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REVIEW ARTICLE

EFFECT OF DIFFERENT LEVELS OF EXERCISE ON TELOMERE LENGTH: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: **To investigate the effect of different levels of exercise on telomere length.**
Methods: **CINAHL, SPORTDiscus (EBSCO), OVID (Medline) and EMBASE databases were searched for eligible studies. Methodological quality was evaluated using the Newcastle-Ottawa Scale, and heterogeneity among the studies was assessed using the I-squared test. When heterogeneity among studies was high ($I^2 > 50\%$), a random-effects model was used (Review Manager version 5, Cochrane Collaboration, Copenhagen, Denmark); otherwise, a fixed-effects model was used.**
Results: **Eleven eligible studies involving 19,292 participants were included in this meta-analysis. Longer telomere length was associated with physically active individuals, with a mean difference (MD) of 0.15 (95% confidence interval; 95% CI 0.05, 0.24); $I^2 = 99\%$. Longer telomere length was significantly associated with robust exercise (MD 0.08 (95% CI 0.04, 0.12)); $I^2 = 99\%$, as was moderate exercise (MD 0.07 (95% CI 0.03, 0.11)); $I^2 = 100\%$. Subgroup analysis revealed that longer telomere length was positively associated with exercise, regardless of sex, but was not statistically significant in elderly populations.**
Conclusion: **Compared with inactive individuals, telomere lengths were longer in active subjects, regardless of the intensity of exercise.**

Key words: exercise; telomere length; meta-analysis.

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Telomeres are special structures located at the end of human eukaryotic chromosomes that help maintain chromosomal stability and integrity (1, 2). Telomerase is a critical ribonucleoprotein enzyme that synthesizes G-rich repeats to maintain telomere length (3), but is suppressed in most mammalian somatic cells. As a result, 25–200 base-pair pieces are removed from chromosomal termini with each round of cell division (4). Therefore, many studies investigating ageing regard telomere length as an important biomarker. In addition, many age-related diseases, including diabetes, dementia and chronic psychiatric disorders, have been found to be significantly associated with shortened telomere length (5–7).

LAY ABSTRACT

Telomeres are structures found at the end of human chromosomes that help to protect the chromosome. Telomeres become shorter with ageing and age-related diseases. This study investigated the effect of different levels of exercise on telomere length. Research databases were searched for relevant studies and these were checked for eligibility. Studies included in this meta-analysis were analysed for heterogeneity, using the random-effects or fixed-effects models. Longer telomere length was found to be associated with physically active individuals, and significantly associated with robust and moderate exercise. Subgroup analysis revealed that longer telomere length was positively associated with exercise, regardless of the person's sex, but this was not statistically significant in elderly populations. In conclusion, compared with inactive individuals, people who were active had longer telomere lengths, regardless of the intensity of exercise.

Exercise has been shown to decrease the incidence of morbidity and mortality in individuals with age-related diseases (8, 9). For example, aerobic exercise contributes to higher aerobic cardiovascular fitness, which is closely related to good health and lengthened telomeres (10). In addition, resistance exercise and yoga have been found to have a positive effect on survival and telomere length (11). The proposed potential mechanisms include reduced oxidative stress and reduced systemic inflammation (12, 13). However, the results of existing studies investigating whether telomeres are longer in active individuals are contradictory. Some studies have reported that physical activity is not associated with longer telomeres in leukocytes and muscle cells (13–15).

The current study therefore aimed to evaluate the effect of different intensities and types of exercise on telomere length through a literature search and meta-analysis.

METHODS

Search strategy

This study was performed according to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) checklist. CINAHL, SPORTDiscus (EBSCO), OVID (Medline) and EMBASE databases were searched to retrieve potentially eligible studies in April 2017; the search was updated in November 2017.

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Different combinations of key words and subject terms were used, including: [('exercise') or ('physical fitness') or ('exercise tolerance') or ('physical endurance') or ('sports') or ('dancing') or ('yoga')] and [('telomere')]. References to relevant reviews and included studies were also searched manually to screen for additional, potentially eligible, studies. The full search strategy using the 4 databases is shown in Appendix S1[1].

Eligibility and exclusion criteria

Observational studies fulfilling the following criteria were included in the systematic review and meta-analysis: (*i*) study investigated the relationship between exercise and telomere length; (*ii*) study reported telomere length as mean (standard deviation; SD) or median (interquartile range; IQR); and (*iii*) sample size >100. Studies with insufficient data, conference abstracts or reviews, and articles not published in English were excluded (see Appendix S1[1]).

Study selection

The titles and abstracts of all the studies were independently examined by 2 of the authors (XL and JZ). Disagreements between the reviewers were resolved by discussion and re-examination until a consensus was reached.

Data extraction and risk of bias assessment

Data extraction from the eligible studies was performed independently by 2 of the authors (XL and JZ). However, when data in potentially eligible original studies were lacking, the authors of these studies were contacted by e-mail to obtain information regarding mean (SD) values of telomere length. Methodological quality was evaluated using the Newcastle-Ottawa Scale (NOS) (12). The quality of the included studies was assessed according to 3 variables: (*i*) selection; (*ii*) comparability; and (*iii*) exposure/outcome, with a total score ranging from 0 to 9. The quality assessment was independently conducted by 2 reviewers, and disagreements were resolved through discussion and re-examination.

Statistical analysis

The aim of the current study was to investigate the relationship between physical exercise and telomere length. Heterogeneity among the studies was assessed using the *I*-squared test. When heterogeneity among studies was high (I^2>50%), a random-effects model was used (Review Manager version 5, Foundation for Statistical Computing, Vienna, Austria); otherwise, a fixed-effects model was used. Subgroup analyses were performed to analyse the source of heterogeneity, and according to country, sex, age, study type, tissue source, and type of exercise.

RESULTS

Search results

A total of 6,763 relevant articles were retrieved using the search strategy (Appendix S1[1]), of which 4,112 remained after removal of duplicates. Seventy-one studies were considered potentially eligible when title and abstract were screened, of which 60 were excluded due to a sample size <100 (n=10), 25 that did not provide mean (SD) telomere length, and 25 were either conference abstracts or review articles. A final total of 11 studies were included in the analysis (Fig. 1), including 1 cross-sectional, 7 case-control, and 3 cohort studies (Table I) (16–26).

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2560

Table I. Characteristics of studies examining the association between telomere length and exercise

Author (ref.)	Year	Country	Exercise	Design	Male, %	Sample number	Age, years	Tissue	Method of evaluation of telomeres	Quality* assessment
Mason et al. (16)	2013	USA	>3.55 MET-h/week	Cohort study	0	202	50–75	Leukocyte	PCR/TS ratio	8
Cherkas et al. (17)	2008	England	Self-reported moderate or robust activity	Case-control study	11.6	1,477	18–81	Leukocytes	TRF	7
Woo et al. (18)	2008	Hong Kong	Robust: PASE Score >112.89 Moderate: 61.04 <PASE Score <112.88	Case-control study	48.7	1,999	≥65	Leukocytes	TRF	8
Krauss et al. (19)	2011	USA	Robust: >7 METS Moderate: >5–7 METS	Cross-sectional study	83.3	944	66.7±10.7	Leukocyte	PCR/TS ratio	8
Denham et al. (20)	2013	Australia	Ultra-marathon runners	Case-control study	100	124	43.6±9.2	PBMC	PCR/TS ratio	7
Sun et al. (21)	2012	USA	Robust: >2.5 MET-h/week Moderate: 1–1.5 MET-h/week	Case-control study	0	4,141	30–55	Leukocyte	PCR/TS ratio	8
Garland et al. (22)	2014	USA	Self-reported moderate or robust activity	Case-control study	0	392	61.97±10.36	Leukocytes	TRF	8
Laine et al. (23)	2015	Finland	Robust: >22.6–45.0 MET-h/week Moderate: >6.1–22.5 MET-h/week	Case-control study	100	599	72.3±6.0	Leukocyte	PCR/TS ratio	8
Tucker et al. (24)	2017	USA	Robust: >16.67 MET-h/week Moderate: >8.33–16.67 MET-h/week	Case-control study	47.9	5,025	20–84	Leukocytes	PCR/TS ratio	8
Shadyab et al. (25)	2017	USA	Robust: ≥17.00 MET-h/week Moderate: 1.25–17.00 MET-h/week	Cohort study	0	1,476	50–79	Leukocytes	Southern blot	8
Savela et al. (26)	2012	Finland	Physical activity determined by a 4-step scale	Cohort study	100	2,913	47.9±4.1	Leukocytes	TRF	7

PBMC: peripheral blood mononuclear cell; qPCR: real-time quantitative PCR detecting system; TRF: terminal restriction fragment; T/S ratio: telomere (T), single copy gene (S) ratio T/S; IPAQ: International Physical Activity Questionnaire; PACE: Physical Activity Scale for the Elderly; MET: metabolic equivalent tasks.

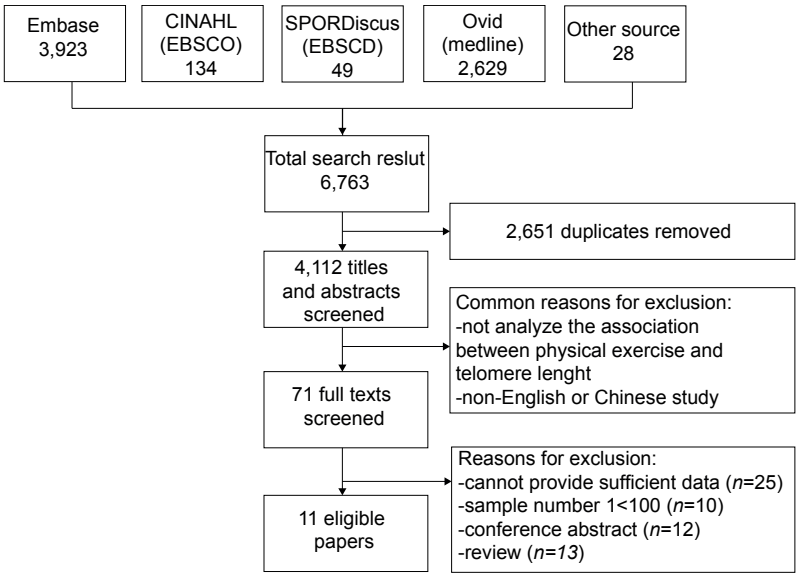

Fig. 1. Search results and study selection.

Included studies

The characteristics of the included studies, involving 19,292 participants, are summarized in Table I. Telomere length in these studies was determined using quantitative polymerase chain reaction (q-PCR), telomere restriction fragment (TRF) methodology, and Southern blot using leukocytes and peripheral blood mononuclear cells. Quality evaluation revealed that one study achieved the maximum score of 9, while the score for the remainder of the studies was >7. The definition of moderate and robust physical exercise in the included studies varied. The intensity of robust exercise was defined as >2.5 metabolic equivalent tasks (MET) h/week, while the definition of moderate exercise ranged from 1 to 22.5 MET h/week.

Pooled results

Active individuals were significantly associated with longer telomere length, with a mean difference (MD) of 0.15; 95% CI 0.05, 0.24; I^2=99%)(Fig. 2). Analysis also revealed that both robust and moderate exercise could significantly increase telomere length (MD 0.08; 95% CI 0.04, 0.12; I^2=99% (Fig. 3) and MD 0.07; 95% CI 0.03, 0.11; I^2=100% (Fig. 4), respectively. Details of the subgroup analysis are summarized in Table SI. The subgroup analysis demonstrated that longer telomere length was not found in individuals who engaged in aerobic exercise (MD 0.07; 95% CI –0.02, 0.17; p=0.14).

In addition, longer telomere length was positively correlated with exercise in both sexes (MD 0.11; 95% CI 0.02, 0.21; p=0.02 for males; MD 0.20; 95% CI 0.02, 0.37; p=0.03 for females). Longer telomere length was also found in individuals <65 years of age (MD 0.25; 95% CI 0.09, 0.40; p=0.002), but not in elderly individuals (MD 0.11; 95% CI –0.09, 0.31; p=0. 27). Subgroup analysis also demonstrated a positive relationship in all tissue sources and study types. However, longer telomere length was not significant in active people of European descent (MD 0.07; 95% CI –0.01, 0.16; p=0.09), or in the PCR group (MD 0.12; 95% CI –0.01, 0.25; p=0.07).

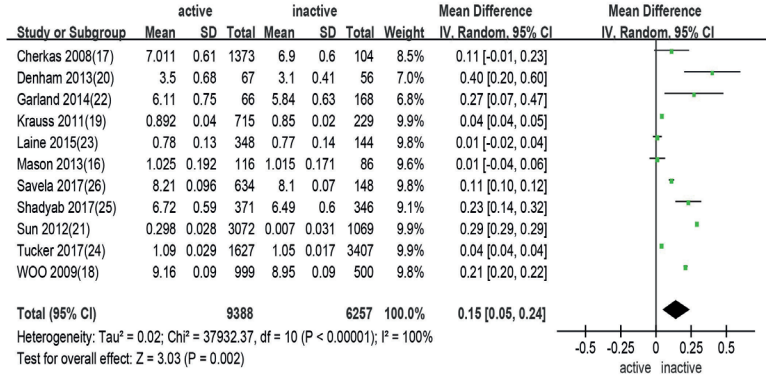

Fig. 2. Meta-analysis of the association between telomere length and exercise. 95% CI: 95% confidence interval; SD: standard deviation.

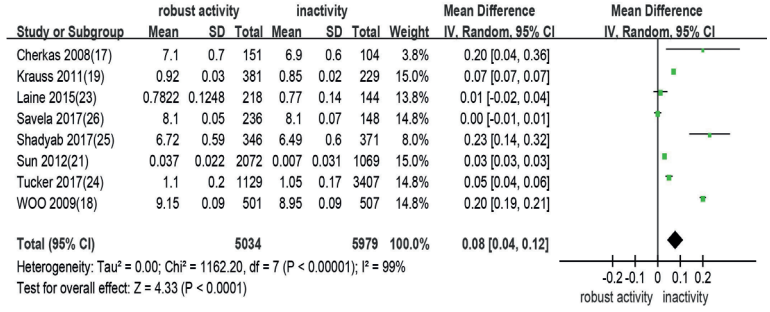

Fig. 3. Meta-analysis of the association between telomere length and robust exercise. 95% CI: 95% confidence interval; SD: standard deviation.

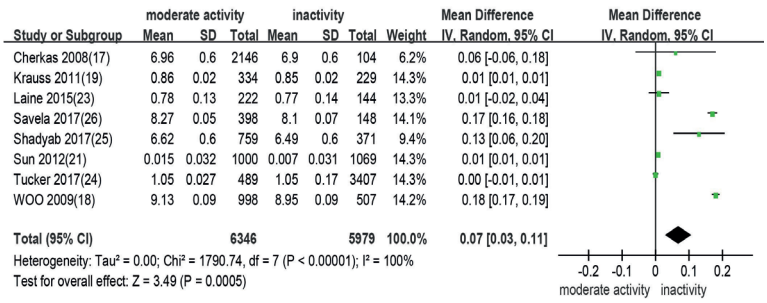

Fig. 4. Meta-analysis of the association between telomere length and moderate exercise. 95% CI: 95% confidence interval; SD: standard deviation.

Sensitivity analyses

Sensitivity analyses were performed to detect influential studies. Table SII lists the pooled mean differences, with one study at a time removed from the meta-analysis. Exercise was positively associated with telomere length regardless of whether any study was removed from the meta-analysis.

DISCUSSION

This meta-analysis found that exercise had a positive effect on telomere length. There are several possible reasons for this phenomenon. First, inactivity may reduce the expression of telomerase reverse transcriptase and telomeric repeat-binding factor 2, which could lead to decreased activity of telomerase and telomere stabilizing protein (27). Secondly, the longer telomere lengths associated with increased physical activity levels may be explained by the overall diminished burden of oxidative stress and inflammation, such as decreased levels of high-sensitivity C-reactive protein, interleukin-6, tumour necrosis factor-alpha, granulocyte colony-stimulating factor, and F2-isoprostane. These inflammatory indicators have been found to contribute to telomere attrition (28–30). Thirdly, physical inactivity may increase the risk of insulin resistance and obesity, which may also accelerate telomere attrition (31, 32). Nevertheless, many studies did not report a linear relationship between telomere length and intensity of exercise (15, 16, 20, 26, 33). These discordant findings may be due to differences in the methods of DNA extraction, telomere measurement, sample size, and/or genetic differences.

The current study also found that moderate and robust exercise had positive effects on telomere length, although the intensity of exercise across these studies differed. These results were consistent confirmed in many studies (18, 19, 21, 23–25), while other studies found that the highest, but not the lowest, levels of activity, had a significant association with telomere length (26, 34). This result may be explained by higher cardiorespiratory fitness (35). Active individuals tend to exhibit higher cardiorespiratory fitness, which is associated with increased telomere length (36). Savela et al. reported that men in the highest physical activity group had the lowest mortality rate (37). Ludlow et al. found that moderate levels of physical activity may have a more protective influence on telomere length than both low and high levels of exercise (34). The inconsistency in our study could be due to the increased breadth of physical activity, genetic diversity of participants, and sample size.

Aerobic exercise is an ordinary physical activity that is positively associated with telomere length (20, 33, 38). Aerobic exercise can improve maximal oxygen uptake, which is positively related to telomere length through the activation of telomerase (39). Werner et al. reported that aerobic endurance subjects (e.g continuous running) exhibited increased telomerase activity and telomere-stabilizing proteins compared with untrained controls, which contributes to chromosomal stability and integrity (40).On the other hand, individuals who engaged in long-term aerobic exercise have significantly improved body mass index and decreased low-density lipoprotein values(41), which is beneficial for maintaining telomere length through the modulation of shelterin and telomerase dynamics (42, 43). In the current study, however, subgroup analysis did not find that aerobic exercise was positively related to longer telomere length. The source of this discrepancy may be attributed to differences in the intensity and duration of aerobic exercise, participant genetic diversity, sample size, and physical activity measurements.

Some studies have reported a positive relationship between longer telomere length and other types of exercise when subgroup analysis was performed according to type of exercise, such as resistance exercise and yoga. Resistance exercise is also positively associated with telomere length, although there has been only one study reporting the effect of resistance training on telomere length (43). Resistance exercise not only diminished the burden of oxidative stress and inflammation, but was also associated with a higher level of satellite cell recruitment and promoted type II muscle fibre hyperplasia and hypertrophy (44). In addition, individuals with sarcopaenia exhibited lower walking speed and grip strength due to low muscle mass (45, 46). Compared with non-sarcopaenia patients, telomere lengths were shorter in older outpatients with sarcopaenia (47). Resistance exercise has been shown to be effective in improving sarcopaenia status and reducing the risk of functional decline (48, 49). Yoga, which

includes breathing exercises and meditation, was also found to be positively associated with telomere length. Breathing exercises and meditative components have been shown to have positive effects on psychological health, including alleviation of stress, anxiety and depression, which are significantly associated with shortened telomere length (50, 51).

In addition, in subgroup analysis according to age, the current study found that exercise had a positive effect on leukocyte telomere length in younger individuals, but not in elderly subjects. Some researchers found that exercise did not positively affect leukocyte telomere length in a group of young subjects (33, 38). However, another study involving healthy adolescents found that exercise resulted in increased leukocyte telomere length (51). This discrepancy may be attributed to differences in sample size and methods of telomere measurement and, perhaps, selection bias in these studies.

The current study has several limitations that should be addressed. First, the strength of evidence may be weakened due to deficiency of data in some studies, and differences in tissue sources, sample size and methods of evaluation of telomeres. Secondly, it was not possible to perform formal subgroup analysis according to age, except for the elderly group, because age varied widely across the included studies. Thus, the current study could not provide sufficient evidence to support the association between exercise and telomere length according to age. Finally, the pooled synthesis of observational studies in this meta-analysis may have limited the quality of evidence compared with larger, randomized controlled trials.

Conclusion

Compared with inactive individuals, active subjects had longer telomere lengths, especially those who engaged in moderate and robust physical exercise. Further prospective, large, randomized controlled studies are needed to determine the effect of different types of physical activity on telomere length.

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The authors have no conflicts of interest to declare.

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