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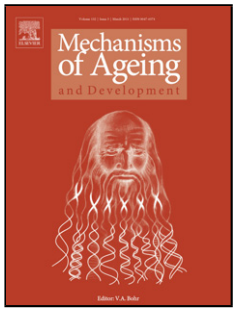

Telomere length and physical performance among older people – the Helsinki Birth Cohort Study

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Telomere length and physical performance among older people – the Helsinki Birth Cohort Study

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Highlights

- There was an association between telomere length and physical performance
- Greater telomere attrition was associated with poorer physical performance
- Results were significant only for women
- Telomeres could potentially be used as a biomarker of physical performance

Abstract

Telomere length has been suggested a biomarker of aging and is associated with several chronic diseases. However, the association between telomere length and physical performance is not well known. Using both cross-sectional and longitudinal data, we studied 582 women and 453 men from the Helsinki Birth Cohort Study at two time-points; a baseline examination in 2001-2004 at a mean age of 61 years and a follow-up examination approximately 10 years later in 2011-2013. Telomere length was measured both at baseline and at follow-up using real-time quantitative polymerase chain reaction. Physical performance was evaluated only at follow-up using the Senior Fitness Test (SFT), which assesses strength, flexibility and endurance. In women, shorter telomere length at follow-up ($p=0.044$) and greater telomere attrition during follow-up time ($p=0.022$) were associated with poorer physical performance after adjusting for covariates (age at baseline, smoking status, body mass index at baseline, follow-up time and educational attainment). No similar associations were found for men. This indicates that, at least in women, telomere length could potentially be used as a biomarker for physical performance, however, more longitudinal studies are needed to confirm this association.

Keywords: Biomarkers, Physical function, Aging, Epidemiology

Abbreviations

HBCS, Helsinki Birth Cohort Study; LTPA, leisure-time physical activity; MET, metabolic equivalent of task; SFT, Senior Fitness Test

1. Introduction

Aging can be defined as a gradual event causing decline in biological functions and is a major risk factor for both morbidity and mortality (Simm et al., 2008). However, due to the heterogeneity of the aging process, chronological age is a poor indicator of health and function (Mitnitski et al., 2002). Therefore, studies from the past decade have used other methods for assessing the biological age of an individual (Martin-Ruiz et al., 2011). Telomere length has been proposed as one potential

biomarker of aging (von Zglinicki and Martin-Ruiz, 2005). Telomeres are repetitive nucleoprotein complexes at the ends of eukaryotic chromosomes that protect functional DNA (Blackburn, 2001). Telomeres shorten at each cell division due to incomplete DNA replication at chromosome ends, however, the rate of telomere attrition is further induced by inflammation and oxidative stress as well as e.g. smoking and obesity (Lorenzi et al., 2018). Telomere length has been shown to correlate inversely with age and several age-related diseases including type 2 diabetes, cardiovascular disease, renal failure and Alzheimer's disease (Bernadotte et al., 2016). The association between telomere length and mortality has been inconsistent in previous studies (Cawthon et al., 2003; Martin-Ruiz et al., 2005).

Among older people, physical performance is an important indicator of both current and future health status. With decreased physical function, the risk of morbidity such as cardiovascular disease and cognitive decline increases, and poor physical performance also predicts future hospitalization and institutionalization (Cooper et al., 2010a). In community-dwelling populations, objectively measured poor physical performance has been shown to increase the risk of all-cause mortality (Cooper et al., 2010b). Aging is associated with a loss of muscle mass, known as sarcopenia, which is an important reason for decreased physical function among older people (Legrand et al., 2014). To avoid rises in health care costs (Fried et al., 2001) there is an inevitable need for finding ways to predict and prevent decline in physical performance at an early stage among older people.

The association between telomere length and physical performance is not well known. Only little evidence is available and the results have been inconsistent, most having shown no association between the two variables (Mather et al., 2010; Maynard et al., 2015). Cross-sectional studies have assessed telomere length at only one time-point thereby unable to report any change in telomere length over time. As inflammation and oxidative stress are associated with both decreased physical performance and increased rate of telomere attrition, an attractive hypothesis is that changes in

telomere length better predicts subsequent physical decline compared to using a single measure of telomere length. Previous longitudinal studies have assessed physical performance using simple test batteries only assessing limited aspects of physical performance, such as grip strength or standing balance (Gardner et al., 2013). These tests may thereby not give an accurate representation of the overall physical performance of the individuals.

The aim of this study was to assess if telomere length was related to objectively measured physical performance 10 years later. We also assessed if telomere attrition over a 10-year period or telomere length in cross-sectional analysis was associated with physical performance. We studied individuals from the Helsinki Birth Cohort Study at an average age of 61 years and assessed physical performance with the validated Senior Fitness Test (SFT).

2. Material and methods

2.1. Study population

This study is part of the Helsinki Birth Cohort Study (HBCS) and uses data from a subpopulation of the HBCS consisting of 8760 individuals born between 1934 and 1944 at the Helsinki University Central Hospital. All subjects visited child welfare clinics in Helsinki and were residents of Finland in 1971, when they received a unique personal identification number (Åström et al., 2018). In the year 2000, random-number tables were used to invite 2902 individuals to a baseline clinical examination, of which 2003 cohort members participated in an examination between 2001 and 2004. From this clinical cohort, those still alive and living within a 100-km radius of Helsinki were invited to a follow-up examination in 2011. A total of 1097 of the invited 1404 cohort members participated in this follow-up examination between 2011 and 2013. The present study sample consists of 1035 cohort members with adequate data on both telomere length and physical performance. The clinical

study protocol was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa and follows the guidelines of the Declaration of Helsinki. A written, informed consent was obtained from all participants.

2.2. DNA extraction and telomere length

DNA was extracted from EDTA-anti-coagulated peripheral whole blood both at the baseline clinical examination in 2001-2004 and at the clinical follow-up examination in 2011-2013 using a commercially available kit, QIAamp Blood Maxi Kit and DNeasy Blood & Tissue Kit (Qiagen, The Netherlands), respectively. The samples were stored at -20°C before and after DNA extraction. DNA concentration and purity were assessed by measuring ultraviolet absorbance at 260nm for salts and 280nm for other contaminants. DNA integrity was tested by electrophoresis in 0.8% agarose gel. There was no difference in DNA integrity and quality between the two kits.

Telomere length was assessed in leukocytes and measured using real-time quantitative polymerase chain reaction (PCR) as previously described (Guzzardi et al., 2015). At the baseline examination, telomere length was determined as the ratio of telomere DNA intensity to hemoglobin beta single-copy gene signal intensity (Cawthon, 2002; Kajantie et al., 2012; O'Callaghan et al., 2008). A multiplex real-time quantitative PCR using a 384-well plate (CFX384 Touch Real-Time PCR Detection System, Bio-Rad Laboratories, USA) was used to measure telomere length at the follow-up examination (Cawthon, 2009; Guzzardi et al., 2015). All plates included 3 or 4 genomic DNA control samples for calibrating the plate effect and for monitoring the inter-assay coefficient of variation, which was 21.0% at baseline and 6.2% at the follow-up examination. Telomere length at both time points correlated with each other ($r=0.255$, $p<0.001$).

Telomere length is expressed as a T/S ratio, calculated as the ratio of telomere repeat copy number (T) to single gene copy number (S) for each sample compared to a reference sample. Absolute change

in telomere length during follow-up was calculated by subtracting baseline telomere length from follow-up telomere length. Relative telomere length after the follow-up period was calculated as follow-up telomere length divided by telomere length at baseline.

2.3. Physical performance

Physical performance was assessed at the follow-up examination in 2011-2013 using the validated SFT (Rikli and Jones, 1999). A modified test battery consisting of 5 tests was used to objectively evaluate the level of physical fitness: 1) Arm curl: holding hand weight (2kg for women and 3kg for men), number of full-range biceps curls during 30-s to assess upper-body strength; 2) Chair stand: number of full chair stands during 30-s with arms folded across chest to evaluate lower-body strength; 3) Chair sit-and-reach: sitting at the front of the chair with legs fully extended, distance (in centimeters) between extended fingers and tip of toes to assess lower-body flexibility; 4) Back scratch: number of centimeters between tip of extended fingers, with one hand reaching over shoulder and the other hand up middle of back to evaluate upper-body flexibility; 5) 6-min walk: number of meters walked in 6 minutes to assess aerobic endurance. All tests were performed at a research facility and measurements were done by trained research assistants.

For each test, sex-standardized percentile tables of normative data for 5-year age groups were used to rate the score of the participants (Rikli and Jones, 2013). Based on 5-percentile ranges, the rating for each test varied between 1 and 20, those with a score in the lowest 5-percentiles receiving a rating of 1 and those with a score in the highest 5-percentiles receiving a rating of 20. The overall SFT score was then calculated by summing the normalized ratings of the SFT test components and varied between 5 and 100.

2.4. Study variables and covariates

At the baseline examination, height and weight were measured and body mass index (BMI) was calculated as kg/m^2. Information on current health status, disease history, smoking status, level of education and lifestyle characteristics were acquired using questionnaires. Blood was drawn after fasting in order to measure glucose and lipids. The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) 12-month leisure-time physical activity (LTPA) history questionnaire was used to assess physical activity (Lakka and Salonen, 1992). This validated exercise questionnaire assigns a metabolic equivalent of task (MET) value based on intensity grade for the most common LTPA and assesses physical activity during the last 12 months. The results are presented as MET-hours per year.

2.5. Statistical analysis

Data are presented as means with standard deviations (SD) or as counts with percentages. The study population was divided into tertiles based on the overall SFT score. In univariate analysis, linearity across SFT tertiles for baseline variables and telomere measurements were evaluated using the Cochran-Armitage test for trend and analysis of variance (ANOVA) with an appropriate contrast. In the adjusted model, linearity (orthogonal polynomial) of telomere measurements across SFT tertiles was evaluated using analysis of covariance (ANCOVA) and regression analysis. In the case of violation of the assumptions (e.g. non-normality), a bootstrap-type test was used. In the adjusted model, we controlled for age at baseline, smoking status, BMI at baseline, follow-up time and years of education. A possible nonlinear relationship between SFT and relative telomere length at follow-up was assessed using 3-knot-restricted cubic spline regression. The length of the distribution of knots were located at the 10th, 50th, and 90th percentiles; knot locations were based on Harrell's recommended percentiles or user-specified points (Harrell Jr., 2001). Correlation coefficients with 95% CI were calculated using the Spearman method. The normality of the variables was tested using the Shapiro–Wilk W test. Stata 15.1 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

3. Results

Characteristics for the 582 women and 453 men included in the analysis are shown in Table 1. Baseline measurements were assessed at a mean age of 61 (SD 3) years. Physical performance was measured 9.7 years later (range 7.7 to 11.5 years). For both men and women, those with the highest BMI, highest glucose and triglyceride levels as well as the lowest HDL cholesterol fell into the lowest tertile of the SFT. The prevalence of cardiovascular disease and diabetes were highest in the lowest SFT tertile, whereas individuals with the highest education had the best physical performance, for both men and women. In addition, smoking status showed a negative association and LTPA a positive association across SFT tertiles for women but not men.

Mean telomere length T/S ratio at baseline was 1.42 (SD 0.29) for women and 1.38 (SD 0.29) for men, whereas the corresponding values at follow-up were 0.89 (SD 0.32) and 0.81 (SD 0.27) for women and men, respectively. Table 2 presents the unadjusted associations between telomere length measurements and SFT score tertiles. Telomere length at baseline was not associated with the SFT score 10 years later for neither women (p=0.87) nor men (p=0.45). At follow-up, however, longer telomere length was associated with a higher overall SFT score for women (p=0.021) but not for men (p=0.56). Adjustment for age at baseline, smoking status, BMI at baseline, follow-up time and years of education attenuated the association but it remained statistically significant for women (p=0.044) and non-significant for men (p=0.13). Greater absolute telomere change between baseline and follow-up examinations was also associated with a lower overall SFT score, but only for women (p=0.039). Adjusting for age at baseline, smoking status, BMI at baseline, follow-up time and years of education did not attenuate this association (p=0.022). The corresponding p-values for men were p=0.86 (crude) and p=0.65 (adjusted). Similarly, there was a linear association between relative telomere length at

follow-up and the SFT score for women but not for men. No correlation was found between telomere measurements and individual SFT components in neither women nor men (Table 3).

Figure 1 shows a scatter-plot on the association between baseline telomere length and SFT at follow-up. Baseline telomere length was not related to physical performance at follow-up in women (β=-0.02, 95% CI -0.10 to 0.05) or in men (β=0.00, 95% CI -0.09 to 0.09). The corresponding coefficients for the association between follow-up telomere length and physical performance for women (β=-0.09, 95% CI 0.00 to 0.17) and men (β= 0.04, 95% CI -0.05 to 0.13) are shown in figure 2. The association between SFT score and relative telomere length after follow-up is illustrated in Figure 3. Greater relative telomere length was associated with better physical performance, but only in women.

4. Discussion

In this cohort study of older people, we found a linear association between telomere length and physical performance among women in cross-sectional analysis. No similar association was observed for men. In addition, greater change in telomere length during the 10-year follow-up correlated with poorer physical performance among women but not men. Controlling for BMI, smoking and years of education did not attenuate the associations.

Ideally, telomere length could be used as a marker to assess and predict multicomplex age-related conditions, including decline in physical performance. However, findings in previous studies on the association between telomere length and physical performance have been inconsistent. In a meta-analysis by Gardner and colleagues (Gardner et al., 2013) comprising 4 studies, only chair rise speed and grip strength showed weak associations with telomere measurements. However, telomere length did not correlate with the other tests of physical performance, including walking speed and balance. Similarly, the Cardiovascular Health Study found a positive association between telomere length and

chair stand result (Soares-Miranda et al., 2015). Some studies have also assessed the association between telomere length and frailty. Our earlier findings from the Helsinki Birth Cohort Study showed an inverse association between telomere length and risk of frailty (Haapanen et al., 2018). In contrast, a meta-analysis consisting of 3268 participants found no association between the two variables (Zhou et al., 2018).

Telomere length can be linked to physical performance by both direct and indirect pathways. When telomeres reach a critical point of shortening (less than 200–300 base pairs), cell cycle arrest, cellular senescence and apoptosis are triggered, which may cause loss of functional tissue (Aubert and Lansdorp, 2008). Thus, loss of muscle mass and muscle function due to telomere attrition could be a cause of poor physical performance (Zaslavsky et al., 2013). Another possible mechanism is oxidative stress and chronic inflammation, which has been shown to correlate with both telomere attrition (Lorenzi et al., 2018) and poor physical performance among older people (Cesari et al., 2004). This explanation is further supported by previous findings showing that senescent cells also secrete inflammatory mediators, such as interleukin-6 (Rodier et al., 2009).

Several reasons may account for the inconsistent findings in previous studies on the association between telomere length and physical performance. An obvious reason is differences in sample size, as smaller studies may not have enough statistical power to show an association. Another reason for discrepancy between results may be the technique used for measuring telomere length. The interindividual variation of telomere length is large and quantitative PCR has been shown to have a high coefficient of variation (Martin-Ruiz et al., 2015). If follow-up time in longitudinal studies is inadequate, this may lead to undetectable changes in telomere length and thereby non-significant results. Finally, the age-range of the study population could affect the results, as telomere length may

be a stronger predictor of health outcomes for younger adults compared to older people (Brown et al., 2018).

We found that telomere attrition and telomere length associated with physical performance only among women, and this may be due to several factors. There were greater differences in lifestyle characteristics among women with better physical performance compared to men, regarding e.g. smoking and prevalence of cardiovascular disease, which could explain the difference observed in the association between the sexes. Besides evaluating muscle strength, the SFT used in our study also tests for flexibility, which may be another reason we found a relationship between the overall SFT score and physical performance only in women. Previous studies have generally reported longer telomere length in women (Woo et al., 2008; Yu et al., 2015), which may be due to hormonal differences between the sexes. Estrogen has been shown to upregulate telomerase activity, which increases the regeneration potential of telomeres (Kyo et al., 1999). In addition, estrogen reduces the burden of oxidative stress, thereby decreasing the rate of telomere attrition (Aviv, 2002). On the other hand, longer telomeres at baseline have been shown to correlate with a higher telomere attrition rate (Nordfjäll et al., 2009). Thus, although women have slower telomere attrition at younger age, the longer telomere length at older age may cause greater relative change in telomere length compared to men, when studying older people.

The strengths of this study are numerous. In this longitudinal study we included over 1000 well-phenotyped men and women who were followed-up for almost 10 years. Physical performance was assessed objectively using the validated SFT, which can be considered an appropriate method for measuring physical performance. SFT evaluates strength, flexibility and endurance, all important components of physical function. Furthermore, we measured telomere length at two time points,

which allowed us to investigate how telomere attrition over time correlates with physical performance.

A weakness of this study is that we did not measure physical performance at baseline. We were therefore not able to evaluate a potential change in physical performance during follow-up and investigate if this correlates with either telomere length or telomere attrition. We found no association between baseline telomere length and physical performance 10 years later, thus, the follow-up time needed for predictive results remains unclear. Although the SFT measures overall physical performance, it should be noted that 40% of the score consists of measures on flexibility but no exhaustive test on endurance is included. This warrants further studies on the topic as different performance test batteries may reveal other kind of associations. We were able to account for several covariates in the analyses including BMI and smoking but acknowledge the possibility of other unmeasured variables affecting our results. We assessed telomere length from peripheral blood leukocytes, however, we cannot exclude that telomere length measured from e.g. muscle cells would better correlate with physical performance. Telomere length has been shown to have high heritability (Broer et al., 2013) and our study consisted of a homogenous group of participants living in a restricted area of Finland. This should be considered before generalizing our results.

In conclusion, we found evidence suggesting that shorter telomere length in cross-sectional analysis and greater telomere attrition over a 10-year period were associated with poorer physical performance among older women. However, further longitudinal studies with sufficient follow-up times and larger study populations assessing physical performance at all time points are needed to confirm these findings in order to evaluate the usability of telomere length as a biomarker for physical performance.

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Author contributions: MÅ, MBvB, HK and JGE conceived and designed the study. JGE, EK, MKS, MBvB, PP, MS, TR, MH, MG, PI and MP planned and participated in data collection. HK carried out the statistical analysis. MÅ, MBvB, HK and JGE interpreted the data. MÅ wrote the first draft of the manuscript. All authors contributed to the critical review of the manuscript and have approved the final manuscript.

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Figure captions

Fig. 1. Scatter-plot for univariate associations between baseline telomere length (TL) measured in 2001-2004 and Senior Fitness Test (SFT) results from follow-up in 2011-2013 for women and men.

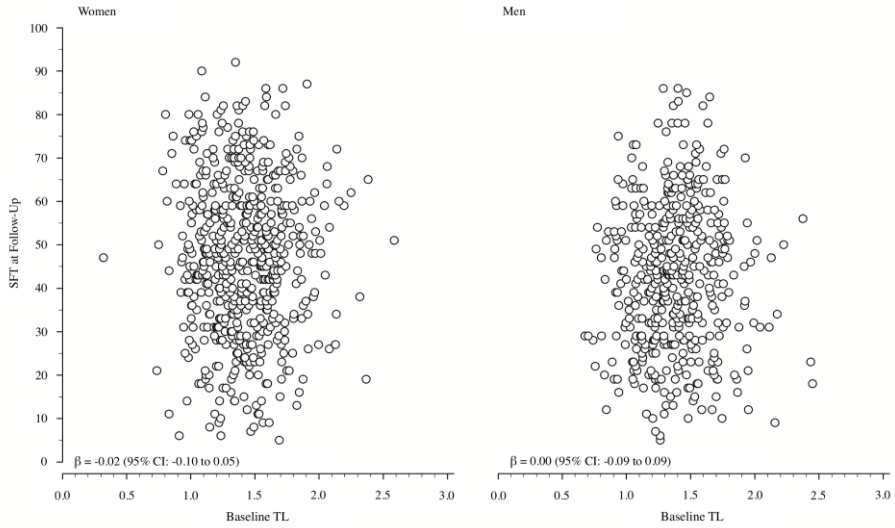

Fig. 2. Scatter-plot for univariate associations between follow-up telomere length (TL) and Senior Fitness Test (SFT) results for women and men.

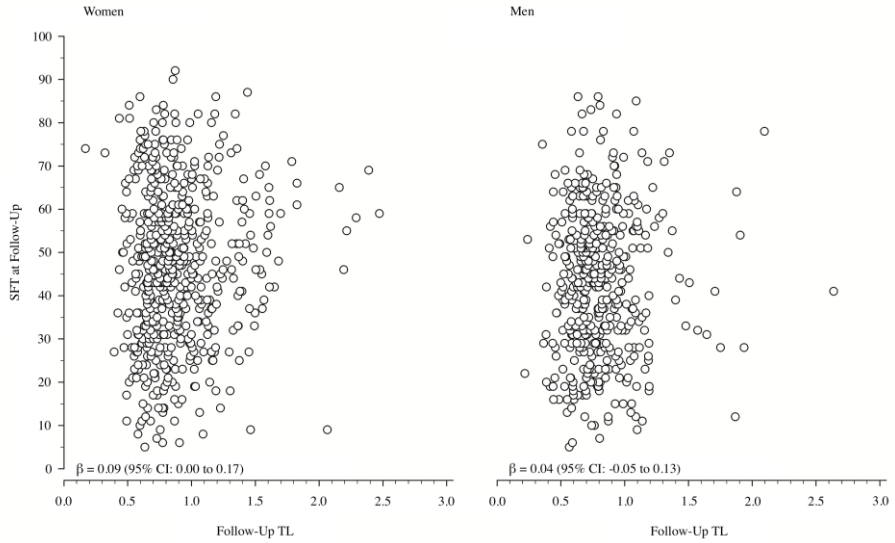

Fig. 3. Relationship between Senior Fitness Test (SFT) results from follow-up in 2011-2013 and relative telomere length at follow-up, measured as follow-up telomere length/baseline telomere length, for women and men. The curves were derived from 3-knot restricted cubic spline regression models. The models were adjusted for age, BMI, education years, smoking and follow-up time. Grey area represents 95% confidence intervals.

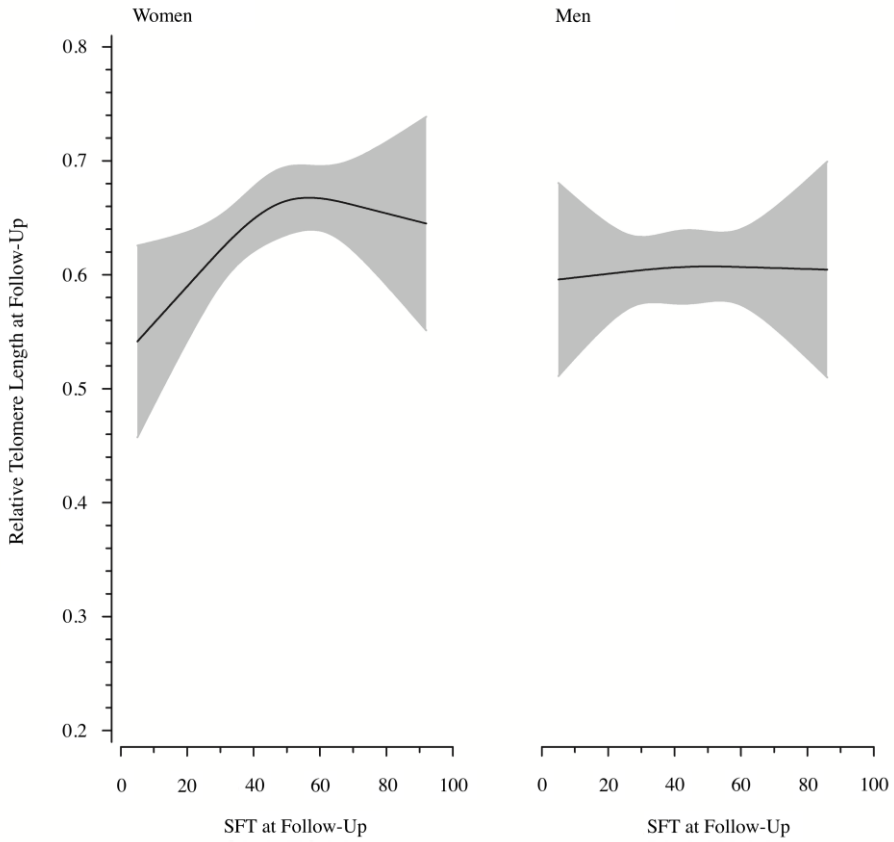

Table 1. Baseline characteristics of cohort members grouped by SFT tertiles at follow-up. Results are presented as means and standard deviations unless otherwise stated

	Women (n=582)					Men (n=453)			
SFT tertile (score range)	I (5–39)	II (40–55)	III (56–100)	p-value[a]		I (5–33)	II (34–50)	III (52–100)	p-value[a]
N	198	194	190			149	152	152	
Age (years)	61 (3)	61 (3)	61 (3)			61 (3)	61 (3)	60 (2)	
Body mass index (kg/m^2)	29.0 (5.3)	26.8 (4.2)	25.4 (3.2)	<0.001		28.4 (3.8)	27.2 (3.5)	26.1 (2.6)	<0.001
Current smoker or ex-smoker, n (%)	95 (48)	74 (38)	59 (31)	<0.001		106 (71)	99 (65)	106 (70)	0.8
Health status									
Cardiovascular disease, n (%)	39 (20)	29 (15)	15 (8)	<0.001		35 (23)	30 (20)	19 (12)	0.01
Diabetes, n (%)	17 (9)	4 (2)	1 (1)	<0.001		22 (15)	9 (6)	3 (2)	<0.001
Asthma, n (%)	14 (7)	13 (7)	15 (8)	0.8		14 (9)	4 (3)	12 (8)	0.6
Plasma glucose (mmol/l)	5.7 (1.0)	5.5 (1.0)	5.3 (0.6)	<0.001		6.4 (1.9)	5.9 (0.8)	5.7 (0.7)	<0.001
Plasma total cholesterol (mmol/l)	6.0 (1.1)	5.9 (0.9)	6.1 (1.0)	0.6		5.7 (1.1)	5.8 (1.0)	5.7 (1.0)	0.96
Plasma HDL cholesterol (mmol/l)	1.7 (0.4)	1.7 (0.4)	1.9 (0.5)	<0.001		1.4 (0.3)	1.5 (0.3)	1.6 (0.4)	<0.001
Plasma triglycerides (mmol/l)	1.5 (0.7)	1.4 (0.6)	1.2 (0.6)	<0.001		1.7 (0.9)	1.5 (0.6)	1.3 (0.7)	<0.001
Education (years)	11.5 (3.4)	12.2 (3.4)	12.9 (3.4)	<0.001		11.9 (3.5)	13.6 (3.9)	13.6 (3.8)	<0.001
LTPA (MET-h/year), median (IQR)	1672 (895, 2556)	1607 (966, 2561)	1983 (1218, 2853)	0.009		1506 (992, 2397)	1809 (1020, 2720)	1662 (1248, 2572)	0.1

[a]p-values are calculated for linearity across tertiles

SFT= Senior Fitness Test; HDL= High-density lipoprotein; LTPA= Leisure-time physical activity; MET= Metabolic equivalent of task; IQR= Interquartile range.

Table 2. Cross-sectional and longitudinal univariable associations between telomere length and SFT result tertiles.

	Women (n=582)					Men (n=453)			
SFT result (score range)	I (5-39)	II (40-55)	III (56-100)	p-value[a]		I (5-33)	II (34-50)	III (52-100)	p-value[a]
N	198	194	190			149	152	152	
Telomere length (T/S ratio)									
Baseline, mean (SD)	1.42 (0.28)	1.41 (0.30)	1.42 (0.30)	0.87		1.37 (0.32)	1.38 (0.28)	1.39 (0.26)	0.45
Follow-up, mean (SD)	0.85 (0.26)	0.91 (0.33)	0.92 (0.36)	0.021		0.80 (0.27)	0.80 (0.26)	0.82 (0.27)	0.56
Telomere attrition									
Absolute change (T/S ratio), mean (95% CI)	-0.58 (-0.62 to -0.53)	-0.50 (-0.55 to -0.44)	-0.50 (-0.55 to -0.44)	0.039		-0.56 (-0.62 to -0.50)	-0.58 (-0.63 to -0.52)	-0.57 (-0.63 to -0.52)	0.86
Relative telomere length[b]	0.61	0.67	0.66			0.60	0.60	0.61	

[a]p-values are calculated for linearity across tertiles
[b]Calculated as follow-up telomere length/baseline telomere length
SFT= Senior Fitness Test

Table 3. Correlation between telomere length and individual SFT components

	Telomere length	
SFT component	Baseline	Absolute change
	r (95% CI)	r (95% CI)
Women (n=582)		
Arm curl	0.01 (-0.07 to 0.09)	0.04 (-0.04 to 0.13)
Chair stand	0.04 (-0.04 to 0.12)	0.05 (-0.03 to 0.13)
Chair sit-and-reach	-0.01 (-0.09 to 0.08)	0.04 (-0.04 to 0.12)
Back scratch	-0.05 (-0.13 to 0.04)	0.06 (-0.03 to 0.14)
6-min walk	0.01 (-0.07 to 0.09)	-0.01 (-0.09 to 0.08)
Men (n=453)		
Arm curl	0.07 (-0.02 to 0.16)	0.00 (-0.09 to 0.09)
Chair stand	0.10 (-0.01 to 0.19)	-0.06 (-0.15 to 0.03)
Chair sit-and-reach	0.02 (-0.08 to 0.10)	0.02 (-0.07 to 0.11)
Back scratch	-0.02 (-0.11 to 0.07)	0.02 (-0.07 to 0.11)
6-min walk	0.09 (-0.01 to 0.18)	-0.05 (-0.14 to 0.04)

SFT= Senior Fitness Test