

The Association Between Physical Activity in Leisure Time and Leukocyte Telomere Length

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Background: Physical inactivity is an important risk factor for many aging-related diseases. Leukocyte telomere dynamics (telomere length and age-dependent attrition rate) are ostensibly a biological indicator of human aging. We therefore tested the hypothesis that physical activity level in leisure time (over the past 12 months) is associated with leukocyte telomere length (LTL) in normal healthy volunteers.

Methods: We studied 2401 white twin volunteers, comprising 2152 women and 249 men, with questionnaires on physical activity level, smoking status, and socioeconomic status. Leukocyte telomere length was derived from the mean terminal restriction fragment length and adjusted for age and other potential confounders.

Results: Leukocyte telomere length was positively associated with increasing physical activity level in leisure time ($P < .001$); this association remained significant af-

ter adjustment for age, sex, body mass index, smoking, socioeconomic status, and physical activity at work. The LTLs of the most active subjects were 200 nucleotides longer than those of the least active subjects (7.1 and 6.9 kilobases, respectively; $P = .006$). This finding was confirmed in a small group of twin pairs discordant for physical activity level (on average, the LTL of more active twins was 88 nucleotides longer than that of less active twins; $P = .03$).

Conclusions: A sedentary lifestyle (in addition to smoking, high body mass index, and low socioeconomic status) has an effect on LTL and may accelerate the aging process. This provides a powerful message that could be used by clinicians to promote the potentially antiaging effect of regular exercise.

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REGULAR EXERCISE PLAYS A role in health and well-being. Frequent exercisers display reduced cardiovascular risk factors¹ and reduced cardiovascular-related mortality and morbidity.² Also, frequent exercisers have a lower risk for type 2 diabetes mellitus,³ cancer, hypertension, obesity, and osteoporosis,⁴ which are considered aging-related diseases. Despite the known benefits of physical activity, inactivity continues to be a major public health problem.⁵ A sedentary lifestyle increases the propensity to aging-related diseases and premature death.⁴ Inactivity may diminish life expectancy not only by predisposing to aging-related diseases but also because it may influence the aging process itself.

Aging is the progressive loss of metabolic and physiologic functions,⁶ but the biological features of aging vary considerably among individuals. This variability may be because of a host of genetic and environmental factors that affect oxida-

tive stress⁷ and inflammation⁸ and, consequently, leukocyte telomere dynamics (telomere length and age-dependent attrition rate).

See also pages 131 and 147

Telomeres consist of tandemly repeated DNA sequences that play an important role in the structure and function of chromosomes. Telomeres and associated proteins cap eukaryotic chromosomes, protecting them from degradation and end-to-end-fusion.⁹ Telomeres of cultured somatic cells undergo erosion with each cell division, ultimately leading to replicative senescence. Therefore, telomeres progressively shorten in somatic cells and their length diminishes with age.¹⁰⁻¹² Oxidative stress enhances telomere erosion with cell replication,¹³ whereas inflammation entails an increase in turnover of leukocytes. Telo-

mere dynamics in leukocytes might, therefore, chronicle the cumulative burden of oxidative stress and inflammation and, as such, serve as an index of biological age.¹⁴

Leukocyte telomere length (LTL) is short in diseases associated with increased oxidative stress, such as coronary artery disease,¹⁵ diabetes mellitus,¹⁶ heart failure,¹⁷ and osteoporosis,¹⁸ and predicts early myocardial infarctions.¹² Moreover, LTL is associated with systemic oxidative stress¹⁹ and is inversely correlated with body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared).²⁰ Given that BMI ultimately reflects caloric consumption and expenditure, we tested the a priori hypothesis that physical activity level may have an effect on telomere attrition independent of other risk factors influencing the aging process.

METHODS

PARTICIPANTS AND PROCEDURES

We studied 2401 white twins (2152 women and 249 men) from the UK Adult Twin Registry. Twins were recruited from the general population through national media campaigns in the United Kingdom and have been used previously in various studies since 1992 (described in more detail elsewhere).²¹ Twins who had measurements of LTL performed and who responded fully to a postal questionnaire, detailing their self-reported physical activity level during the past 12 months (crude response rate, 86.8%), were selected for the study. The sample used comprised 167 monozygotic twin pairs, 915 dizygotic twin pairs, and 237 unpaired twins. Zygosity was determined using a validated questionnaire,²² and in cases of uncertainty, DNA fingerprinting was used for confirmation. Twin volunteers have been shown to be comparable to age-matched population singletons for lifestyle and disease characteristics.²³ Individuals in this sample completed questionnaires covering a wide range of health and lifestyle issues and underwent detailed clinical assessment. All subjects provided written informed consent approved by the St Thomas' Hospital Research Ethics Committee.

Subjects completed a questionnaire detailing their self-reported physical activity level during leisure time and at work during the past 12 months, where 1 indicates inactive; 2, light activity; 3, moderate activity; and 4, heavy activity. Individuals also completed a questionnaire involving an in-depth physical activity assessment recording how much time subjects spent in moderate and vigorous non-weight-bearing and weight-bearing activity, on average per week (based on the Allied Dunbar National Fitness Survey).²⁴ This assessed current and retrospective physical activity level (when subjects were in their 20s).

Height and weight were recorded during a clinical visit, from which BMI was calculated. Smoking—ascertained from a self-reported measure—was recorded as a dichotomous variable with 2 levels: 0, never smoked or ex-smoker; and 1, current smoker. Subjects were assigned to a socioeconomic status (SES), in accordance with the new UK National Statistics Socio-Economic Classification measure, as described previously.²⁵ For this study, SES was then grouped into manual and nonmanual workers.

Subjects were also asked in the questionnaire about current disease status and whether they had ever been diagnosed as having any of the following conditions: heart disease, heart attack, stroke, diabetes mellitus (type 1 or 2), osteoarthritis (of the hip or knee), Parkinson disease, or cancer (skin, breast, or colon). This information enabled us to assess whether any difference in LTL between active and inactive subjects was because of a greater prevalence of chronic disease in inactive subjects.

The female sample was stratified into 2 subsets (those <50 and those ≥50 years) that served as proxies for menopausal sta-

tus because full accurate data were unavailable because of hormone therapy use and hysterectomies. The age of 50 years is the median age of menopause in these twins, as used previously.²⁶

A venous blood sample was taken from each twin following an overnight fast from midnight. DNA was extracted from isolated leukocytes. The mean of the terminal restriction fragment length was used as a measure of LTL. The terminal restriction fragment length was measured in duplicate using the Southern blot method, as described previously.¹¹ The laboratory conducting the terminal restriction fragment length measurements was blinded to all characteristics of the leukocyte donors, who were identifiable only by coded identification numbers.

STATISTICAL ANALYSIS

Standard multiple linear regression techniques were used to correlate continuous variables. The relationship between physical activity level (categorical variable) and other continuous variables was measured using a nonparametric test for trend. Unpaired 2-tailed *t* tests were used to test for differences in LTL within dichotomous variables (smoking and SES). χ^2 Tests were performed to test for physical activity level differences within dichotomous variables (smoking and SES). A test for difference of proportions was performed to look for disease status differences between active and inactive groups. Leukocyte telomere length was adjusted for age, sex, smoking status, BMI, and SES (to account for the contribution of risk factors that have been shown to relate to LTL^{20,25,27}), physical activity at work, and year of DNA extraction for LTL measurements to account for batch effects. In all analyses, the clustering of twins within pairs was taken into account and the level of significance was fixed at .05. Stata 8.2 software was used (Statacorp LP, College Station, Texas; <http://www.stata.com>).

DISCORDANT TWIN-PAIR ANALYSIS

As a further confirmation of the larger analysis, we looked at within-twin-pair LTL differences (using a paired 2-tailed *t* test) for 67 twin pairs who were raised together but who are currently discordant for physical activity in leisure time by at least a 2-point difference in physical activity level (ie, 1 vs 3, 1 vs 4, and 2 vs 4, because there were only 2 pairs in the most extreme discordant group [1 vs 4]). The discordant twin pairs comprised 52 dizygotic pairs and 15 monozygotic pairs. This comparison helped to reduce the effect of random genetic and environmental variation on terminal restriction fragment length because monozygotic twins share 100% of their genes, dizygotic twins share 50% of their genes, and both shared near-equal environments as children.

RESULTS

Descriptive statistics of participants (aged 18-81 years), by sex and physical activity level, are presented in the **Table**. Age, sex, and extraction year-adjusted LTL was highly variable and ranged from 4.9 to 9.1 kilobases (kb), with a mean (SD) of 7.0 (0.6) kb. (Age and extraction year-adjusted LTL was 7.0 (0.6) kb in women and 6.8 (0.7) kb in men separately.) The coefficient of variance of the telomere assay in this study was 1.5%. Leukocyte telomere length decreased with age, with a mean (SE) loss of 21.0 (1.3) nucleotides (nt) per year, and a significant negative correlation was detected ($r = -0.38$, $P < .001$).

In a subsample of individuals who had full information on more in-depth assessments, including current lei-

Table. Descriptive Statistics of the Sample by Sex and Physical Activity Level in Leisure Time^a

Characteristic	Total Sample (N = 2401)	Sex		Physical Activity Level			
		Females (n = 2152)	Males (n = 249)	Inactive (n = 104)	Light Activity (n = 924)	Moderate Activity (n = 1222)	Heavy Activity (n = 151)
Age, sex, and extraction year-adjusted LTL, kb	7.0 (0.6)	7.0 (0.6)	7.0 (0.7)	6.9 (0.6)	6.9 (0.6)	7.0 (0.6)	7.1 (0.7)
Age, y	48.8 (12.9)	48.6 (12.8)	48.3 (13.7)	47.0 (12.9)	48.5 (12.4)	49.0 (13.0)	47.1 (14.1)
BMI	25.9 (5.5)	25.7 (5.5)	27.4 (5.5)	28.4 (8.0)	26.6 (5.9)	25.3 (4.9)	24.7 (4.9)
Current smoker, %	15.3	14.9	19.8	23.3	17.8	13.6	10.2
Manual worker, %	20.4	20.8	14.6	29.2	22.4	17.9	21.7

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); kb, kilobases; LTL, leukocyte telomere length.
^aData are given as mean (SD) unless otherwise indicated.

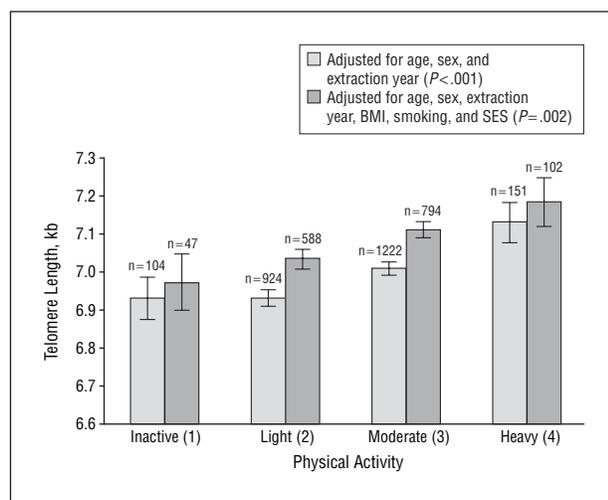


Figure 1. Mean telomere length and standard error bars by physical activity level in leisure time. See the "Methods" section for an explanation of the activity levels. BMI indicates body mass index; kb; kilobases; and SES, socioeconomic status.

sure time, physical activity level (4-point scale) was significantly correlated with time spent in that activity ($P < .001$). The mean time spent in physical activity per week for each physical activity level was as follows: inactive, 16 minutes; light activity, 36 minutes; moderate activity, 102 minutes; and heavy activity, 199 minutes.

Increasing BMI was significantly associated with a decreased physical activity level ($P < .001$), and there was a significant difference in physical activity level between smokers and nonsmokers ($P = .005$) and between manual and nonmanual workers ($P = .05$). There was no significant relationship between age and physical activity level ($P = .69$). Increasing BMI ($P = .001$), being a smoker ($P = .01$), and being a manual worker ($P = .02$) were also significantly associated with a shorter age-adjusted LTL.

Figure 1 shows the mean adjusted LTL for each current physical activity level in leisure time. There was a significant positive association of LTL (adjusted for age, sex, and year of extraction) with increasing leisure time physical activity level ($P < .001$). The same trend between LTL (adjusted for age, sex, and year of extraction) and physical activity level was found separately in men ($P = .27$) and women ($P < .001$). However, there was probably insufficient power to detect a significant association in men be-

cause of the small sample size ($n = 249$). Subdividing the female sample into 2 age and menopause subgroups still resulted in significant associations between age-adjusted LTL and physical activity level for subjects younger than 50 years ($P < .001$) and for those 50 years and older ($P = .04$). After further adjustment for BMI, smoking, and SES, in a subsample of individuals who had full information on these variables ($n = 1531$), the association for the whole sample remained significant ($P = .002$). Leukocyte telomere length was then additionally adjusted for physical activity at work, and the association between LTL and physical activity in leisure time remained significant ($P < .001$). There was no significant difference in the proportion of current disease status between active (groups 2-4) and inactive (group 1) individuals ($P = .23$).

Age, sex, and extraction year-adjusted LTL of the most active subjects (group 4) was on average 200 (SE, 79) nt longer than that of the inactive subjects (group 1) ($P = .006$). This difference was increased to 213 nt after further adjustment for BMI, smoking, and SES in a subsample of individuals who had full information on these variables ($P = .02$). A similar result was found when examining physical activity levels of individuals in the past. Age, sex, and extraction year-adjusted LTL of the most active subjects (> 6 hours of activity per week during subjects' 20s) was on average 151 (SE, 53) nt longer than that of the inactive subjects (no time spent in activity in subjects' 20s) ($P = .002$). This difference was relatively unchanged at 150 nt, after further adjustment for BMI, smoking, and SES ($P = .009$).

Leukocyte telomere length has been shown to be heritable, ranging from 36% to 78%.^{10,28} To check the consistency of the main analysis and to partly adjust for the influence of genetic, cohort, and shared early life effects, we looked at the difference in LTL within twin pairs discordant for physical activity (≥ 2 -point difference on the physical activity score). Summing the difference between 67 discordant pairs, there was a mean difference in LTL between more active and less active twins of 88 (SE, 46) nt ($P = .03$) (**Figure 2**).

COMMENT

Our key finding is that women and men who were less physically active in their leisure time had a shorter LTL

(adjusted for age, sex, and extraction year) than their more active peers, regardless of the age group. Such a relationship between LTL and physical activity level remained significant after adjustment for BMI, smoking, SES, and physical activity at work. The mean difference in LTL between the most active and least active subjects was 200 nt, which means that the most active subjects had telomeres the same length as sedentary individuals up to 10 years younger, on average. This difference suggests that inactive subjects may be biologically older by 10 years compared with more active subjects. Therefore, individuals who are more sedentary are subjected to factors (other than obesity, smoking, and low SES) that speed up leukocyte telomere erosion. The data suggest that intermittent physical activity specifically in leisure time is beneficial, because adjusting LTL for physical activity at work did not affect the results. Findings in twins discordant for physical activity level in leisure time further support those in the population at large. There was no significant difference in prevalence of reported chronic disease status between more active and less active subjects, showing that the shorter LTL in sedentary subjects could not be explained by differences in disease status leading to reduced physical activity.

Our findings are compatible with previous evidence^{1-4,29} linking regular physical activity with health and decreased risk of aging-related diseases. The relationship between physical activity level in leisure time and LTL suggests that a sedentary lifestyle, low SES, high BMI, and cigarette smoking share metabolic pathways that incrementally affect leukocyte telomere dynamics. The likely culprits that are involved in these metabolic pathways are oxidative stress and inflammation because these 2 processes accelerate the rate of leukocyte telomere attrition.¹⁴

Exercise has been reported to decrease some oxidative stress-related diseases and paradoxically increase oxidative damage.²⁹⁻³¹ Hormesis theory, which suggests that there are beneficial effects of low doses of potentially harmful substances²⁹ (ie, some stress is good for you), is controversial but may be one possible explanation of this apparent paradoxical effect, possibly also because of up-regulation of anti-inflammatory processes.³² Therefore, the longer LTL associated with increased physical activity level may be mediated through an overall diminished burden of oxidative stress and inflammation.

Several recent studies^{25,33-35} support an association between perceived stress levels and telomere length. Therefore, it is plausible that the relationship between leisure time physical activity and LTL may be mediated in part by a reduction in psychological stress levels induced by exercise.

The US guidelines recommend that 30 minutes of moderate-intensity physical activity at least 5 days a week can have significant health benefits.³⁶ Our results underscore the vital importance of these guidelines. They show that adults who partake in regular physical activity are biologically younger than sedentary individuals. This conclusion provides a powerful message that could be used by clinicians to promote the potential antiaging effect of regular exercise.

A limitation of this type of study is that physical activity level was self-reported. Moreover, a large variation in exercise frequency, duration, and intensity probably ex-

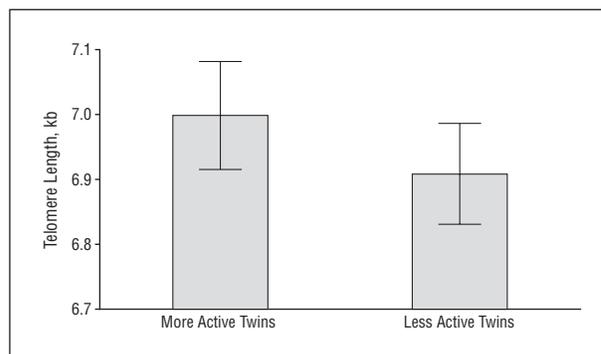


Figure 2. Mean telomere length and standard error bars for physical activity-discordant twin pairs (n=67 pairs). The mean for more active twins was 6.9968; for less active twins, 6.9091. Data were adjusted for age, sex, and extraction year. kb indicates kilobases.

isted within each of the 4 physical activity categories. Operational definitions of regular exercise in leisure time have differed across studies,³⁷ and there is no universal standard of assessment. However, the assessment of physical activity in the present study (4-point scale) was strongly correlated with a more in-depth current assessment of time spent in physical activity, based on the Allied Dunbar National Fitness Survey.²⁴ In addition, large differences in LTL between most active and inactive subjects were present for current and past activity (activity in individual's 20s).

Similar recalled scores have been used in other populations, and good correlations have been shown with aging-related diseases, such as osteoporosis.³⁸ Furthermore, self-reported measures of exercise have been used successfully by other groups. Similar self-reported physical activity measures from 7 countries have been used to assess the genetic contribution to exercise participation.³⁹ Highly comparable heritability estimates were found in all countries (median, 62%). If individuals were misclassified for exercise participation, this would increase the error term and therefore reduce heritability. Accordingly, self-reported measures of physical activity are ostensibly valid. Moreover, the use of the discordant twin analysis helped to minimize the effects of any cultural and environmental or cohort differences that may have led to differences in reporting of physical activity.

For future research, a long-term prospective study monitoring intensity, duration, and frequency of exercise in participants over different periods of life (or monitoring consumption of kilojoules per day) would help in the understanding of the complex relationship and the key periods of life for maximal benefit of exercise.

The results of this study can be extrapolated to other white individuals (men and women) of North European origin because twins have been shown to be comparable to age-matched population singletons in disease and lifestyle factors.²³

In conclusion, physical activity in leisure time affects leukocyte telomere dynamics. An increased physical activity level is associated with longer LTL in white individuals, an effect that cannot be explained by variations in age, sex, genes, smoking, BMI, or SES. These findings underscore the importance of health promotion of regular exercise to retard aging and diminish the risk of aging-related diseases.

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Authors Contributions: Ms Hunkin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Spector and Aviv. *Acquisition of data:* Cherkas, Hunkin, Gardner, Surdulescu, and Kimura. *Analysis and interpretation of data:* Cherkas, Hunkin, Kato, Richards, Surdulescu, Kimura, Lu, Spector, and Aviv. *Drafting of the manuscript:* Hunkin. *Critical revision of the manuscript for important intellectual content:* Cherkas, Kato, Richards, Surdulescu, Kimura, Lu, Spector, and Aviv. *Statistical analysis:* Cherkas, Hunkin, Kato, Richards, and Kimura. *Obtained funding:* Spector and Aviv. *Administrative, technical, and material support:* Gardner, Spector, and Aviv. *Study supervision:* Cherkas, Gardner, Spector, and Aviv.

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