)	**203 (65.7)**	**712 (42.2)**

Note. Mean ± standard deviation shown for continuous variables and n (%) for categorical variables; PFS = Pittsburgh Fatigability Scale.
Bolded values statistically significantly differ between generations (two sample t-test for continuous variables, chi-squared for categorical, $p < .05$).
[a] Defined as PFS Physical scores ≥15.
[b] Framingham Physical Activity Index score.
[c] Diabetes defined as hemoglobin A1c ≥6.5 %, fasting glucose ≥126, or self-reported doctor diagnosis defined diabetes.
[d] Hypertension defined as systolic ≥130 mm Hg and/or diastolic ≥80 mm Hg or taking blood pressure medication.
[e] Self-reported doctor diagnosis (prevalence/history).
[f] Center for Epidemiological Studies – Depression Scale, scores ≥16 denote depressive symptomatology.

white, and 83.6 % had more than a high school education. Participants in the proband generation were more likely to be women ($p = .01$). Probands also had higher PFS Physical scores, lower BMI, lower levels of physical activity, and reported a higher prevalence of hypertension, depressive symptoms, arthritis and non-skin cancer (all $p < .0001$) compared to offspring. The prevalence of diabetes did not significantly differ between study generations ($p = .07$) (Table 1).

The overall mean LTL was 5.35 ± 0.48 (median 5.25, IQR [5.05, 5.51]) kilobase pairs. In unadjusted Spearman correlations, shorter LTL was correlated with older age ($r_s = -0.31$, $p < .0001$) and higher PFS Physical scores ($r_s = -0.08$, $p = .0002$). Mean telomere length was 55.0 base pairs shorter in men ($p = .01$) compared to women.

3.2. Age-adjusted association between LTL and perceived physical fatigability

Older age ($p < .0001$), having lower levels of physical activity ($p < .0001$), hypertension ($p = .03$), and history of cancer diagnosis ($p < .0001$) were all independently associated with having shorter LTL after accounting for family structure and adjusting for field center (Table 2), without adjusting for age. Associations bordering on significance were observed for being male ($p = .055$) and having higher levels of depression symptoms ($p = .056$); both were related to shorter LTL. Adjusting for age attenuated all associations except sex ($p = .01$). BMI, diabetes, and arthritis were not associated with LTL.

Shorter LTL at baseline was associated with higher PFS Physical scores ($\beta = 2.7$, $p < .0001$) after 8 years (Visit 2) and accounting for family structure and adjusting for field center. Adjusting for follow-up time, sex, chronic conditions, physical activity, and BMI slightly attenuated the association ($\beta = 1.8$, $p < .0001$). In models that included age, LTL was not associated with perceived physical fatigability ($\beta = 0.1$, $p = .78$, Table 3).

Table 2
Univariate associations of each covariate with Pittsburgh Fatigability Scale (PFS) Physical score and leukocyte telomere length (LTL): Long Life Family Study.

Independent variable*	PFS Physical score		LTL	
	β ± SE	p-Value	β ± SE	p-Value
LTL	2.7 ± 0.5	<.0001	–	–
Age at Visit 2, years	0.5 ± 0.02	<.0001	−12.8 ± 1.0	<.0001
Generation (ref = Offspring)	13.5 ± 0.6	<.0001	−245.5 ± 28.6	<.0001
Sex (ref = men)	1.7 ± 0.4	<.0001	53.0 ± 19.1	.006[†]
Body mass index, kg/m^2	0.19 ± 0.04	<.0001	−0.7 ± 2.2	.75
Physical activity[a]	−0.60 ± 0.04	<.0001	6.1 ± 1.5	<.0001
Diabetes[b] (ref = no)	2.9 ± 0.7	<.0001	−45.7 ± 31.6	.15
Hypertension[c] (ref = no)	0.78 ± 0.5	.11	−67.0 ± 22.0	.003
Cancer[d] (ref = no)	2.0 ± 0.5	.45	−82.8 ± 20.5	<.0001
Depressive symptomatology[e]	0.83 ± 0.07	<.0001	−5.2 ± 2.7	.056
Arthritis[d] (ref = no)	4.8 ± 0.4	<.0001	−27.7 ± 20.7	.18

[*] All models adjusted for field center and family structure.
[†] Association with LTL remained significant after age adjustment.
[a] Framingham Physical Activity Index continuous score in MET-h/day.
[b] Diabetes defined as hemoglobin A1c ≥6.5 %, fasting glucose ≥126, or self-reported doctor diagnosis defined diabetes.
[c] Hypertension defined as systolic ≥130 mm Hg and/or diastolic ≥80 mm Hg or taking blood pressure medication.
[d] Self-reported doctor diagnosis (prevalence/history).
[e] Center for Epidemiological Studies – Depression Scale score.

3.3. Generation-specific association between LTL and perceived physical fatigability

In the model adjusting for follow-up time, sex, generation, chronic conditions, physical activity, and BMI, a term for the interaction between LTL and familial generation was statistically significant ($p = .029$, Table 3). In generation-specific models, the association between LTL and PFS Physical scores was significant among the proband generation ($\beta = 2.9$, $p = .032$) but not among offspring ($\beta = 0.5$, $p = .18$). Similar results were observed in models stratified by five-year age cut-points instead of LLFS generation (Supplemental Table 1). When generation models were further stratified into participants genetically related to the proband and spousal controls, the association between LTL and PFS Physical scores trended towards significance among offspring spousal controls ($\beta = 1.5$, $p = .07$), but not genetically-related offspring ($\beta = 0.2$, $p = .58$) (Supplemental Table 2a). The strength of the associations was similar among probands ($\beta = 3.5$, $p = .30$ for controls and $\beta = 3.0$, $p = .04$ for relatives). The associations were non-significant within all strata when additionally adjusting for age (Supplemental Table 2b).

4. Discussion

We found that, when not adjusting for age, shorter LTL predicted higher PFS Physical scores 8 years later in a population of older adults ranging from 60 to 108 years old. LTL was highly correlated with age, and when age was included as a covariate in generalized estimating equations, LTL was not associated with fatigability. Thus, LTL may be an alternative method for estimating an individual's lifetime exposure to chronic stressors, but does not appear to provide additional information not captured by chronological age.

Shorter LTL being associated with future greater perceived physical fatigability supports the idea that LTL is either causally related to phenotypic aging or shares common causes. In this analysis, some of the effect of LTL on perceived physical fatigability was attenuated by adjusting for chronic diseases, physical activity, and BMI, but the association remained significant. This is evidence that LTL shares common causes with phenotypic aging, but also has an independent effect on

Table 3
Association of leukocyte telomere length on Pittsburgh Fatigability Scale (PFS) Physical scores by generation.

Models[a]	All (N = 1997)			Probands (n = 309)			Offspring (n = 1688)		
	β ± SE	p-Value	QICu	β ± SE	p-Value	QICu	β ± SE	p-Value	QICu
Base model	2.6 ± 0.5	<.0001	2003	1.9 ± 1.5	.19	315	0.7 ± 0.4	.09	1694
Age at Visit 2	−0.4 ± 0.4	.29	2004	0.1 ± 1.3	.91	316	−0.2 ± 0.4	.63	1695
Sex, BMI, physical activity, chronic conditions[b]	1.8 ± 0.4	<.0001	1861	2.9 ± 1.3	.03	273	0.5 ± 0.4	.19	1566
Sex, BMI, physical activity, chronic conditions, age at Visit 2	0.1 ± 0.4	.78	1826	2.0 ± 1.3	.12	274	−0.2 ± 0.4	.49	1567
Sex, BMI, physical activity, chronic conditions, generation[c]	0.8 ± 0.4	.25	1826	–	–		–	–	

Beta coefficients shown are for a one kilobase pair shorter leukocyte telomere length.
Physical activity measured in MET-h/day using the Framingham Physical Activity Index, BMI = body mass index in kg/m^2.
[a] All models include LTL, account for family structure and adjust for field center and follow-up time.
[b] Chronic conditions: diabetes (defined as hemoglobin A1c ≥6.5 %, fasting glucose ≥126, or self-reported doctor diagnosis defined diabetes), hypertension (defined as systolic ≥130 mm Hg and/or diastolic ≥80 mm Hg or taking blood pressure medication) self-reported doctor diagnosis (prevalence/history of cancer and arthritis).
[c] LTL × generation interaction term was significant (p = .029) when added to this model.

fatigability that is not explained by other factors except chronological age.

Evidence of an interaction between generation and LTL indicated that the relation between LTL and perceived physical fatigability may vary with age. When analyses were stratified by generation, LTL was a far stronger correlate of perceived physical fatigability in the older, proband generation than the younger, offspring generation. This may be because LTL is mechanistically related to aging phenotypes, such as fatigability (Schrack et al., 2020), but the effect is only noticeable when telomeres are closest to being completely degraded (Sanders and Newman, 2013). Interestingly, we further examined the generation-stratified models by genetic relative/spousal control status and observed strong associations between LTL and perceived physical fatigability among spousal controls, but not genetic relatives. This finding suggests LTL may be more strongly related to aging outcomes among the general population, as compared to members of longevity-enriched families who may be resistant to common aging exposures (Newman et al., 2011).

One potential limitation of this study was that LTL was only assayed once, at baseline, and our perceived physical fatigability measure was introduced 8 years later at Visit 2. This prevented the analysis from taking into account how changes in LTL over time were associated with changes in perceived physical fatigability. The shortening of telomeres with age is not linear and progressive (Pavanello et al., 2021), as such longitudinal analyses of LTL are an important area for future research. If LTL is truly a biological indicator of aging, faster decreases in LTL throughout midlife and older age would be expected to predict earlier development of negative health outcomes related to the aging process. Another limitation of this analysis is that results among LLFS relatives may not be generalizable to other populations. The selection process for LLFS participants resulted in a study population that is disproportionately white, healthy, long-lived, and well-educated compared to the general population (Wasson et al., 2019). However, examining the association between LTL and fatigability in non-genetically related spousal controls, a potentially more generalizable population despite their known survival advantage (Pedersen et al., 2017), provided insight into the potential association of LTL and fatigability among those not selected for longevity.

A strength of this study is the wide age range among LLFS participants, allowing for a more complete investigation of aging among young-old, old-old, and oldest-old individuals. The PFS is a valid and reliable measure of susceptibility to fatigue in older adults (Glynn et al., 2015). The PFS has strong predictive validity for mobility decline, fitness, physical function, and all-cause-mortality (Simonsick et al., 2018; Glynn et al., 2022; Glynn et al., 2015). This analysis corroborates the association between LTL and fatigue outcomes using fatigability, which has been shown to be a more sensitive measure (Schrack et al., 2020; Simonsick et al., 2018; Simonsick et al., 2016). The PFS has less uncontrollable variability than traditional global measures of fatigue, which lack specificity related to activity, intensity, and duration. The large sample size gave sufficient statistical power for the analyses of LTL and fatigability. Of the participants that completed Visit 2, 2.8 % has missing or incomplete PFS that could not be imputed. Those with missing data were older and more likely to be women, indicating that inclusion of those individuals would bias the sample away from the null, as both factors are associated with shorter LTL and greater fatigability.

In conclusion, we examined the relation between LTL, a potential genomic marker of advanced aging, and perceived physical fatigability. LTL being associated with higher fatigability scores 8 years later is consistent with LTL being a biological marker of the aging process and fatigability being an outcome related to aging; however, LTL does not appear to provide additional information that is not captured by chronological age. LTL and fatigability are both associated with a variety of covariates and outcomes related to aging. Further research will focus on understanding the relation between LTL, fatigability, and aging and how these variables interact with the disablement pathway in older adults. Identification of genomic biomarkers that can predict fatigability of older adults is useful for clinical research and practice. Understanding biological markers that precede declining health and function in older adults may produce targets for interventions that prevent or slow the disability cascade, allowing older adults to remain healthier through the aging process.

CRediT authorship contribution statement

Rain Katz: Conceptualization, Writing – original draft, Formal analysis, Visualization, Writing – review & editing. **Emma L. Gay:** Writing - review & editing. **Allison L. Kuipers:** Writing - review & editing. **Joseph H. Lee:** Funding acquisition, Writing – review & editing. **Lawrence S. Honig:** Writing – review & editing. **Kaare Christensen:** Funding acquisition, Writing – review & editing. **Mary Feitosa:** Writing – review & editing. **Mary K. Wojczynski:** Writing – review & editing. **Nancy W. Glynn:** Supervision, Writing - review & editing.

Declaration of competing interest

None declared.

Data availability

Data will be made available on request.

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Appendix A. Supplementary materials

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