Association of telomere length with general cognitive trajectories: a meta-analysis of four prospective cohort studies

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ABSTRACT

To investigate the association of telomere length (TL) with trajectories of general cognitive abilities, we used data on 5955 participants from the Sex Differences in Health and Aging Study and the Swedish Adoption/Twin Study of Aging in Sweden, and the Mayo Clinic Study of Aging, and the Health and Retirement Study in the United States. TL was measured at baseline, while general cognitive ability was assessed repeatedly up to 7 occasions. Latent growth curve models were used to examine the associations. One standard deviation increase of TL was associated with 0.021 unit increase (95% confidence interval [CI]: 0.001, 0.042) of standardized mean general cognitive ability. After controlling for sex, the point estimate remained similar (0.019) with a wider CI (95% CI: −0.002, 0.039). The association was attenuated with adjustment for educational attainment (0.009, 95% CI: −0.009, 0.028). No strong evidence was observed for the association of TL and decline in general cognitive ability. Longer TL was associated with higher general cognitive ability levels in the age-adjusted models but not in the models including all covariates, nor with cognitive decline.

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1. Introduction

Telomeres are repetitive nucleotide sequences at the end of the chromosomes, protecting them from degradation. Because of its protective properties against cellular senescence, telomere length (TL) has been postulated as a biomarker of aging in humans. Short TL has been associated with increased risk for mortality (Bakaysa et al., 2007; Mons et al., 2017), cardiovascular diseases (Hammadah et al., 2017; Zhan et al., 2017), some cancers (Barthel et al., 2017; Telomeres Mendelian Randomization Collaboration et al., 2017), and neurodegenerative disorders (Honig et al., 2012; Zhan et al., 2015). Several studies also reported a significant association of TL with cognitive performance (Hägg et al., 2017; Harris et al., 2006, 2016; Martin-Ruiz et al., 2006; Valdes et al., 2010; Yaffe et al., 2011); however, the results were not consistent. Moreover, most published studies used cross-sectional data or repeated measurements with only a few different time points available for cognition. Longitudinal studies with several repeated measurements of cognition are largely lacking. In this study, we hypothesized that longer baseline TL would be associated with better average level of general cognitive ability and slower cognitive decline in 4 prospective cohorts from Sweden and the United States.

2. Methods

2.1. Study population

The Sex Differences in Health and Aging (GENDER) is a population-based cohort study of unlike-sexed twins born between 1906 and 1925 in Sweden (Gold et al., 2002). Four hundred ninety-eight individuals of European ancestry participated in the first in-person testing including cognitive tests, health examination, and blood sample collection from 1995. In-person testing follow-up was conducted up to 3 times on a 4-year interval during the years 1995−2005 with an average of 5.6 years (standard deviation [SD]: 2.0 years) of follow-up. In total, 400 participants had at least

1 cognitive test and 404 participants had TL assessed. The combined data for TL and general cognitive ability were available for 327 participants.

The Swedish Adoption/Twin Study of Aging (SATSA) was a population-based study initiated in 1984 to study twin pairs reared apart or reared together, and 859 individuals of European ancestry participated in at least 1 wave of in-person testing (Finkel and Pedersen, 2004; Pedersen et al., 1991). In the present study, 632 participants had at least 1 cognitive assessment during the third, fifth, sixth, eighth, and ninth in-person testing, and 638 participants had TL measured. In total, 566 participants had both TL and general cognitive ability assessed. The follow-up was conducted up to 5 times during years 1992—2012 with an average of 10.5 years (SD: 5.0 years) of follow-up.

The Mayo Clinic Study of Aging (MCSA) is a prospective population-based study using a stratified random sampling design that began in 2004 in Minnesota, US (Roberts et al., 2008). The study population consisted of participants aged 50 years and above. In this study, 1267 participants had TL assessed and 1225 participants had at least 1 cognitive measurement. The present analyses included 1205 participants primarily of European ancestry with available data on both TL and at least 1 cognitive testing. Participants were followed up at 15-month intervals for up to 7 times from the year 2008 to 2017 with an average of 3.9 years (SD: 1.6 years) of follow-up.

The Health and Retirement Study (HRS) is a nationally representative longitudinal survey of more than 37,000 individuals over the age of 50 years in 23,000 households in the United States. The survey, which has been fielded every 2 years since 1992, was established to provide a national resource for data on the changing health and economic circumstances associated with aging at both individual and population levels. Details of HRS were described elsewhere (Sonnega et al., 2014). Cognitive ability was assessed up to 4 times in 20,819 participants during years 2008—2014 with an average of 5.0 years (SD: 1.5 years) of follow-up. A subset of participants (n = 5808) had TL assessed. In the present study, we included 3857 participants of European ancestry who had data available on both TL and general cognitive ability.

Informed consent was obtained from all participants in each cohort. This study was approved by the Regional Ethics Board in Stockholm (2014/1757-31/2, 2017/353-32).

2.2. TL assessment

TL was measured using a quantitative polymerase chain reaction—based technique by comparing the telomere sequence copy number in each participant's sample (T) to a single-copy gene copy number (S). The resulting T/S ratio is proportional to the average length of telomere. TL was measured in peripheral blood leukocytes in GENDER, SATSA, and MCSA and in saliva in HRS. The details of the measurement procedures can be found in the Supplementary File.

2.3. General cognitive ability

In GENDER and SATSA, a general cognitive ability score based on performance of all cognitive tests was derived through the extraction of the first principal component analysis of Synonyms, Block design, Thurstone's Picture Memory, and Symbol Digit tests, excluding any prevalent dementia cases (Pedersen et al., 1992; Reynolds et al., 2005). The principal component analysis scoring coefficients were applied from the baseline wave to the subsequent waves with subtests z-transformed to their respective baseline means and SDs so that intraindividual change could be assessed. For MCSA, a global

cognitive z-score was calculated using the z-score—transformed means of the 4 cognitive domain z-scores for memory, language, executive function, and visuospatial skill domains (Mielke et al., 2017). For HRS, a total cognitive score was constructed from immediate and delayed word recall, serial 7, backward counting from 20, and object naming and then z-transformed (Fisher et al., 2017).

2.4. Educational attainment

Educational attainment was the self-reported highest education. In GENDER, it was classified as less than elementary school, elementary school, more than elementary school, vocational school, high school, and university. In SATSA, education attainment was classified as elementary school, vocational school, high school, and university or higher. Educational attainment was defined as the number of years in school in MCSA, while it was defined as the highest degree of education that was classified as no degree, general education development, high school diploma, 2-year college degree, 4-year college degree, Master degree, professional degree (PhD, MD, or JD), and degree unknown/some college in HRS.

2.5. Statistical analysis

For ease in comparison across studies, we standardized both TL and longitudinal general cognitive ability scores to the mean of 0 and SD of 1 across all waves in all cohorts. We also centered educational attainment in each cohort. We used latent growth curve models to examine the association of TL with mean general cognitive ability levels and trajectories. Attained age was used as the time scale and centered at age of 73 years based on the age ranges of the 4 cohorts. We performed analyses for 3 models. Model 1 included a random intercept (to allow different participants to have different intercepts) and a fixed slope for attained age. Model 2 included an additional adjustment for sex. Model 3 was fitted with a random intercept and a random slope (to allow different participants to have different slopes) for attained age with adjustment for sex. Analyses also accounted for the correlation within twin pairs by modeling individuals nested in twin pairs as random effects in GENDER and SATSA. Study-specific estimates were meta-analyzed using inverse-variance weighted method. Fixed effects models were used if no significant heterogeneity was observed, otherwise random effects models applied to estimate the pooled effect sizes (Lumley, 2012). We also performed additional analysis by adjusting for educational attainment. The association of TL with general cognitive ability decline was assessed by including an interaction term between TL and centered age in years. The details of our model specification are in the Supplementary File. All statistical analyses were performed using SAS 9.4 (Cary, NC) and R 3.3.

3. Results

Characteristics of the study participants in each cohort are presented in Table 1 and the number of participants in each follow-up wave is shown in Supplementary Table 1. The mean ages at the first measurement occasion of the total 5955 participants (women: 54.7%) ranged from 67.8 to 75.0 years across the 4 cohorts, while the average follow-up duration spanned from 3.9 to 10.5 years.

Fig. 1 describes the cognitive trajectory in each of these cohorts. General cognitive ability declined with increasing age over time. Latent growth curve models were fitted to examine general cognitive ability and its association with TL (Table 2). In the first and random intercept model, controlling for attained age, longer TL was associated with a higher mean level of general cognitive ability at the age of 73 years (β: 0.021, 95% confidence interval [CI]: 0.001, 0.042 p-value = 0.043) in the meta-analysis. Additional adjustment