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Research Report

Midlife Leukocyte Telomere Length as an Indicator for Handgrip Strength in Late Life

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Abstract

Background: Telomere attrition has been proposed as a hallmark of aging. We previously reported on the association between blood leukocyte telomere length (LTL) at midlife and risk of chronic diseases and mortality.

Methods: In this study, we investigated the effect of midlife LTL and genetic proxies on 5 markers of aging outcomes, namely handgrip strength, timed up-and-go (TUG), Singapore-modified Mini-Mental State Examination (SM-MMSE) scores, anxiety, and depression indices, measured after a median 20-year follow-up in the Singapore Chinese Health Study (N = 9581).

Results: We observed a significant association between midlife LTL and handgrip strength later in life (p = .004, p_{adjust} = .020), as well as a nominal significant association between midlife LTL and TUG later in life (p = .036, p_{adjust} = .180). The weighted Genetic Risk Score (wGRS) comprising 15 previously reported LTL reducing loci in East Asians was not significantly associated with handgrip strength. However, results from Structural Equation Modeling showed that the effect of this wGRS on handgrip strength was mediated through LTL (proportion of wGRS effect on handgrip strength mediated through LTL = 33.3%, p = .010).

Conclusions: Longer midlife LTL was associated with increased handgrip strength later in life.

Keywords: Aging outcomes, Mediation, Telomere variants

Chronological age is a relatively imprecise indicator of an individual's functional and health status (1). Considerable research efforts have thus been devoted to identify biomarkers that can reflect biological aging, and telomere attrition has been proposed as a biomarker of biological aging (2). Telomeres are gene-poor regions located at the ends of chromosomes that serve to maintain genomic integrity and stability (3). In most somatic cells, telomeres shorten with each cell division, eventually triggering cellular senescence or apoptosis. Leukocyte telomere length (LTL) has been shown to be heritable (4) and genetic studies have identified a total of 16 loci associated with LTL at genome-wide levels of significance in East Asians, including those that may be ethnic-specific (5).

Previous studies have shown that LTL are associated with various chronic diseases, age-related traits, and mortalities (5–7). In this study, we investigated the effect of midlife LTL on 5 markers of aging outcomes, including handgrip strength, timed up-and-go (TUG), Singapore-modified Mini-Mental State Examination (SM-MMSE) scores, anxiety, and depression indices measured after a median 20-year follow-up in a Chinese cohort living in Singapore.

Methods and Results

Our study was conducted in the Singapore Chinese Health Study (SCHS), a long-term population-based prospective cohort study that focuses on dietary, genetic, and environmental determinants of cancer and other chronic diseases prevalent in Singapore (8). Detailed information for cohort description (8), study outcomes (9,10), LTL measurement, genotyping and imputation for genetic markers (5), and statistical analysis are available in the Supplementary Methods. Briefly, a total of 9581 study participants who were interviewed and examined in follow-up 3 also had genotype data. We constructed a weighted Genetic Risk Score (wGRS) for genetically determined LTL (details in Supplementary Methods). This wGRS was constructed from 15 single-nucleotide polymorphisms (SNPs) previously reported to be associated with LTL in East Asians (5). In this wGRS, the weights used were the individual effect estimates for each of these 15 LTL-associated SNPs in the East Asian genome-wide association study (5). This wGRS, in addition to midlife LTL, was evaluated for its association with the aging outcomes. Leukocyte telomere length and the 5 aging outcomes were assessed as continuous variables, and they were normalized using rank-based inverse normal transformations to obtain expected *Z*-scores.

Demographic characteristics of study participants in SCHS are shown in Table 1.

We first separately tested the association between the 5 aging outcomes and LTL using linear regression models, and with age and sex included as covariates. Longer midlife LTL was significantly associated with increased handgrip strength later in life (β = 0.023, p = .004, p_{adjust} = .020; Table 2). Further adjustment for additional covariates, including body mass index, smoking, alcohol consumption, and diet (alternate Mediterranean Diet [aMED] score), did not meaningfully affect the association between handgrip strength and LTL (β = 0.023, p = .004, p_{adjust} = .020). Longer LTL was also nominally associated with decreased TUG. However, after adjusting for multiple comparisons, the association did not reach statistical significance (β = –0.021, p = .036, p_{adjust} = .180; Table 2).

As sensitivity analysis, we also dichotomized the 5 aging outcomes based on clinically meaningful cutoff points (Supplementary Methods). We separately tested the association between the 5 dichotomized aging outcomes and midlife LTL using logistic regression models with age and sex included as covariates. Longer midlife LTL was significantly associated with a reduced risk for having weak handgrip strength later in life (odds ratio [OR] = 0.930, p = .010, p_{adjust} = .050, Supplementary Table S1). In this analysis, longer midlife LTL was also significantly associated with a reduced risk for having slow TUG later in life (OR = 0.911, p = .004, p_{adjust} = .020, Supplementary Table S1).

Another approach toward demonstrating the usefulness and validity of an aging biomarker involves examining how the effect of chronological age is attenuated after the addition of that biomarker into the model. As further sensitivity analysis, we examined the associations between chronological age and the 5 continuous aging outcomes before and after the inclusion of midlife LTL into a linear regression model with sex included as a covariate. The association between age and handgrip strength was attenuated by 1.52% after midlife LTL was included in the model (β_{before} = –0.0461, β_{after} = –0.0454). Meanwhile, the association between age and TUG was attenuated by 0.78% after midlife LTL was included in the linear regression model (β_{before} = 0.0770, β_{after} = 0.0764).

We then investigated the genetic association between LTL and handgrip strength using a wGRS comprising previously reported LTL loci in East Asians (5). In our study population, with age and sex included as covariates, the wGRS was expectedly robustly associated with shorter midlife LTL (β = –0.092, $p = 5.616 \times 10^{-98}$). However, the association between the wGRS and handgrip strength did not reach statistical significance (β = –0.006, p = .094; Table 3). Nevertheless, we conducted mediation analysis using Structural Equation Modeling with age and sex included as covariates to quantify how much the wGRS affected handgrip strength through LTL. Results from this analysis showed that the effect of this wGRS on handgrip strength was mediated through LTL. The proportion of the wGRS's effect on handgrip strength mediated through LTL was 33.3% (p = .010; Table 3).

Table 1. Characteristics of Study Participants in This Study

Number	9581 (100%)
Men (%)	4061 (42.39%)
Age (year)	52.30 (48.16, 57.38)
Handgrip strength (kg)	21.30 (17.10, 27.40)
Timed up-and-go (s)	10.00 (9.00, 13.00)
Singapore-modified MMSE score	26.00 (23.00, 28.00)
Geriatric Depression Scale	2.00 (1.00, 5.00)
Geriatric Anxiety Inventory	1.00 (0.00, 3.00)
Telomeres (T/S ratio)	1.04 ± 0.23
Weighted GRS (wGRS)	22.36 (20.80, 23.74)
Body mass index (kg/m^2)	23.11 ± 3.18
Smoking	
Nonsmoker	7426 (77.51%)
Ex-smoker	888 (9.27%)
Current smoker	1267 (13.22%)
Alcohol consumption	
Nondrinker/monthly drinker	8475 (88.46%)
Weekly drinker	839 (8.76%)
Daily drinker	267 (2.79%)
Alternate Mediterranean Diet (aMED) index score	4.00 (3.00, 5.00)

Notes: Data are presented as mean ± standard deviation, *N* (%) or median (interquartile range). GRS = Genetic Risk Score; MMSE = Mini-Mental State Examination.

Table 2. Associations Between Midlife LTL and Aging Outcomes

	β	*SE*	p	p_{adj}
Handgrip strength	0.023	0.008	.004	.020
Timed up-and-go	–0.021	0.010	.036	.180
Singapore-modified MMSE score	0.018	0.014	.183	.915
Geriatric Depression Scale	0.003	0.010	.743	1.000
Geriatric Anxiety Inventory	–0.004	0.009	.679	1.000

Notes: LTL = leukocyte telomere length; MMSE = Mini-Mental State Examination; p_{adj} = p-value adjusted for multiple comparisons.

Table 3. Effect of wGRS on Handgrip Strength Mediated Through LTL

	Direct Effect			Indirect Effect			Total Effect		
	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Handgrip strength	−0.004	0.004	.281	−0.002	0.001	.010	−0.006	0.003	.094

Notes: LTL = leukocyte telomere length; wGRS = weighted Genetic Risk Score.

Discussion

Telomere length is hypothesized to be a biological marker of both cognitive and physical aging (11). In this study, we investigated the effect of midlife LTL on 5 intermediate aging outcomes measured after a median 20-year follow-up in a Chinese population. Longer LTL was significantly associated with increased handgrip strength. We also showed that the effect of genetically determined LTL on handgrip strength was significantly mediated through LTL.

Previous studies have investigated whether LTL was associated with biological, physical, and cognitive aging markers, especially those related to physical performance. Most of these studies were conducted in populations of European ancestry, and yielded null findings (12–14). However, in a prospective cohort of older community-dwelling Chinese persons (aged 65 years and older) followed up for 5 years, LTL was associated with slower decline in handgrip strength (15), which was consistent with our finding. This controversy in findings between the earlier European populations and Chinese populations, including ours, may be reflective of potential ethnic-specific differences in LTL attrition and its effect on aging outcomes. In another study, it was reported that increased telomere attrition was associated with reduced grip strength, but this association was driven by the inflammaging burden (16). In our mediation analysis however, we did not find significant evidence for potential pleiotropic pathways (besides LTL itself) that mediated the effects of genetically determined LTL on handgrip strength (p = .281). Nevertheless, due to the lack of appropriate inflammation biomarkers in our study, we were unable to firmly validate this.

Previous studies have also evaluated the genetic association between LTL and age-related outcomes. One study assessed the association between a single SNP at the *TERT* locus with 30 age-related phenotypes. However, they did not observe any significant association and concluded that the SNP assessed was not an important contributor to markers of aging (4). Similarly, another study that utilized variants from 5 LTL-related regions also did not find any association with aging-related outcomes (17). Although our wGRS was more comprehensively constructed with all the recently identified LTL loci, including ethnic-specific associations (5), we also did not show statistically significant association with handgrip strength (p = .094). Nevertheless, our mediation analysis suggested that the specific contribution through LTL for genetically determined telomere length on subsequent handgrip strength in older Chinese was still significant.

Our study had some limitations. First, we only had one time-point measurements for LTL at midlife and aging outcomes at late life. Some studies have suggested that prospective telomere attrition might be a more relevant indicator for biological aging (12). Second, compared to LTL, telomere length measured from skeletal muscle might have better biological relation to handgrip strength. Although previous studies have shown that telomeres are likely to be longer in less replicative tissues such as skeletal muscles and shorter in leukocytes, there is still substantial correlation in telomere lengths between tissues. Furthermore, the rates of telomere attrition are likely to be similar (18). Thus, LTL may still act as a proxy for muscle telomere length. Third, like previous studies in European populations, we also did not observe a significant genetic association between LTL and handgrip strength (4,17). This may be due to the relatively modest overall LTL variability that could be explained by identified genetic loci thus far. Additional studies are needed to identify the full complement of genetic determinants of telomere length that may enable a more thorough evaluation for the potential causality of LTL on aging-related traits. Lastly, our study could only include SCHS participants who had survived long enough to participate in the follow-up 3 interviews. As shown in a previous publication, those who participated in the follow-up 3 interviews were generally younger, had healthier lifestyles, and less comorbidities compared to those who did not participate in the follow-up 3 interviews (10). Furthermore, when the participants in this study were compared to a group of 7365 participants who had aging outcomes measured but did not have genotype or LTL data, the participants in this study were on average 0.4 years younger, more likely to be men, have slightly stronger handgrips, slightly faster TUG times, slightly higher SM-MMSE scores, and slightly lower Geriatric Depression Scale (GDS) scores. As such, the generalizability of our findings may have been limited by survivorship and response bias.

In conclusion, longer midlife LTL was associated with increased handgrip strength later in life; and approximately one third of the total effect of LTL wGRS on handgrip strength was mediated through LTL. These results suggest that midlife LTL might be an indicator for late-life muscle strength in older Chinese adults.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

C.-K.H., W.-P.K., and R.D. conceived and designed the experiments. W.-P.K. and J.-M.Y. contributed to the recruitment, sample collection, and data processing. R.D., L.W., J.L., C.-C.K., W.-P.K., and J.-M.Y. generated

genotyping data. X.C. and K.Y.C. contributed to the statistical and bioinformatics analyses. X.C., K.Y.C., C.-K.H., W.-P.K., and R.D. drafted the manuscript. All authors critically reviewed the manuscript.

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