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Title: Effect of Intensive Exercise in Early Adult Life on Telomere Length in Later Life in Men

Year: 2015

Version:

Please cite the original version:

Laine, M. K., Eriksson, J. G., Kujala, U., Raj, R., Kaprio, J., Bäckmand, H. M., Peltonen, M., & Sarna, S. (2015). Effect of Intensive Exercise in Early Adult Life on Telomere Length in Later Life in Men. Journal of Sports Science and Medicine, 14(2), 239-245. http://www.jssm.org/research.php?id=jssm-14-239.xml

©Journal of Sports Science and Medicine (2015) **14,** 239-245
http://www.jssm.org

Research article

Effect of Intensive Exercise in Early Adult Life on Telomere Length in Later Life in Men

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Abstract

A career as an elite-class male athlete seems to improve metabolic heath in later life and is also associated with longer life expectancy. Telomere length is a biomarker of biological cellular ageing and could thus predict morbidity and mortality. The main aim of this study was to assess the association between vigorous elite-class physical activity during young adulthood on later life leukocyte telomere length (LTL). The study participants consist of former male Finnish elite athletes (n = 392) and their age-matched controls (n = 207). Relative telomere length was determined from peripheral blood leukocytes by quantitative real-time polymerase chain reaction. Volume of leisure-time physical activity (LTPA) was self-reported and expressed in metabolic equivalent hours. No significant difference in mean age-adjusted LTL in late life (p = 0.845) was observed when comparing former male elite athletes and their age-matched controls. Current volume of LTPA had no marked influence on mean age-adjusted LTL (p for trend 0.788). LTL was inversely associated with age (p = 0.004).Our study findings suggest that a former elite athlete career is not associated with LTL later in life.

Key words: Aging, athlete, DNA repeats, physical activity.

Introduction

Physical activity has a positive influence on health and general well-being and it has been associated with increased longevity, better physical functioning and self-rated heath in older age (Backmand et al., 2010; Cherkas et al., 2008; Kettunen et al., 2014; Warburton et al., 2006). A career as an elite-class athlete during young adulthood seems to improve metabolic heath and reduce coronary heart disease in later life (Kujala et al., 2013; Laine et al., 2014; Kujala et al., 2013; Sarna et al., 1997).

Telomeres consist of DNA repeats and associated proteins located at the ends of the chromosomes (Blackburn et al., 2006; de Lange, 2005). Telomeres play an important role in maintaining genomic stability and regulating cellular replicative capacity (Allsopp et al., 1992; Blackburn et al., 2006). Telomere length is heritable, and length declines with increasing age (Njajou et al., 2012; Nordfjall et al., 2005; Shammas, 2011). Especially in early life, the impact of inheritance on telomere length is strong, but it seems to diminish by age (Svenson et al., 2011). Shorter telomeres have been associated with increased incidence of several chronic non-communicable diseases and with shorter life span (Ludlow and Roth 2011; Shammas, 2011; Salpea and Humphries, 2010; Wong and Collins 2003). Several factors including smoking, obesity and an unhealthy diet, all conditions associated with an increase in oxidative stress and inflammation, have been linked with telomere shortening (Crous-Bou et al., 2014; Ornish et al., 2013; Shammas, 2011; Tiainen et al., 2012; Woo et al., 2010;). It is believed that telomere length could be a biomarker of biological cellular age and thus predicts morbidity and mortality (Bojesen, 2013; Woo et al., 2014; von Zglinicki and Martin-Ruiz, 2005).

Few studies have investigated the association between exercise training and leukocyte telomere length (LTL) with inconsistent results: positive, none and inverted U-shaped associations have been described (Du et al., 2012; Savela et al. 2013; Woo et al., 2008). Interestingly, a U-shaped relationship has been observed in both sedentary and extremely active individuals (Ludlow et al., 2013). Most commonly moderate levels of physical activity have been associated with longer LTL (Kim et al., 2012; Mirabello et al., 2009).

In Finland, a questionnaire-based study focusing upon former male elite athletes and their age -matched controls was initiated in 1985 (repeated 1995 and 2005). Twenty-three years later in 2008 clinical examinations including a physical examination and laboratory tests were performed.

We could not identify any previous studies that have evaluated the association of long-term influence of vigorous elite-class physical activity during young adulthood on later life LTL.

We hypothesized that the male former elite athletes having a history of vigorous physical activity during

Received: 26 November 2014 / Accepted: 20 January 2015 / Published (online): 01 June 2015

young adulthood have longer LTL than the controls later in life thus explaining the former athletes' better metabolic health and longer life expectancy (Kettunen et al., 2014; Laine et al., 2014).

Methods

Study subjects

A detailed description of the study design and participants has been published previously (Laine et al., 2014). Briefly, in Finland in the year 1985 a questionnaire-based study was initiated including former male elite athletes and their age- and area-matched healthy controls. Former elite male athletes consist of those who had represented Finland in major international competitions between 1920 and 1965. They were divided into three groups: endurance sports (long and middle distance running, cross country skiing), mixed sports (soccer, ice hockey, basketball, track and field: jumpers, sprinters, hurdlers, decathletes) and power sports (boxing, wrestling, weight lifting, track and field throwers). The division was made according to the type of training needed to achieve optimal results. In 2008, an invitation to a clinical study was sent to those alive, whom had answered at least once to the previous questionnaires sent in 1985, 1995 or 2001 (n = 1183). All together 599 men participated (392 former athletes and 207 controls) and they composed the present study cohort. Compared with the controls, the former athletes have longer life expectancy, lower cancer incidence, and better metabolic health (Laine et al., 2014; Kettunen et al., 2014; Sormunen et al., 2014).

The ethics committee of the Hospital District of Helsinki and Uusimaa approved the study, and all subjects have provided written informed consent.

The clinical examinations

Trained study nurses performed the physical examinations including assessment of height, weight and blood pressure (BP) as well as taking the blood samples.

Height was measured without shoes by a measuring tape against a wall to an accuracy of 0.1 cm. Weight was measured in light indoor clothing by a body composition device (InBody 3.0, Biospace, Seoul, Korea) to an accuracy of 0.1 kg. If the participant had a pacemaker (n = 14), weight was measured by a digital scale with the same accuracy. BMI was calculated as weight (kg) divided by height squared (m2). Plasma high sensitive C-reactive protein was measured by latex immunoturbidometric method (Sentinel Diagnostics, Milan, Italy).

Leukocyte telomere length measurement

Leukocyte telomere length was measured from DNA extracted from peripheral blood. We used a quantitative polymerase chain reaction (qPCR) -based method (Cawthon 2002), as described previously (Eerola et al., 2010; Kananen et al., 2010; Kao et al., 2008). We used β-hemoglobin (Hgb) as a single copy reference gene. Separate reactions for telomere and Hgb reaction were carried out in paired 384-well plates in which matched sample well positions were used. Ten nanograms of DNA were used for each reaction, performed in triplicate. Every plate included a 7-point standard curve, which was used to create a standard curve and to perform absolute quantification of each sample. Samples and standard dilutions were transferred into the plates using a DNA Hydra 96 robot and dried overnight at +37oC. Specific reaction mix for telomere reaction included 270 nM tel1b primer (5´-CGGTTT(GTTTGG)5GTT-3´) and 900 nM tel2b primer (5´-GGCTTG(CCTTAC)5CCT-3´), 150 nM ROX (Invitrogen), 0.2X SYBR Green I (Invitrogen), 5 mM DTT (Sigma-Aldrich), 1% DMSO (Sigma-Aldrich), 0.2 mM of each dNTP (Fermentas), and 1.25 U AmpliTaq Gold DNA polymerase (Applied Biosystems) in a total volume of 15 µl AmpliTaq Gold Buffer I. Hgb reaction mix included 300 nM Hgb1 primer (5´-GCTTCTGACACAACTGTGTTCACTAGC-3´) and Hgb2 primer (5´-CACCAACTTCATCCACGTTCACC-3´) in a total volume of 15 µl of iQ SyBrGreen supermix (BioRad). The cycling conditions for telomere amplification were: 10 minutes at 95 °C followed by 25 cycles at 95 °C for 15 s and 54°C for 2 min with signal acquisition. The cycling conditions for Hgb amplification were: 95 °C for 10 min followed by 35 cycles at 95 °C for 15 s, 58 °C for 20 s, 72 °C for 20 s with signal acquisition. Reactions were performed with CFX384 Real-Time PCR Detection System (Bio-Rad). Melt-curve analysis was carried out in the end of the run to ensure specific primer binding.

We used the Bio-Rad CFX Manager software to perform quality control, and samples with standard deviation of >0.5 between triplicates were omitted from the analysis. Five control samples analyzed on each plate were used for calculating the coefficient of variation, which was 7.14%. Thirteen participants had missing data of LTL.

Assessment of life-style factors

Information on smoking status, consumption of alcohol, educational attainment and marital status were self-reported and obtained from structured questionnaires. There were missing data from nine participants regarding smoking habits, for 32 participants on alcohol consumption, for four participants on educational attainment and for one participant about marital status. Participants were classified as smokers if they reported having smoked over 100 cigarettes in their lifetime and still smoked daily or almost daily at least one cigarette or quit smoking less than six months ago.

Assessment of leisure-time physical activity

Leisure-time physical activity (LTPA) was assessed by a questionnaire that included information about average intensity, duration and frequency of the activity during the previous three months. Intensity of LTPA was asked by the following question "Is your physical activity during leisure time about as tiring (intensive) on average as? 1 = walking (4 metabolic equivalent [MET]), 2 = walking and jogging alternately (6 MET), 3 = jogging (10 MET), 4 = running (13 MET)". Duration of LTPA was asked by the question "What is the mean duration of your average physical exercise session? 1 = < 15 minutes, 2 = 15-29 minutes, 3 = 30-59 minutes, 4 = 1-2 hours, 5= > 2 hours". Frequency of LTPA was asked by the question "How

many times per month you do participate in physical exercise? 1 = < once a month, 2 = 1-2 times/month, 3 = 3-5 times/month, 4 = 6-10 times/month, 5 = 11-19 time/month, 6 = > 20 times/month". For each of intensity category a metabolic equivalent value (MET-value, 1 MET = 3.5 ml O2/kg/min or 1 kcal/kg/h) was determined. The volume of LTPA was expressed in MET-hours, which was calculated by multiplying the intensity (MET), duration and frequency. This method has been validated against detailed physical activity interview (Waller et al., 2008). Fifteen participants had missing data of LTPA.

Statistical analyses

Data has been reported as means ± standard deviations (SD). Percentage differences were tested using cross-tabulation and Chi-Square test. Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction. Correlation was assesses with the Pearson contingency coefficient for continuous variables and with the Lambda contingency coefficient for classified variables. Adjusting with other variables was done by general linear model. Statistical analyses were carried out using IBM SPSS version 21.0 (IBM Ltd, Armonk, New York, USA). P-values <0.05 were considered statistically significant.

Results

Baseline characteristics

The former athletes were older (p = 0.024) and less likely to be smokers (p = 0.014) than the controls (Table 1). No significant difference was observed in BMI (p = 0.285), but age-adjusted fat free mass was significantly higher among the former athletes compared to the controls (p < 0.001, Table 1). The former athletes' current volume of LTPA was significantly higher than that of the controls (p < 0.001, Table 1).

Leukocyte telomere length

Age was inversely associated with LTL (r = -0.119, p = 0.004), no significant associations were observed with the other assessed covariates: fat free mass (r = 0.028, p = 0.511), LTPA (r = 0.058, p = 0.164), smoking (r = 0.015, p = 0.936), alcohol intake (r = 0.005, p = 0.897), high sensitive C-reactive protein (r = -0.007, p=0.859), educational attainment (r = 0.018, p=0.453), and marital status (r = 0.026, p = 0.148). There were no significant differences in mean age-adjusted LTL between the athlete and control groups (p = 0.845, Table 1). Further adjusting for other covariates had only minimal influence on the results (Table 1). There were no significant differences in LTL between the different athlete groups (three group ANOVA p=1.000, data not shown). Participants' current volume of LTPA was not associated with mean age-adjusted LTL (Figure 1; for LTPA categories the p for trend 0.788, Table 2).

Discussion

Our findings of the present study suggest that a former career as an elite-class athlete during young adulthood did not influence mean age-adjusted LTL in later life. Neither did the participants' current volume of LTPA show a significant association with mean age-adjusted LTL. However, as expected participants' age was inversely associated with LTL.

Table 1. Age, smoking, BMI, fat free mass, LTPA and leukocyte telomere length distribution among former athletes and their controls in the clinical study in 2008.

	Endurance n=64	Mixed n=221	Power n=107	All athletes n=392	Controls n=207
Mean age (SD), years	75.3 (5.5)	71.9 (6.0)	72.8 (6.2)	72.7 (6.1)	71.6 (5.6)
p-value	<.001	1.000	.246	.024	
n	64	221	107	392	207
Smokers % (n)	3.1 (2)	6.8 (15)	2.9 (3)	5.1 (20)	10.4 (21)
p-value	.153	.363	.039	.014	
n	64	221	104	389	201
Mean BMI kg/m2 (SD)	25.0 (3.3)	26.1 (3.3)	28.2 (4.7)	26.5 (3.9)	26.8 (3.4)
p-value	<.001	.090	.003	.285	
n	64	221	107	392	207
Mean age-adjusted fat free mass (SD)	57.3 (5.4)	62.3 (6.5)	61.8 (10.9)	61.4 (8.1)	59.4 (6.0)
p-value	.624	<.001	.003	<.001	
n	57	214	104	376	205
Mean age-adjusted LTPA (SD), METh/wk , p-value	42.8 (36.6) <.001	31.0 (27.3) <.001	25.2 (23.2) .252	31.4 (28.5) <.001	20.5(21.7)
n	62	219	102	383	201
Mean LTL (SD)	.77 (.13)	.78 (.14)	.77 (.12)	.77 (0.13)	.78 (.13)
p-value	1.000	1.000	1.000	.666	
Age-adjusted p-value	1.000	1.000	1.000	.845	205
n	62	215	104	381	
Covariate-adjusted p-value	1.000	1.000	1.000	.721	183
n	50	195	86	331	

Percentage differences were tested using cross-tabulation and Chi-Square test. Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction. Adjusting with other variables was done by general linear model. endurance = long and middle distance running, cross country skiing; mixed = soccer, ice hockey, basketball, track and field: jumpers, sprinters, hurdles, decathletes; power = boxing, wrestling, weight lifting, track and field throwers; BMI = body mass index; LTPA = leisure time physical activity; METh/wk = metabolic equivalent-hours/week; LTL = leukocyte telomere length. Covariate-adjusted for age, fat free mass, LTPA, smoking, alcohol intake, high sensitive C-reactive protein, educational attainment and marital status. p-values are compared to controls.

Table 2. The distribution of age, smoking habits, BMI, fat free mass and leukocyte telomere length among participants classified by current volume of LTPA in the clinical study 2008.

	MET I (n=144)	MET II (n=92)	MET III (n=130)	MET IV (n=129)	MET V (n=89)	p-value for trend (MET I-V)
Mean age (SD), years	73.3 (5.7)	72.7 (5.7)	72.2 (6.1)	71.7 (5.6)	70.6 (5.3)	
p-value		1.000	.464	.064	<.001	.006
n	144	92	130	129	89	584
Smokers % (n)	8.6 (12)	6.5 (6)	6.3 (8)	7.9 (10)	4.5 (4)	
p-value		1.000	1.000	1.000	.748	.802
n	140	92	128	127	88	575
Mean BMI, kg/m2 (SD)	27.7 (4.3)	26.9 (3.4)	26.6 (3.4)	25.8 (3.4)	25.5 (2.9)	
p-value		.296	.040	<.001	<.001	<.001
n	144	92	130	129	89	584
Mean fat free mass (SD)	61.1 (7.4)	60.3 (6.9)	60.8 (7.5)	60.5 (8.0)	60.4 (5.7)	
Age-adjusted p-value		1.000	1.000	.636	.428	.506
n	141	91	126	124	87	569
Mean LTL (SD)	.77 (.14)	.78 (0.13)	.78 (.13)	.77 (.12)	.80 (.13)	
p-value		1.000	1.000	1.000	.556	.652
Age-adjusted p-value		1.000	1.000	1.000	1.000	.788
n	139	89	127	129	87	571
Covariate-adjusted p-value		1.000	1.000	1.000	.772	.667
n	126	81	110	116	81	514

Percentage differences were tested using cross-tabulation and Chi-Square test. Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction. Ad. justing with other variables was done by general linear model. BMI = body mass index; MET = metabolic equivalent; LTL = leukocyte telomere length. MET I < 6 METh/week; MET II 6.1-12.0 METh/week; MET III 12.1-22.5 METh/week; MET IV 22.6-45.0 METh/wk; MET V > 45.1 METh/week. p-values are compared to MET I group.Covariate-adjusted for age, fat free mass, smoking, alcohol intake, high sensitive C-reactive protein, educational attainment and marital status.

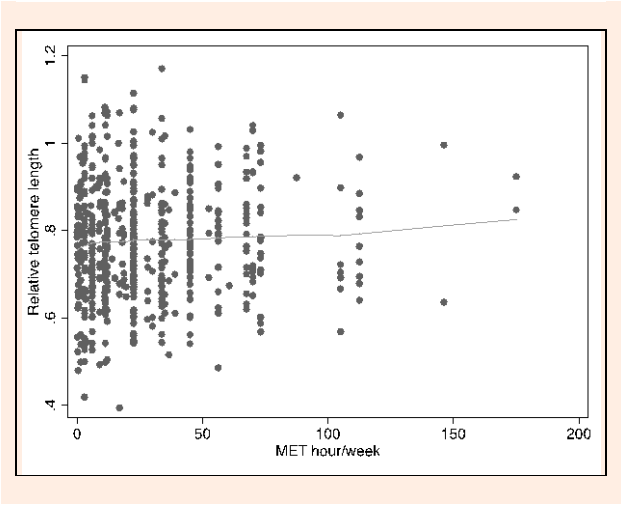

Figure 1. Scatter plot and lowess regression line for relative leukocyte telomere length by MET hours per week.

Reports on the association between physical exercise and LTL have been inconsistent in previous studies (Ludlow et al., 2013). The former male athletes in our study had a history of vigorous exercise training during young adulthood. This is, however, a time period when only minor influence on LTL is expected by exercise training (LaRocca et al., 2010). In later life, current volume of LTPA seems to show no association with LTL supporting the results of a large Chinese study with participants from the same age-group (Woo et al., 2008). However, our results are contrary to a few studies with participants from the same age-group showing a positive association or an inverted U relationship with physical activity in later life or in midlife and LTL (Krauss et al., 2011; LaRocca et al., 2010; Ludlow et al., 2008; Savela et al., 2013).

The underlying mechanisms by which physical activity affects telomere length and the reasons for the different findings between studies are not clear. Oxidative stress, expression of telomere stabilizing proteins, growth- and stress-related hormones and their associated pathways have been suggested to play important roles (Carrero et al., 2008; Cherkas et al., 2008; Ludlow and Roth 2011; Shammas, 2011). Short-term exercise training has not been shown to be associated with LTL, but it modulates telomere-regulating proteins (Werner et al., 2008). Thus, it seems like long-term or more strenuous exercise training is required in order to influence LTL (LaRocca et al., 2010; Ludlow et al., 2013). Moreover, methods used for telomere length determination, cell types used for DNA extraction, the various ages of the individuals in the study cohorts, small study samples as well as variation in collection of exercise and physical activity data likely explain the discrepancies in results (Ludlow et al., 2013).

In most studies evaluating the association between physical exercise and telomere length the mode of exercise has been endurance or aerobic-type training giving a positive (Cherkas et al., 2008; Du et al., 2012; LaRocca et al., 2010), none (Mathur et al., 2013; Woo et al., 2008) or inverted U-shaped association (Collins et al., 2003; Savela et al., 2013). Little is known about the association between resistance training and telomere length. Probably, there is no association between long-term resistance training and telomere length, however negative associations between heavy-resistance training and telomere length has been described when telomeres are measured from skeletal muscles (Kadi et al., 2008).

Generally, oxidative stress and inflammation are both known to cause accelerated telomere shortening (von Zglinicki, 2002). With smoking, a significant dose-dependent relationship has been observed; each pack-year smoked was equivalent to an additional 5 base pairs of telomere length lost (Valdes et al., 2005). Obesity also

increases oxidative stress and inflammation providing a link with accelerated telomere loss (Valdes et al., 2005; Shammas, 2011). Healthy dietary patterns like Mediterranean diet have been shown to be associated with longer LTL (Crous-Bou et al., 2014). Furthermore, depression, psychological stress, poor sleep quality and low educational attainment have all been linked with shorter LTL (Hartmann et al., 2010; Needham et al., 2013; Ornish et al., 2013; Prather et al., 2011).

We acknowledge some limitations to our study. LTL was measured only once and in this study in later life. Thus, with this cross-sectional study design is not possible to estimate the telomere attrition rate, which is thought to be better biomarker of biological cellular aging than once measured telomere length (Nilsson, 2014). Further our data is restricted to only survivors. Later life LTPA as well as other life-style factors were self-reported. Self-reported measures of LTPA have been reported to be both higher and lower than directly measured, but on average, the validity and reliability of questionnaires are better in groups than in individuals (Haskell, 2012; Prince et al., 2008; Wilson et al., 1986). Furthermore, information on long-term dietary habits of the participants was not available; this area should be focused upon in future research. Finally, all our study participants were men and of European ancestry which might influence the generalizability of the results.

Conclusion

In conclusion, we did not observe any significant differences between former male elite athletes and their matched controls in regard to LTL in late life. Neither did the participants' current volume of LTPA associate with mean LTL.

Acknowledgments

The study was funded by the Ministry of Education and Culture, the Juho Vainio Foundation, the Finnish Heart Research Foundation, Paavo Nurmi Foundation, the Finnish Cultural Foundation, and by a grant from Medical Society of Finland, Finska Läkaresällskapet. We would like to thank National Institute for Health and Welfare, Department of Public Health, University of Helsinki, Sports & Exercise Medicine Department of Health Sciences, University of Jyväskylä, Paavo Nurmi Centre, Turku and ORTON Research Institute, Invalid Foundation, Helsinki for collaboration during the large epidemiological and clinical research program in the year 2008. We would like to thank Iiris Hovatta (Research Programs Unit - Molecular Neurology, Biomedicum Helsinki, University of Helsinki, Finland; Department of Biosciences, Viikki Biocenter, University of Helsinki, Finland; Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland) and Laura Kananen (Research Programs Unit - Molecular Neurology, Biomedicum Helsinki, University of Helsinki, Finland) for measuring the leukocyte telomere length.

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Key points

- A career as an elite-class athlete is associated with improved metabolic health in late life and is associated with longer life expectancy.
- A career as an elite-class athlete during young adulthood was not associated with leukocyte telomere length in later life.
- Current volume of leisure-time physical activity did not influence telomere length in later life.

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