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Physical Activity and Telomere Length in American Indians: Strong Heart Family Study

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Abstract

Telomere length, a marker of biological aging, has been associated with many chronic diseases, but its relations with physical activity remains unclear. The purpose of this study was to examine the association of objectively measured ambulatory activity with leukocyte telomere length, a marker of biological aging (LTL) among American Indians (AIs). This cross-sectional study included 2,312 AI participants from the Strong Heart Family Study. Steps per day were measured using Accusplit AE120 pedometers. Quantitative PCR was used to measure LTL. Generalized estimating equations were used to examine the associations of steps per day with LTL. The median steps per day over a one week period was 5,118 steps (interquartile range= 3,163–7,576 steps). Compared to participants in the lowest quartile of steps per day, participants in the upper three quartiles of steps per day had longer LTL: beta±SE=0.0195± 0.0144, 0.0273±0.0139, and 0.0375±0.0143 T/S ratio units longer (p-trend=0.010) after adjustment for potential confounders. These data suggest that ambulatory activity is associated with LTL. Further studies are needed to determine the mechanism by which ambulatory activity influences LTL.

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Conflicts of Interest

The authors report no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Keywords

Physical activity; telomeres; American Indians; pedometer

Introduction

Telomeres are repetitive sequences of DNA at the end of chromosomes that help preserve genetic stability. Telomeres shorten with each cell division, and leukocyte telomere length (LTL) is commonly used as a marker of biological aging (1). Short LTL has been consistently shown to be associated with many age-related chronic diseases, including cardiovascular diseases (CVD), type 2 diabetes, and obesity (1, 2). It has been hypothesized that physical activity may help preserve LTL, but study results have been largely inconsistent, likely due to small sample sizes or use of self-report to estimate physical activity (2). In this study, we examined the relationship of objectively-determined physical activity and LTL among AIs who participated in the Strong Heart Family Study (SHFS).

Methods

Setting & Study Population

The SHFS is a longitudinal study of CVD and its risk factors among AIs in Arizona, Oklahoma, and North and South Dakota. Details of the study have been described previously (3). The institutional review board from each Indian Health Service region and all participating communities approved the study, and written informed consent was obtained from all participants.

Participants who had less than three days of pedometer data were excluded (n=249). Additionally, we excluded participants missing measures of LTL (n=7) or key covariates (i.e., education (n=12), smoking (n=1), alcohol use (n=2), BMI (n=4), diet (n=84), diabetes (n=5), CVD (n=34)). In total, 2,312 participants comprised the analytic sample. Participants excluded due to missing data were older (46.5 years versus 44.4 years), but otherwise similar to participants included in the analyses.

Data Collection

Usual daily ambulatory activity in 2001–2003 was estimated using Accusplit AE120 pedometers (Yamax, Japan) (4). These pedometers have been shown to be reliable and valid in free-living conditions (5). Participants were asked to wear the Accusplit AE120 pedometer on the hip during all waking hours for seven consecutive days, except while bathing or swimming, and to record the number of steps taken per day.

Genomic DNA was isolated from peripheral blood leukocytes collected at the 2001–2003 examination, and LTL was measured by quantitative PCR at Dr. Blackburn’s lab at UCSF. The LTL was quantified as the ratio of telomeric product to a single copy gene (T/S ratio). Details of the laboratory methods and quality control procedures have been described previously (6).

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Statistical Analyses

Analyses examined the cross-sectional association of physical activity with LTL. To account for the family-based sampling of the SHFS, generalized estimating equations (GEE) with an exchangeable working correlation and robust standard errors were used. Due to a right-skewed distribution of steps per day in the cohort, steps per day were assessed categorically using indicator (i.e., dummy) quartiles. LTL was assessed continuously. To assess linear trends, indicator quartiles for physical activity were assessed as a continuous variable. Covariates were selected *a priori* based on their potential association with physical activity and LTL, and three models were fit to examine the association of physical activity with LTL. Model 1 (crude model) adjusted for age, age^2, sex, and site. The second model (primary model) additionally adjusted for potential confounders, including education (years), smoking status, (never, former, current), alcohol consumption (never, former, current), alternative healthy eating index, diabetes (yes/no), and CVD (yes/no). As obesity and inflammation may be in the causal pathway of physical activity and LTL (i.e., physical activity promotes healthy BMI and lowers inflammation) (7, 8), we adjusted for BMI and fibrinogen in a third model to evaluate whether these factors mediate the relationship of physical activity and LTL.

In sensitivity analyses, we re-ran all models using multiple imputations for missing covariates (<2% for most covariates). We included data on age, gender, smoking, education, site, BMI, physical activity, alternative healthy eating index, diabetes and CVD in the imputation. Although we *a priori* chose to model steps per day using indicator quartiles, in sensitivity analyses, we re-ran all models categorizing steps per day in tertiles and continuously (with log-transformation due to skew). All statistical analyses were performed in STATA version 13.1 (Stata Corp, College Station, Texas).

Results

The mean ±SD age of the 2,312 participants was 40.3±16.7 years and 60.3% of participants were female. Mean BMI was 31.2±7.4 kg/m^2 and 18.6% of participants had diabetes. Reported steps per day were slightly right-skewed with a median of 5,119 steps per day (interquartile range: 3,163, 7,576 steps per day; coefficient of variation=66.9). Participants who accumulated more steps per day were younger, more likely to be male, and were less likely to have diabetes than participants who accumulated fewer steps per day. Additionally, participants who accumulated more steps had lower triglycerides, fibrinogen, and BMI when compared to those who accumulated fewer steps.

Participants who accumulated more steps per day had longer LTL than participants who accumulated fewer steps per day (Table 1). Compared to participants in the lowest quartile of steps per day, participants in the upper three quartiles of steps per day had longer LTL: beta±SE=0.0195± 0.0144, 0.0273±0.0139, and 0.0375±0.0143 T/S ratio units longer (p-trend=0.010) after adjustment for age, age^2, sex, site, education, smoking status, alcohol consumption, alternative healthy eating index, diabetes and CVD. Additional adjustment for BMI and fibrinogen attenuated the risk estimates. Results were not meaningfully changed when analyses used imputed data for occasional missing covariate values. Additionally, modeling steps per day continuously or in tertiles did not influence results.

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Discussion

Results from this large multi-tribal study of AIs suggest that objectively measured physical activity is positively associated with LTL. Participants who accumulate more steps per day had longer LTL than participants who accumulated fewer steps per day. These findings support the hypothesis that lifestyle factors (i.e., physical activity) are associated with cellular aging assessed by LTL.

Recent studies suggest that telomere attrition is related to CVD and type 2 diabetes (1). However, the relationship of risk factors for these diseases, including physical activity, with LTL is less clear. Similar to results reported herein, some studies have found positive associations of physical activity and LTL, while other studies have found no association of physical activity with LTL (2). Differences in results are likely due to inadequate sample size (i.e., many studies were small ($n<250$)), non-standardized methods to assess activity (i.e., questionnaires, reported gym visits, accelerometer/pedometer), inadequate adjustment for potential confounders or underlying differences in populations studied. For instance, SHFS participants reported lower levels of physical activity, poorer diet quality, and were more likely to smoke than participants from other large cohort studies (2). Interestingly, the magnitude of our observed risk estimates are very similar to the risk estimates reported in a study of cardiorespiratory fitness and LTL in a national sample of adults in the United States (9).

The mechanisms by which physical activity influences cellular aging are likely to be complex. Physical activity may promote the up-regulation of telomerase reverse transcriptase –which may maintain telomere length or promote telomere lengthening. Exercise also promotes the expression of insulin-like growth-factor 1 (IGF-1), and previous studies have shown that low circulating levels of IGF-1 are associated with shorter LTL when compared to higher levels of circulating IGF-1 (10). Physical activity may also reduce systemic inflammation and lower oxidative stress—factors known to increase telomere attrition. Adjustment for fibrinogen and BMI partly attenuated the magnitude of observed risk estimates for the association of physical activity and LTL. This attenuation may be because of confounding by the independent effects of inflammation and obesity on physical activity and LTL or because of the role of inflammation and obesity as mediators. Unfortunately, we cannot differentiate between confounding and mediation in this cross-sectional analysis.

The present analysis has several strengths. To our knowledge, this is the only study of physical activity and LTL among AIs, a population with a high burden of cardio-metabolic diseases. Most previous studies that have assessed the relationship of physical activity and LTL relied on self-report to estimate usual activity levels; in this analysis, we used an objective measure of activity. This study also has limitations. In this cross-sectional analysis, physical activity and LTL were measured at a single time point and it is not possible to infer temporality. Additionally, although the SHFS has well-characterized data on diet and cardio-metabolic risk factors, data on biomarkers related to LTL (i.e., c-reactive protein, IGF-1) were not available, and we are unable to evaluate if these factors impact the association of

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physical activity and LTL. Finally, it is unknown if the findings are generalizable to other populations.

In summary, our results suggest that higher levels of physical activity are associated with higher LTL. This study adds to the growing body of evidence identifying physical inactivity as an important factor related to cellular aging. As physical activity is a potential modifiable factor, future prospective studies are needed to determine if higher levels of physical activity delay cellular aging and the onset of chronic diseases.

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Table 1.

Association of Pedometer-Determined Steps Per Day & Leukocyte Telomere Length Among Strong Heart Family Study Participants (n=2,312)

Daily steps	**<3,029**	**3,030–4,920**	**4,921–7,366**	**7,367+**	
		β (SE)	**β (SE)**	**β (SE)**	**p-trend**
Model 1[a]	reference	0.0212 (0.0148)	0.0296 (0.0144)	0.0404 (0.0140)	0.005
Model 2[b]	reference	0.0195 (0.0144)	0.0273 (0.0139)	0.0375 (0.0143)	0.010
Model 3[c]	reference	0.0164 (0.0144)	0.0248 (0.0143)	0.0340 (0.0160)	0.026

[a]model 1 adjusts for age, age^2, sex, & site

[b]Model 2 additionally adjusts for education, smoking, alcohol use, alternative healthy eating index, diabetes, & cardiovascular disease

[c]Model 3 additionally adjusts for BMI & fibrinogen.

Abbreviations: β, beta coefficient; SE, standard error