Effect of physical exercise on telomere length: An umbrella review and meta-analysis

Juan Luis Sánchez González, Juan Luis Sánchez-Rodríguez, Rogelio González-Sarmiento, Víctor Navarro-López, Raúl Juárez-Vela, Jesús Pérez, Javier Martín-Vallejo

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Juan Luis Sánchez González[1*]; Juan Luis Sánchez-Rodríguez[2*]; Rogelio González-Sarmiento[1*]; Víctor Navarro-López[3*]; Raúl Juárez-Vela[4*]; Jesús Pérez[1, 5, 6, 7*]; Javier Martín-Vallejo[8*]

[1]Faculty of Nursing and Physiotherapy Department of Physiotherapy University of Salamanca Salamanca ES
[2]Faculty of Psychology Department of Basic Psychology, Psychobiology and Methodology University of Salamanca Salamanca ES
[3]Faculty of Health Sciences Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine Universidad Rey Juan Carlos Madrid ES
[4]Faculty of Health Sciences Department of Nursing University of La Rioja Logroño ES
[5]Department of Psychiatry University of Cambridge Cambridge GB
[6]Cambridgeshire and Peterborough NHS Foundation Trust Cambridge GB
[7]Norwich Medical School University of East Anglia Norwich GB
[8]Faculty of Medicine Department of Statistics University of Salamanca Salamanca ES
[*]these authors contributed equally

Corresponding Author:
Jesús Pérez
Faculty of Nursing and Physiotherapy
Department of Physiotherapy
University of Salamanca
Salamanca
ES

Abstract

Background: Telomere length (TL) is a marker of cellular health and aging. Physical exercise has been associated with longer telomeres and, therefore, healthier aging. However, results supporting such effect vary across studies.

Objective: Our aim was to synthesise existing evidence on the effect of different modalities and duration of physical exercise on TL.

Methods: We performed an umbrella review and meta-analysis. Data sources included PubMed, Embase, Web of Sciences, Cochrane Library, and Scopus. We selected systematic reviews and meta-analyses of randomised and non-randomised controlled clinical trials evaluating the effect of physical exercise on TL.

Results: Our literature search retrieved 12 eligible systematic reviews, five of which included meta-analyses. We identified twenty-two distinct primary studies to estimate the overall effect size of physical exercise on TL. The overall effect size was 0.2780 (95% CI: 0.118; 0.439), with a heterogeneity test value (Q) of 43.08 (p=0.0031) and I^2 coefficient of 51.3%. The number of weeks of intervention explained part of this heterogeneity (Q_B=8.25; p=0.0041), with higher effect sizes found in studies with an intervention of less than 30 weeks. Exercise modality explained additional heterogeneity within this subgroup (Q_B=10.28, p=0.016). The effect sizes were small for aerobic exercise and endurance training, and moderate for High-Intensity Interval Training.

Conclusions: Our umbrella review and meta-analysis detected a small-moderate positive effect of physical exercise on TL, which seems to be influenced by the duration and type of physical exercise. High quality studies looking into the impact of standardised, evidence-based physical exercise programmes on TL are still warranted. Clinical Trial: PROSPERO CRD42024500736

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Juan Luis Sánchez-González[1,2]; Juan Luis Sánchez-Rodríguez[3]; Rogelio González-Sarmiento[2,4]; Víctor Navarro-López[5]; Raúl Juárez-Vela[2,6]; Jesús Perez[2,4,7,8,9,*]; Javier Martín-Vallejo[2,10]

[1] Faculty of Nursing and Physiotherapy, Department of Nursing and Physiotherapy University of Salamanca, Salamanca, Spain, 37007.
[2] Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain, 37007.
[3] Faculty of Psychology, Department of Basic Psychology, Psychobiology and Methodology, University of Salamanca, Salamanca, Spain, 37005.
[4] Faculty of Medicine, Department of Medicine, University of Salamanca, Salamanca, Spain, 37007.
[5] Faculty of Health Sciences, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Madrid, Spain, 28032.
[6] Faculty of Health Sciences, Department of Nursing, University of La Rioja, Logroño, Spain, 26004.
[7] Department of Psychiatry, University of Cambridge, Cambridge, UK, CB20SZ.
[8] Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK, CB215EF.
[9] Norwich Medical School, University of East Anglia, Norwich, UK, NR4 7TJ.
[10] Faculty of Medicine, Department of Statistics, University of Salamanca, Salamanca, Spain, 37007.

Jesus Perez and Javier Martín-Vallejo are joint senior authors.

Corresponding author: Jesus Perez, Department of Medicine, Faculty of Medicine, University of Salamanca, Avenida Alfonso X El Sabio s/n, 37007, Salamanca, Spain. jesusperez@usal.es; jp440@cam.ac.uk

Summary

Background

Telomere length (TL) is a marker of cellular health and aging. Physical exercise has been associated with longer telomeres and, therefore, healthier aging. However, results supporting such effect vary across studies. Our aim was to synthesise existing evidence on the effect of different modalities and duration of physical exercise on TL.

Methods

We performed an umbrella review and meta-analysis. Data sources included PubMed, Embase, Web of Sciences, Cochrane Library, and Scopus. We selected systematic reviews and meta-analyses of randomised and non-randomised controlled clinical trials evaluating the effect of physical exercise

on TL.

Results

Our literature search retrieved 12 eligible systematic reviews, five of which included meta-analyses. We identified twenty-two distinct primary studies to estimate the overall effect size of physical exercise on TL. The overall effect size was 0.2780 (95% CI: 0.118; 0.439), with a heterogeneity test value (Q) of 43.08 (p=0.0031) and I^2 coefficient of 51.3%. The number of weeks of intervention explained part of this heterogeneity (Q_B=8.25; p=0.0041), with higher effect sizes found in studies with an intervention of less than 30 weeks. Exercise modality explained additional heterogeneity within this subgroup (Q_B=10.28, p=0.016). The effect sizes were small for aerobic exercise and endurance training, and moderate for High-Intensity Interval Training.

Conclussions

Our umbrella review and meta-analysis detected a small-moderate positive effect of physical exercise on TL, which seems to be influenced by the duration and type of physical exercise. High quality studies looking into the impact of standardised, evidence-based physical exercise programmes on TL are still warranted.

Registration: PROSPERO CRD42024500736.

Keywords: Aging, Chromosome; Exercise; Meta-analysis, Telomere, Telomerase.

INTRODUCTION

Life expectancy has increased worldwide over the last century. The United Nations World Population Prospects [1] estimates that the world's population aged 65 or older will rise by 16% in 2050, doubling the number of children under 5. This prospect will lead to a significant increase in age-related illnesses, such as cancer, dementia or cardiovascular diseases [2], and is prompting research into the primary mechanisms of aging and, subsequently, strategies to promote a healthy late-life.

López-Otín et al. [3] have recently postulated twelve basic biological mechanisms of aging: epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, dysbiosis, genomic instability and telomere attrition. Indeed, one of the main theories that has attempted to explain aging relates to telomere length (TL) and the role of telomerase, an enzyme responsible for maintaining and elongating telomeres. Telomeres are essential nucleoprotein structures located at the termini of eukaryotic chromosomes that play pivotal roles in safeguarding genomic integrity and regulating processes such as tumor suppression and aging [4]. Typically composed of a repetitive guanine-rich sequence extending from the chromosome end in the 5' to 3' orientation, paired with a complementary cytidine-rich strand [5], telomeres exhibit

variations in sequence among species, yet share a common repetitive pattern across organisms. Measuring around 15 kilobases at birth in human somatic cells, telomeres undergo gradual attrition, with approximately 25 to 200 bases lost from their ends during each cell division in the absence of telomerase [6]. Upon reaching a critical length, telomeres signal cell cycle arrest, leading to cellular senescence and eventual demise [7]. Telomeres serve to shield chromosome ends from degradation and fusion, thereby upholding genomic stability [8,9].

There are different demographic factors that influence TL, such as genetics that may explain the high heritability of TL [10,11]; sex, with longer telomeres found in adult females [12]; or ethnicity, with White usually having longer telomeres than Black or Hispanic ethnic communities [13]. Also, stress levels have been associated with shorter TL, which may be due to oxidative stress and reduced telomerase enzyme activity [14,15]. Obesity [16], alcohol consumption [17] and smoking [16,18] are also factors that negatively influence TL.

Notably, longer telomeres have been found in people who exercise regularly [19] or with higher levels of daily physical activity [20,21]. Indeed, one of the most studied interventions regarding TL is physical exercise. Recent systematic reviews and meta-analyses [22–26] have investigated the effect of physical exercise on the TL of clinical and non-clinical samples, showing some positive, but still inconclusive, results. The aim of this umbrella review was to synthesise existing evidence on the effect of different modalities and duration of physical exercise on TL to inform the implementation of evidence-based physical exercise programmes or recommendations to add healthier years into longer lives.

MATERIAL AND METHODS

This umbrella review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27], and is registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42024500736).

Study design

We selected systematic reviews, with or without meta-analyses, of randomised and non-randomised controlled clinical trials, excluding non-experimental designs, such as observational studies. No restrictions were applied on the basis of any particular language, following current international recommendations [28].

Inclusion criteria

The inclusion criteria and description of studies in this review followed the PICOS (Population,

Intervention, Control, Outcomes, and Study design) framework for reviews [29].

Population

Study participants were people with or without a clinical condition. The systematic reviews had to explicitly state that they included humans in their analyses. Therefore, studies involving experimental animals, such as rodents, were excluded.

Intervention and control

We selected all systematic reviews and meta-analyses comparing the effects of physical exercise vs other intervention, or none, on TL. In addition, we further divided the results according to different types of physical exercise. If any reviews included primary studies combining different types of exercise, they were classified as “combined”.

Outcome measure

The outcome measure was TL-related calculations.

Search strategy

We performed a literature search for scientific articles published until 19 January 2024, using the following databases: PubMed (Medline), PEDro, EMBASE, Web of Sciences and Cochrane Library. Multimedia appendix 1 provides the search strategies, tailored for each database. Two independent reviewers (JLSG and JLSR) conducted the search using the same methodology. Any discrepancies during this process were resolved through consensus including a third reviewer (VNL). Additionally, we manually examined the reference sections of the original studies, and, if needed, contacted the authors for additional information.

Selection criteria and data extraction

Two independent reviewers (JLSG and JLSR) initiated a screening process to evaluate relevance of the systematic reviews and meta-analyses. The initial screening was based on the title, abstract, and keywords for each review. When there was no consensus, or if the abstracts provided insufficient information, the full text was examined. During the second screening phase, the full text was evaluated to confirm inclusion criteria. Data presented in the results section were extracted using a protocol to ensure retrieval of the most relevant information for each study. During the analysis, we checked whether the results were repeated in different reviews/meta-analyses; if the effect sizes coincided, only one of the effect sizes was chosen; if the effect sizes did not match, the primary study ´s was selected.

Methodological quality assessment

Two independent reviewers (JLSG and VNL) evaluated the methodological quality of the systematic

reviews and meta-analyses, using the modified quality assessment scale for systematic reviews (AMSTAR-2). AMSTAR-2 [30] is a questionnaire comprised of 16 domains, with simple categorical options: "yes", when the result is positive; "no", when the standard is not met or there is not enough information to answer it; and "partial yes", when there was partial adherence to the standard. Additionally, we calculated the kappa coefficient (κ) and percentage (%) agreement scores to assess reliability before reaching consensus. Inter-rater reliability was estimated using κ, where $\kappa > 0.7$ indicates a high level of agreement between reviewers, κ of 0.5–0.7 indicates a moderate level of agreement, and $\kappa < 0.5$ suggests a low level of agreement [31].

Risk of bias assessment

We evaluated the risk of bias using the Risk Of Bias in Systematic reviews (ROBIS) assessment, which includes three domains: (1) relevance of assessment (optional); (2) identification of concerns with the review process through four domains related to study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings; and (3) judgment on the risk of bias. The ROBIS tool includes signaling questions to assess specific domains and to guide the judgment of the systematic review's risk of bias, with responses categorised as "yes," "probably yes," "probably no," "no," or "no information." The risk of bias is then categorised as "low," "high," or "unclear" [32].

Two independent reviewers (JLSG and JLSR) assessed the risk of bias in the selected studies. Additionally, we computed the kappa coefficient (κ) and percentage (%) agreement scores to evaluate reliability before reaching consensus.

Grading of evidence

The Physical Activity Guidelines Advisory Committee Grading Criteria (PAGAC) were employed to evaluate grading of evidence. The criteria used for assessing the quality of evidence included: (1) applicability of the study sample, exposures, and outcomes to the research question, (2) generalisability to the population of interest, (3) risk of bias/study limitations, (4) quantity and consistency of findings across studies, and (5) magnitude and precision of the effect. Based on this information, final evidence grades and conclusion statements for each research question were formulated [33].

Overlap of primary studies

The overlap analysis of primary studies among the systematic reviews was performed with the Graphical Representation of Overlap for OVErviews (GROOVE) tool [34]. Using a matrix of evidence, GROOVE establishes the number of primary studies and systematic reviews, the absolute number of overlapped and non-overlapped primary studies, and an overall Corrected Covered Area

(CCA) assessment. GROOVE also offers a detailed CCA assessment for each possible pair of systematic reviews (or "nodes"), with a graphical and easy-to-read representation of these results. Additionally, it provides an optional function that incorporates the structural missingness within the matrix.

Data synthesis and analysis

Given the high variability of designs, patients and endpoints across studies, results were integrated following a random effects model. The Hedges´ unbiased standardised mean difference was employed to determine effect sizes. Heterogeneity was measured using Q-tests, I^2 coefficients and prediction intervals [35]. Metaregression and metapartition [36] were employed to explain heterogeneity. These techniques involve partitioning sum of squares of the homogeneity test into two components Q_E and Q_W to account for quantitative or qualitative variables. If the Q_E value was large and statistically significant compared to the value of Q_W, it was considered that this variable explained part of the heterogeneity found in the integration of results across studies. If the variable was qualitative, subgroups of studies, which differed in the effect size and also showed less heterogeneity, were created. The procedure was repeated for subgroups that still presented large heterogeneity for other variables. Publication bias was assessed using the Contour-Enhanced Funnel Plot, Egger's test, Doi plot and LFK index procedures. 95% confidence intervals were calculated for effect sizes. The significance level was set at 5%. The analyses were carried out with the meta v7.0, metafor v4.6 and metasens 1.5-2 libraries of the R statistics software version 4.4.0.

RESULTS

Study selection

The initial literature search revealed 3628 records. Two more were retrieved manually from the references. A total of twelve systematic reviews were eligible for qualitative synthesis, and five of them allowed a meta-analytic analysis. The study screening strategy is shown in Figure 1.

[Figure 1. Insert here]

Characteristics of the systematic reviews

Table 1 lists the characteristics of the systematic reviews and meta-analyses (type of study, design, sample, intervention, lab technique to measure TL, risk of bias, evaluation of quality and conclusions).

[Table 1. Insert here]

AMSTAR-2 appraisal

The overall confidence ranged from critically low to moderate quality scores. Two studies (16.6%) obtained an overall confidence of moderate, and ten studies (83.4%) had critically low quality (Multimedia appendix 2). The items with the highest scores were: “did the review authors use a comprehensive literature search strategy?”, “did the review authors describe the included studies in adequate detail?”, “did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?” and “did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?” The lowest scoring items were: “did the review authors account for risk of bias in individual studies when interpreting/ discussing the results of the review?”, “did the review authors report on the sources of funding for the studies included in the review?” and “if meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?” The inter-rater reliability of the methodological quality assessment was high ($\kappa = >0.8$).

ROBIS assessment

Multimedia appendix 3 summarises the risk of bias using ROBIS. 40% of the studies (5 out of 12) had a low risk of bias, 20% (2 out of 12) had an unclear risk of bias, and 40% (5 out of 12) had a low risk of bias. The domains related to "data collection" and "synthesis and findings" had the highest risk of bias. On the other hand, the domain related to "eligibility criteria" had the lowest risk of bias. The inter-rater reliability of the risk of bias was high ($k >0.8$).

PAGAC grades of evidence

The grades of evidence were classified as not assignable, limited, moderate, or strong according to the PAGAC. The level of evidence was limited to moderate among the studies. Most reviews evaluated a heterogeneous population of individuals, which limited the applicability and generalisability of the results. The domain “quantity and consistency” was affected because some studies had inconsistency in the direction of or the effect size itself (Multimedia appendix 4).

GROOVE analysis

A total of 39 primary studies were identified across all systematic reviews and meta-analyses, 24 of which were distinct studies. The overall overlap in the matrix of evidence was moderate (CCA = 32,5%) and it remained moderate (CCA = 15,63%) after adjusting for the chronological structural

missingness. Multimedia appendix 5 shows a graphical representation of the GROOVE results.

Telomere length

The number of studies in the systemic reviews that were finally integrated in the quantitative (meta-analytic analysis) was 22. The estimated effect size was 0.2780 (95%CI: 0.118;0.439), with a heterogeneity test value (Q) of 43.08 (p-value=0.0031). The I^2 coefficient was 51.3% and the prediction interval was -0.26;0.81. The number of weeks of intervention explained part of this heterogeneity (Q_B=8.25; p-value=0.0041). This factor explained 28% of the overall heterogeneity. Figure 2 shows that studies where the number of weeks of intervention was greater than 30 had smaller effect sizes. In fact, if the intervention time was categorised into <30 and >=30 weeks, Q_B was 11.97 (p-value<0.001).

[Figure 2. Insert here]

Figure 3A shows that the effect size was 0.40 for studies with an intervention length of less than 30 weeks, and -0.02 for those with interventions longer than 30 weeks. Interestingly, the first group presented a statistically significant heterogeneity (I^2= 44%), whilst the second, despite having a large range of outcomes, did not.

The heterogeneity found in the group of studies with shorter interventions (<30 weeks) was partly explained by the type of physical exercise involved (Q_B=10,28, p-value=0.016). Accordingly, four subgroups of studies were defined (See Figure 3B). One subgroup was comprised of just one study that included a combination of aerobic exercise with endurance training and achieved a large effect size. The other three subgroups did not have a statistically significant heterogeneity between them, although the subgroup of studies defined by an intervention based on High Intensity Interval Training (HIIT), which alternates short periods of intense anaerobic exercise with brief recovery periods, had a marked I^2 value (49%). The HIIT subgroup only included three studies, one of which had a very high effect size compared to the other two. When we compared the effect sizes of the three types of non-combined physical exercises, the value was small for aerobic exercise and endurance training, and moderate for HIIT.

[Figures 3A and 3B. Insert here]

The Contour-Enhanced Funnel plot (Multimedia appendix 6) did not identify publication bias. Many of the effect sizes were not significant and at the top of the funnel there was some

asymmetry, which could be due to the heterogeneity of results. The non-presence of publication bias was confirmed with the Egger's method (p-value=0,10). The Doi plot and LFK-index also found a weak asymmetry (Multimedia appendix 7).

DISCUSSION

This umbrella review studied the effects of physical exercise on TL. The estimated overall effect size indicated a small-moderate positive impact of exercise on TL. However, we found some discrepancies in the results across studies that may be explained by several methodological and contextual reasons, including different methodologies for measuring TL, such as quantitative polymerase chain reaction (qPCR) and terminal restriction fragment (TRF) assays, that can contribute to inconsistencies in TL calculations. In this regard, Smith et al. [37] pointed out that intra-individual TL can vary significantly depending on the lab technique employed to measure it. Differences in study populations could also be a factor responsible for disparities in results. Demographic factors, such as age, sex, ethnicity and health status can influence the relationship between exercise and TL. For instance, LaRocca et al [38] and Puterman et al [21] suggest that the benefits of exercise on TL may be more pronounced in older adults and in those with higher stress levels. Additionally, the duration and intensity of the intervention could be another confounding factor. Our findings suggest that interventions longer than 30 weeks tend to show a lesser positive impact on TL. This could be due to a ceiling effect where additional benefits of exercise do not translate into further increase of TL. This is consistent with Werner et al´s [39], who observed that the beneficial effects of exercise on TL are more evident in the early phases of physical exercise programmes.

The high heterogeneity in study designs, including interventions, participant adherence, and control measures, could have also contributed to different outcomes. In fact, Denham et al [23] and Puterman et al [21] have already highlighted the importance of these methodological issues when interpreting TL results. Studies such as Cherkas et al´s [20] had found that vigorous aerobic physical activity was associated with longer telomeres in adults, which is in line with our finding of a positive effect of aerobic exercise, especially when combined with endurance training, on TL. However, a systematic review by Du et al [40] did not identify a significant association between aerobic exercise and TL in younger populations, suggesting that age may be an important moderating factor. Denham et al [23] found mixed results related to endurance physical training. Our review also found significant variation in the effects of non-combined endurance training, which suggests that factors such as the intensity and duration of this type of physical exercise may influence the magnitude of

the effect on TL. Finally, HIIT had previously shown a significant positive effect on TL [39]. Our review results are consistent with this; nonetheless, the low number of HIIT studies and variety of designs limit generalisability.

Biological understanding of the effect of exercise on telomere length

Reduction of oxidative stress and inflammation

Oxidative stress and chronic inflammation are two major factors contributing to telomere erosion. Studies have shown that regular exercise can mitigate these factors. Acute and chronic physical activity have different effects on oxidative stress. While acute exercise triggers the production of reactive oxygen and nitrogen species, leading to oxidative stress, regular exercise training enhances the body's endogenous antioxidant system, offering protection against the harmful effects of oxidative damage [41]. This antioxidant effect protects cells from oxidative damage, which in turn preserves the integrity of telomeres. Additionally, exercise reduces the levels of inflammatory markers such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), which can protect telomeres from inflammation-induced damage [42].

Increase in telomerase activity

Telomerase is a crucial enzyme for maintaining telomere length, as it adds repetitive sequences to the end of chromosomes. Research suggests that exercise can increase telomerase activity. Ornish et al [43] demonstrated that an intensive lifestyle change programme, which included regular exercise, significantly increased telomerase activity in men with prostate cancer. This finding suggests that exercise can directly influence telomere biology by activating telomerase, which helps maintain telomere length and protects cells from premature aging.

Improvement of cardiovascular capacity and metabolic health

Improved cardiovascular capacity and metabolic health are also associated with longer telomeres. Puterman et al [21] found that better aerobic capacity and higher insulin sensitivity are associated with longer telomeres. These cardiovascular and metabolic benefits reduce oxidative stress and inflammation, creating a healthier cellular environment that protects TL. Regular exercise enhances cardiovascular system efficiency, increases blood circulation, and facilitates the delivery of oxygen and nutrients to cells, which can contribute to the preservation of telomeres.

Strengths and limitations

We present a comprehensive analysis of systematic reviews and meta-analyses of the effect of physical exercise on TL, providing a broad and robust synthesis of the available evidence. The methodology used to assess the quality of studies and the application of standardised tools for evaluating the risk of bias and heterogeneity strengthens the validity of our results. However, our

work has some limitations. The methodological quality of the reviews included in this analysis varies, with many of them classified as critically low. Also, the heterogeneity in study designs, samples, and interventions makes difficult to generalise the results, even after the use of a random effects model to integrate outcomes. Furthermore, some meta-analyses reported results only using post-intervention measures, whilst others used post-intervention differences adjusted for pre-intervention measures; this may lead to variations in effect sizes.

Clinical implications

The implementation of exercise programmes into clinical practice could be an effective strategy to limit telomere shortening, promoting healthy aging and reducing the incidence of age-related diseases. HIIT and the combination of aerobic exercise with endurance training may be promising interventions in this regard, but still require to be further tested in high-quality studies. In addition, physical exercise should be tailored to each individual´s physical capability and health condition to maximise cellular health benefits. Implementing physical exercise programmes will also require ongoing health education and monitoring to ensure adherence to and adjustment of interventions based on observed outcomes. Future studies should investigate sex and ethnic TL differences in response to various types of physical exercise. This could help personalise recommendations and optimise benefits on cellular health and aging.

CONCLUSIONS

Our umbrella review and meta-analysis identified a small-moderate positive effect of physical exercise on TL, which seems to be influenced by the duration and type of physical exercise. The implementation in healthcare systems of evidence-based physical exercise and training programmes and/or recommendations tailored to each individual might be a valuable preventive strategy for a healthy-aging. More studies, with larger sample sizes, testing the impact of standardised, evidence-based physical exercise interventions on TL, are warranted.

What is already known on this topic

Systematic reviews and meta-analyses have explored the impact of different physical exercise modalities on TL. The evidence suggests that regular physical activity is associated with longer telomeres. However, methodologies, including interventions, vary significantly across studies and the results are inconsistent, which makes difficult to provide guidance for implementation in healthcare systems.

What this study adds

This study synthesises evidence from existing systematic reviews and meta-analyses to provide a comprehensive review of the effect of different types of exercise on TL. It stresses the importance of exercise modality and duration on such effect. Additionally, it identifies the need for more high-quality studies with larger sample sizes, including well-structured, evidence-based interventions. This review suggests the potential of personalised physical exercise programmes as a strategy to preserve telomere length and, therefore, contribute to a longer and healthier late-life.

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Notes

Contributors: JLSG, JLSR, RGS, JP and JMV contributed to the design of this review. JLSG, VNL, JP and JMV conducted study selection, data extraction and analysis, and wrote the first draft of this manuscript. RJV provided a detailed review of the statistical analysis. All authors reviewed and approved the final version of the manuscript. The corresponding authors (JP) confirms that all listed authors meet authorship criteria and that no others meeting these criteria have been omitted.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patients and public communities: After publication, the findings of this review will be disseminated to appropriate audiences, such as academia, clinicians, policy makers, and the general public, through various channels including blogs, press releases, and social media.

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Ethics statements

Ethical approval

Not needed

Data availability statement

All data related to this review and meta-analysis are available from the authors upon request.

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Tables

Table 1. Characteristics of the systematic reviews.

				RCCTs or CCTs with physical exercise intervention							
	Type of study	**Study design**		**Sample**		**Intervention**		**Lab technique for TL**	**Risk of bias**	**Evaluation of quality**	**Conclusions**
		Interventional	**Observational**	**n**	**Condition (number of studies)**	**Type (n)**	**Duration: weeks (n)**				
Song et al 2022	Systematic review and meta-analysis	7 (RCCTs)	0	939	Healthy (3) Breast cancer (2) Polycystic ovary syndrome (1) Obese (1)	Aerobic exercise (4) Endurance training (3)	48 (2) 24 (3) 16 (2)	qPCR	Yes	No	The type and duration of exercise for positive improvement in telomere length is aerobic exercise for more than 6 months
Buttet el al 2022	Systematic review and meta-analysis	13 (RCCTs) and 3 CCTs	5	908	Healthy (5) Obese (1) Myocardial infarction (1)	Endurance training (7) Strength (1) HIIT (1)	48 (2) 32 (1) 24 (4)	qPCR	No	No	A lifestyle intervention with physical activity + diet can increase telomere length, independently of population characteristics or baseline TL
Sánchez-González et al 2024	Systematic review and meta-analysis	8 (RCCTs) 1 (CT)	0	1320	Healthy (9)	Endurance training (4) Aerobic exercise (4) HIIT (3) Aerobic +	8 (1) 16 (1) 24 (4) 52 (3)	qPCR	Yes	Yes	The findings suggest that HIIT seems to have a positive effect on telomere length compared with other types of exercise such as endurance training or aerobic exercise in

						endurance (1)					healthy population
Valente et al 2021	Systematic review and meta-analysis	6 (RCCTs)	16 (Case-Control studies) 2 (Prospective cohort) 3 (Cross-sectional) 3 (Retrospective cohort)	612	Healthy (5) Obese (1)	Endurance training (5) Strength (1) Aerobic exercise (1) HIIT (1)	56 (1) 48 (1) 24 (4)	qPCR	Yes	No	There is very low certainty that physically active individuals have longer telomeres with a moderate effect, but this effect is probably overestimated
Denham et al 2021	Systematic review and meta-analysis	12 (NR)	0	487	Healthy (6) Chronic fatigue (1)	HIIT (1) Aerobic exercise (3) Pilates Training (1) Endurance training (2)	52 (1) 24(2) 22 (1) 8 (2) 1 (1)	qPCR	Yes	No	Exercise training as an inexpensive lifestyle factor that increases TERT expression and telomerase activity. Regular exercise training could attenuate telomere attrition through a telomerase-dependent mechanism and ultimately extend health-span longevity
Barragán et al 2021	Systematic review	12 (NR)	53 (Cross-sectional studies) 13 (Case-control) 9 (longitudinal)	1.056	Healthy (12)	Endurance training (5), Combined training (1), Aerobic exercise (6), NR (1) and HIIT (1)	56 (1) 52 (2) 24 (3) 8 (2) 1 (2) NR (2)	qPCR	No	Yes	Although fewer sedentary activities, optimal sleep habits, and non- or ex-smoker status have been associated with less telomere shortening, several methodological issues were detected, including the need for more targeted interventions and standardised protocols to better understand how

											physical activity and sleep can impact TL and aging.
Schellnegger et al 2022	Systematic review	8 (RCCTs) 7 (CCTs)	27 (Observational studies)	1.700	Healthy (13) Obese (2)	Aerobic exercise (8) Endurance training (8), HIIT (1)	1 (6) 6 (1) 8 (1) 12 (1) 24 (5) 52 (2)	qPCR	No	No	Physical activity with regular aerobic training of moderate to vigorous intensity appears to help preserve TL.
Prathap et al 2021	Systematic review	2 (RCCTs): 1 in rodents	3 (Literature review)	151	Breast cancer (1)	Aerobic exercise (1)	24 (1)	qPCR	No	No	Based on the evidence collected it can be suggested that chronic moderate intensity aerobic exercise in a lifelong practice shows beneficial effects in a dose-response manner in cancer prevention by modulating telomeres through epigenetic mechanism.
Quiao et al 2020	Systematic review	16 (RCCTs) 14 (CCTs)		562	Myocardial infarction (1) Healthy adults (4) Obese (1) Polycystic ovary syndrome (1)	Combined training (1) Endurance training (3) Aerobic exercise (3)	8 (1) 12 (1) 16 (2) 20 (1) 24 (1) 48 (1)	qPCR	No	Yes	Weight-loss and comprehensive lifestyle intervention strategies show encouraging impacts in delaying telomere shortening. More rigorous studies targeting populations at different age stages through life span are needed

Min et al 2022	Systematic review	2 (RCCTs)	3 (Cross-sectional study)	247	2 (breast cancer survivor)	Aerobic exercise (2)	24 (1) 48 (1)	qPCR	No	No	Three of the five studies reported that physical activity has a significant relationship in delaying TL shortening, but others observed no association between physical activity and TL in breast cancer survivors.
Adilson-Marques et al 2020	Systematic review	4 (RCCTs)	16 (Cross-sectional)	647	Obese (1) Healthy (3)	Aerobic exercise (4) HIIT (1) Endurance training (1)	24 (3) 48 (1)	qPCR	No	Yes	Better cardiorespiratory fitness or a large cardiorespiratory training load are associated with an increase in TL. Although, TL was related to regular moderate-to-vigorous aerobic exercise and cardiorespiratory fitness in older healthy humans, it was not related to cardiorespiratory fitness among young subjects.

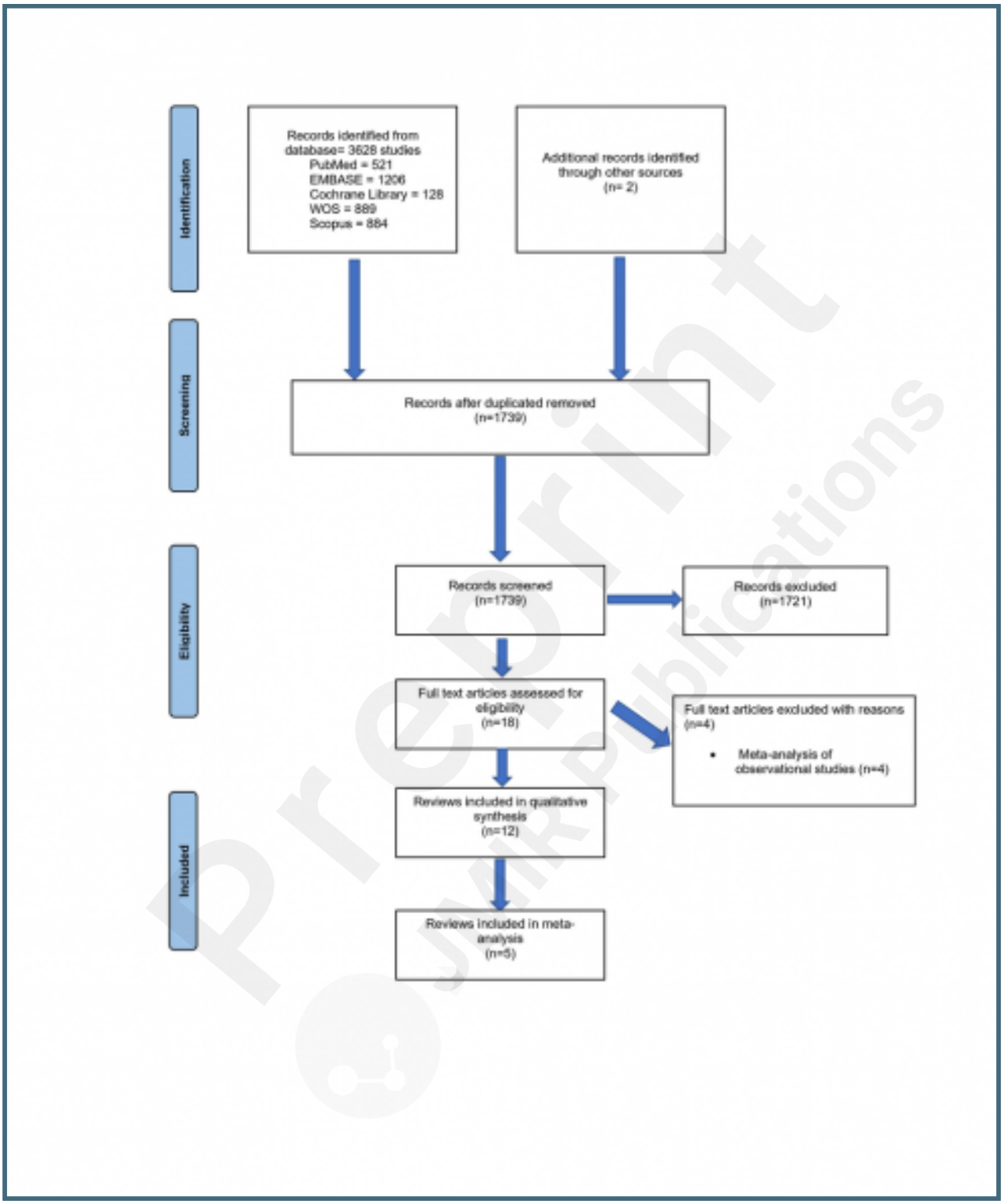
Himbert et al 2017	Systematic review	10 (RCCTs) 11 (CCTs)		439	Obese (1)	Aerobic exercise (1)	48 (1)	qPCR	No	No	The inconsistent effects of weight loss on telomere length or DNA repair suggest the need for a re-assessment of intervention designs and assay methodology to definitively address this topic

RCCT= Randomised Controlled Clinical Trial; CCT= (Non-randomised) Controlled Clinical Trials; NR= Not reported; qPCR= Polymerase Chain Reaction Quantitative; HIIT: High Intensity Interval Training

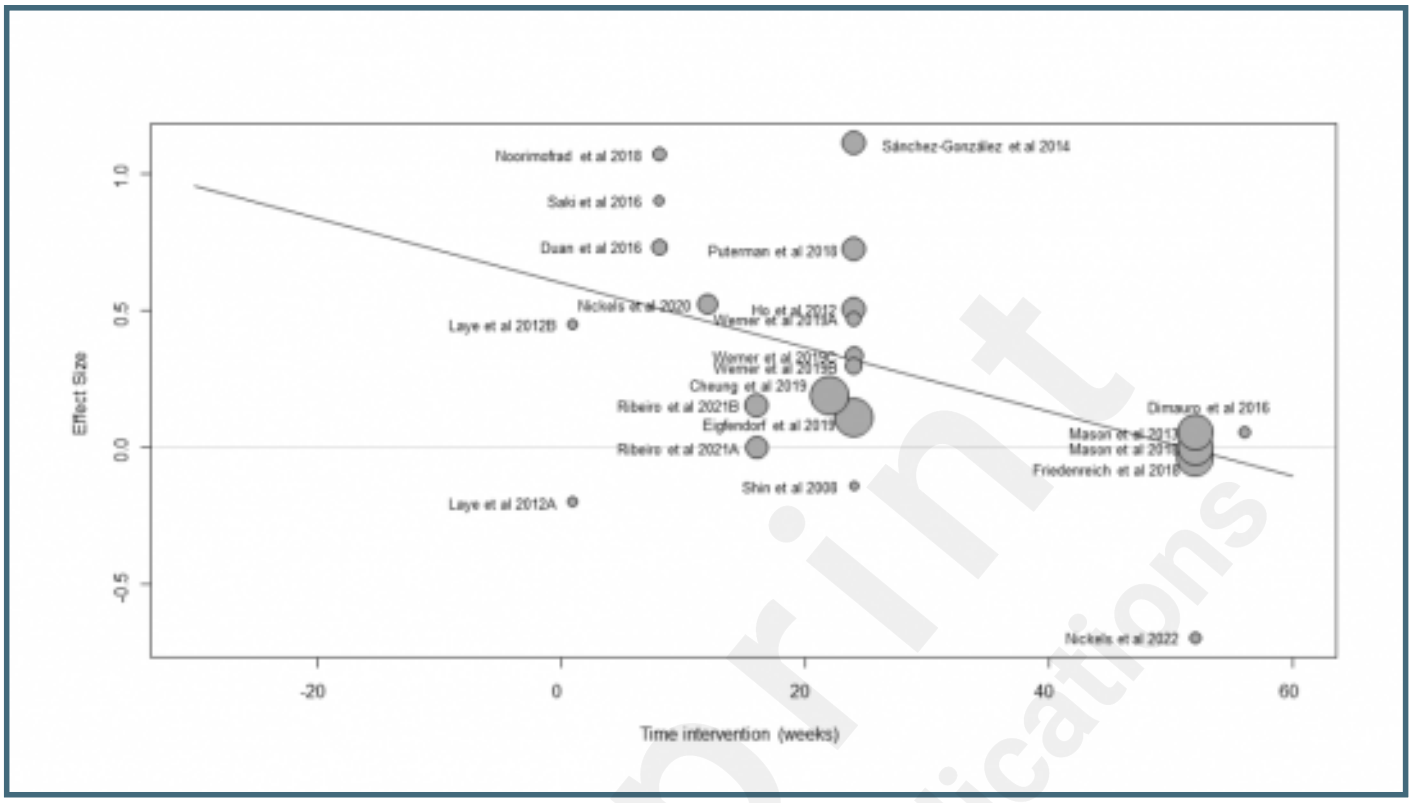
Supplementary Files

Figures

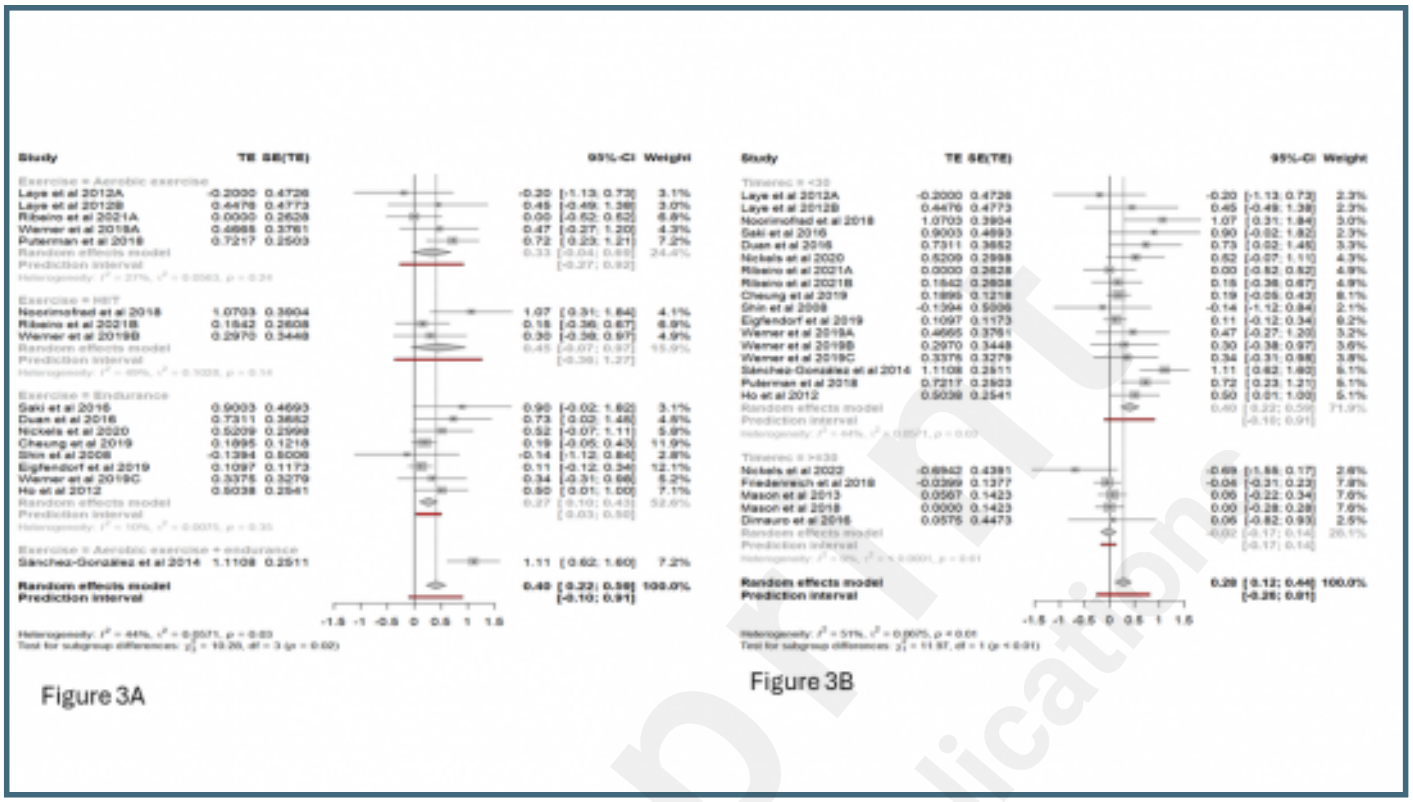
Flowchart.


Identification
Screening
Eligibility
Included
Records identified from database= 3628 studies
PubMed = 521
EMBASE = 1206
Cochrane Library = 128
WOS = 889
Scopus = 884
Additional records identified through other sources (n= 2)
Records after duplicated removed (n=1739)
Records screened (n=1739)
Records excluded (n=1721)
Full text articles assessed for eligibility (n=18)
Full text articles excluded with reasons (n=4)
Meta-analysis of observational studies (n=4)
Reviews included in qualitative synthesis (n=12)
Reviews included in meta-analysis (n=5)

Scatterplot of primary studies including effect size and number of weeks of intervention.



A: Forest plot of subgroups of primary studies defined by length of intervention. B:Forest plot of subgroups of primary studies defined by type of exercise.



Multimedia Appendixes

Database formulas during literature search.
URL: http://asset.jmir.pub/assets/77dec678f244c82e7389730e2919f7fd.docx

Quality assessment scores (AMSTAR-2).
URL: http://asset.jmir.pub/assets/67da8cd25a438984e4595f296734daa6.docx

Risk of bias.
URL: http://asset.jmir.pub/assets/54a11e4417f736ac836350e3578293a1.png

Summary of findings and quality of evidence (PAGAC).
URL: http://asset.jmir.pub/assets/ca1aa31f10acf5720c3d1bf9b88980dc.docx

Graphical representation of the overlap of primary studies between reviews.
URL: http://asset.jmir.pub/assets/7c843e012de368c21425e1d0502d2f58.png

Contour-Enhanced Funnel Plot of the primary studies included in the meta-analysis.
URL: http://asset.jmir.pub/assets/edfb5ad4f651d7e2db563a8aab6aab77.png

Doi plot and LFK index of the primary studies included in the meta-analysis.
URL: http://asset.jmir.pub/assets/95269d7238e8faf80bb50e0e716d34b0.png