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Review in Depth

A Systematic Review and Meta-analysis Highlights a Link Between Aerobic Fitness and Telomere Maintenance

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Abstract

Cardiorespiratory fitness declines with aging and is a major risk factor of cardiometabolic diseases and early death. Although the benefits of regular exercise are well established, whether maximal oxygen uptake (VO_{2max}) is associated with biological aging remains unclear. Given that telomere shortening is a hallmark of aging, the purpose of this systematic review and meta-analysis was to determine the association between VO_{2max} and telomere length. Articles were retrieved from PubMed, Scopus, and ScienceDirect and deemed eligible if they: (i) involved human participants with relatively low and high VO_{2max} values objectively assessed by pulmonary analysis; (ii) quantified telomere length using an established technique; and (iii) were peer-reviewed journal articles written in English. Relative to individuals with below-average VO_{2max} based on age- and sex-adjusted norms, fit participants with relative VO_{2max} values in the 70th percentile or higher possessed longer telomeres (standardized mean difference [95% confidence interval {CI}]: 0.36 [0.14–0.59], $p = .002$). A similar difference was observed between individuals with below-average VO_{2max} and those above the 90th percentile (0.28 [0.03–0.53], $p = .03$). However, no statistically significant telomere length differences were observed between individuals in the 70th to 90th percentile compared to those above the 90th (−0.08 [−0.40 to 0.24], $p = .62$). The findings provide evidence linking metabolism to telomere biology. They encourage individuals to regularly engage in endurance exercise to attenuate telomere attrition and promote healthy biological aging. Importantly, the results suggest that extensive endurance training may not be required to protect the telomeres, rather moderate amounts of training may be sufficient to reach more achievable VO_{2max} targets.

Keywords: Cardiorespiratory fitness, Endurance training, Physical exercise, Telomere length, Telomere shortening

Cardiorespiratory fitness is a clinically relevant indicator of health and vitality. Convincing evidence indicates that low cardiorespiratory fitness is a risk factor of age-related noncommunicable diseases and traditional risk factors (1–4), as well as cardiovascular and all-cause mortality in healthy and clinical populations (5,6). Changes in cardiorespiratory fitness during aging also demonstrate linear associations with the risk of death, emphasizing the importance of increasing aerobic fitness in the short term or retaining as much as possible over the long term (7,8). The gold-standard objective assessment of cardiorespiratory fitness involves cardiopulmonary exercise testing (CPET), which entails the quantification of maximal oxygen uptake (VO_{2max}) via pulmonary analysis during an incremental test to exhaustion. Despite the large genetic contribution to VO_{2max} (9,10), it is highly trainable and can be improved by up to 900 mL $O_2 \cdot min^{-1}$ after endurance training interventions in less than 6 months (11–13).

While endurance athletes engage in extensive aerobic exercise training programs to maximize their cardiorespiratory fitness and endurance performance, CPET is also a key focus for those in exercise rehabilitation and hospital settings. Endurance athletes possess superior VO_{2max}, expressed relative to body weight ($ml \cdot kg^{-1} \cdot min^{-1}$). For example, relative VO_{2max} values range from 70 to 80 for male Tour de France participants (14) and ~85 for Tour winners (15,16). Tour de France cyclists are reported to live 17% longer than the general population (17) and 20 years longer in cyclists who have led the race at some point (18), but not all lifespan data from endurance athletes are consistent (19). At the other extreme, low VO_{2max} (eg, <15 $ml \cdot kg^{-1} \cdot min^{-1}$) significantly increases the risk of death following lung resection surgery (20), reduces the likelihood of 5-year survival in chronic obstructive pulmonary disease patients (21), and increases all-cause mortality risk in individuals with cardiovascular disease (5). There is also a dose–response relationship between cardiorespiratory fitness and morbidity and mortality in the general population (22). For instance, mortality risk is reduced by 11%–17% for every 1-metabolic equivalent of task increase in aerobic fitness (ie, 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) (22). These findings indicate a role for VO_{2max} not only in health span, but also lifespan. However, the molecular mechanisms responsible for these observations are incompletely understood.

Telomeres preserve genomic stability by forming protective complexes at the ends of linear chromosomes with the help of 6 shelterin proteins (23,24). The shortening of telomeric DNA (in vertebrates, 5′-$TTAGGG^n$-3′) is considered one of the hallmarks of aging, as extending the telomeres increases health and lifespan, while the accumulation of critically short—dysfunctional—telomeres accelerates biological aging and leads to early death (25). Telomeres shorten due to the end

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replication problem (26) and poorly expressed or undetectable levels of telomerase (27), the enzyme responsible for telomere extension. Short telomeres may also have a causal role in many age-related diseases burdening most modern societies (eg, cardiovascular disease (28) and dementia (29,30)). Many age-related diseases exhibit short telomeres (28,31), whereas few lifestyle factors are linked to telomere maintenance (32).

Physical activity and exercise training are associated with telomerase-mediated telomere maintenance (33–35), such that those regularly engaged in physical activity (36) or endurance athletes (37,38) generally exhibit longer telomeres, on average, compared to less active or sedentary individuals. Previous work has estimated that endurance athletes may prevent up to 16 years' worth of age-related telomere shortening (39). One analysis indicated that the longer telomeres observed in endurance athletes compared to controls was largely explained by VO_{2max} (38). Furthermore, using data from 405 891 UK Biobank participants, faster walking pace was associated with leukocyte telomere length (40). Thus, while exercise training and traits of endurance performance are linked to telomere length maintenance, the optimal exercise recommendations remain unclear. Given the importance of objectively assessed VO_{2max} for health and endurance performance, its trainability via exercise, and its clinical utility, we conducted a systematic review and meta-analysis to determine the association between VO_{2max} and telomere length.

Method

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This systematic review and meta-analysis was specifically designed to address the following research question: "Is there a statistically significant difference in the average telomere length between individuals with high versus low maximal aerobic fitness (VO_{2max}) expressed relative to body mass?" The review protocol was prospectively registered at PROSPERO (CRD42024500196).

Literature Search

A thorough search of 3 relevant online databases (PubMed, Scopus, and ScienceDirect) was undertaken between January 8 and February 2, 2024. The search was conducted utilizing predefined search terms as described in Supplementary File 1. The search terms included: Exercise (MeSH heading [mh]) or VO2max or VO2peak or physical fitness or exercise tolerance (mh) or physical fitness (mh) or cardiorespiratory fitness or endurance training (mh) or physical endurance and telomere (mh), telomere length, telomere shortening (mh). While the PubMed database was queried without filters, the Scopus database was limited to articles (document type) and journals (source type) written in English (language), and ScienceDirect was restricted to research articles, case reports, and short communications. To ensure a comprehensive review, bibliographies of all eligible journal articles were meticulously examined, resulting in the identification of one additional manuscript meeting the inclusion criteria. Conference proceedings, abstracts, and unpublished works were excluded from this review, due to concerns around whether they had been peer-reviewed.

Eligibility and Screening

This systematic review and meta-analysis focused exclusively on published, peer-reviewed journal articles written in English, adhering to strict inclusion criteria. Studies were deemed eligible for inclusion if they: (i) involved individuals with relatively low versus high VO_{2max}; (ii) objectively measured VO_{2max} by pulmonary analysis (ie, using a metabolic system) in human participants; (iii) quantitatively measured telomere length using an established technique (eg, qPCR, Southern Blot, FISH, TESLA, STELA, etc.)—studies that predicted telomere length from other methods (eg, from DNA methylation data) were not included in the analysis; and (iv) were peer-reviewed journal articles using a cross-sectional, case–control, cohort, prospective longitudinal design, or randomized controlled trial.

To facilitate the management of references, all retrieved articles were exported from the search databases and organized using EndNote (version X9.3.3, Clarivate Analytics). Articles were initially screened for duplicates using the "Find duplicates" function in Endnote. Duplicate records were deleted. Titles and abstracts were screened to determine eligibility. For studies where inclusion was uncertain based on this initial screening, full texts were retrieved for a second screening according to the inclusion/exclusion criteria, wherein each article was reviewed by C.R. and independently verified by J.D. The PRISMA diagram is shown in Figure 1.

Data Extraction

Following confirmation of eligibility, the following data were compiled and managed in Excel (Microsoft 365, version 2402): first-author names, citation, study design, country (of the corresponding author), year of publication, participant characteristics (*n*, age, biological sex, relative VO_{2max} in ml·kg^{-1}·min^{-1}), cell type, telomere length assessment method, and CPET method (Supplementary Table 1). Considering that this systematic review and meta-analysis was on individual participant data, email requests were sent to one of the named researcher/s from each study. Three separate emails were sent over multiple weeks to attempt to obtain as much data as possible. Data from 11 eligible studies were not obtained, as they were no longer available for several reasons (eg, extended period between publication and request, discarded or failed to respond to email requests—Supplementary Table 2).

Quality Assessment

Risk of bias was independently assessed by C.R. and J.D. using the AXIS tool. Disagreements were resolved by discussion. The risk of bias on the AXIS tool was assessed as 1, 2, or 3, as low, medium/unclear, or high, on 20 criteria. An aggregate score was calculated to assess the overall risk of bias out of 60 (Figure 2).

Data Analysis

Data were initially managed and analyzed in Excel (Microsoft 365, version 2402). An age- and sex-based VO_{2max} percentile score was assigned to each participant using normative data (41). Telomere length data (*n*, mean, and standard deviation) were calculated for each comparator group. Specifically, individuals with a VO_{2max} in the 70th percentile or higher were considered "fit," those with a VO_{2max} below the 50th percentile were considered "unfit," and those in the 90th percentile or higher were considered "extremely fit," according to normative data (41). This stratification aimed to discern any potential association between VO_{2max} and telomere length in humans (ie, individuals with excellent, good,

or below-average fitness—extremely fit, fit, and unfit, respectively). Owing to the large interindividual variation in relative VO_{2max} in the untrained state and telomere length, large separation between fitness groups were necessary. The telomere length standardized mean difference (SMD) was calculated from random-effects models and presented with a 95% confidence interval (CI) for each comparison using Review Manager (version 5.4). The percentage of men included and the ratio between the number of participants with a VO_{2max} >70th and ≤50th percentile were calculated to assess the potential sex and fitness bias in each study, respectively. Pearson's correlation was used to determine linear relationships between effect sizes and the sex and fitness bias scores, and visualized using GraphPad Prism (version 10.3.1). Significance was set at $\alpha = .05$. Funnel plots were visually assessed to evaluate publication bias.

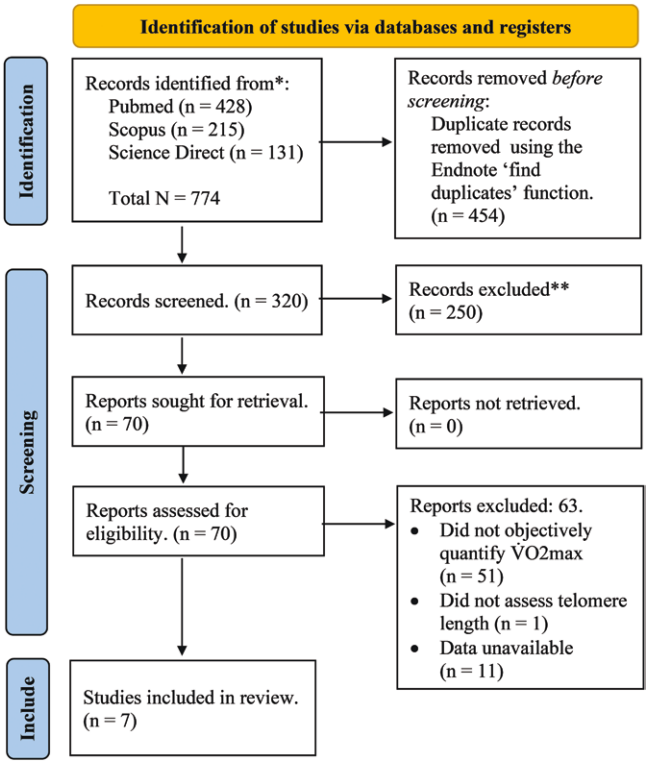

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

Results

Eligible Studies

Of the 18 studies eligible for inclusion in the meta-analysis, data were retrieved from 7 (8 comparisons). The studies that were eligible based on the inclusion criteria but failed to provide data are summarized in Supplementary Table 2. Of the 7 that provided data, whole blood leukocytes were the most common cell type used in telomere length analyses ($n = 3$) (38,42,43). Other studies analyzed telomere length in isolated skeletal muscle satellite cells (44), peripheral blood mononuclear cells (PBMCs) (45), and spermatozoa (46). One study analyzed telomere length in skeletal muscle and leukocytes (47). Three studies analyzed VO_{2max} using incremental protocols on bicycle ergometers, while 1 used a treadmill and another 3 used either a treadmill or cycle ergometer test. A notable sex bias, favoring males (87%), was noted across the included studies. Most studies used a qPCR-based method for analyzing telomere length, while 1 used a quantitative FISH method, and another quantified terminal restriction fragments by Southern blot (Supplementary Table 1).

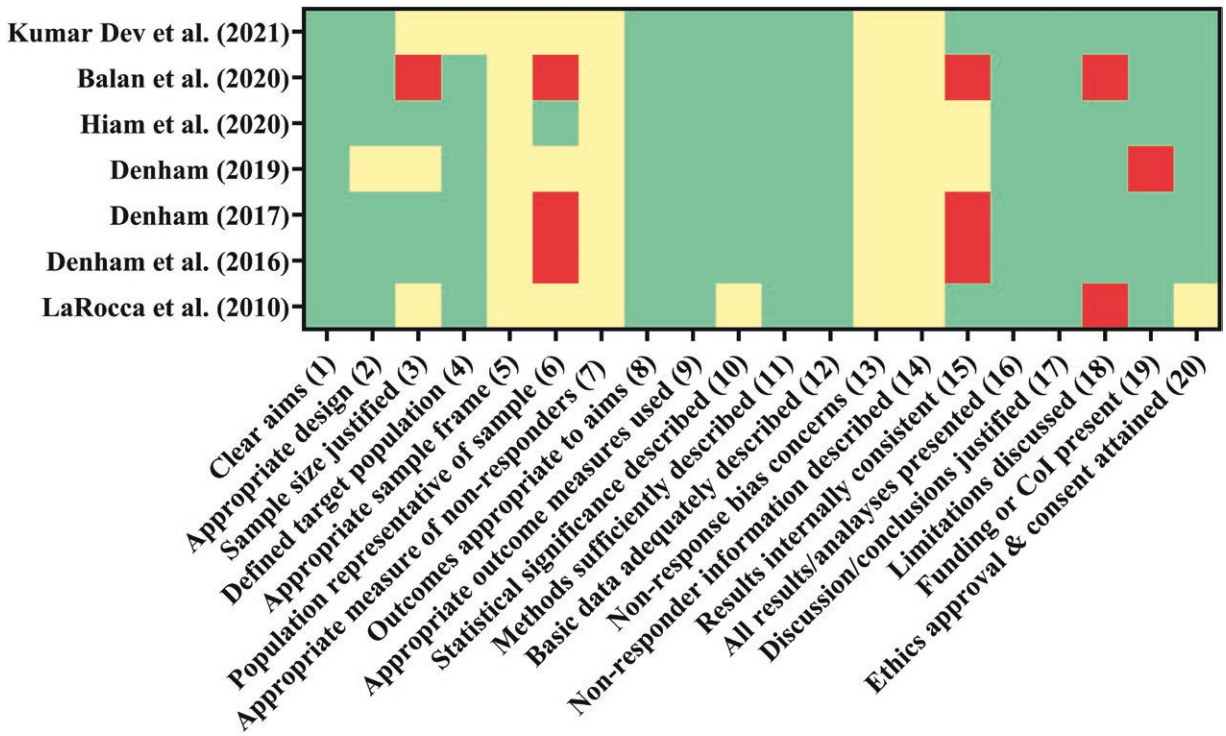

Figure 2. Risk of bias. Green = low risk (1), yellow = moderate risk/unclear (2), red = high risk (3); CoI = conflict of interest.

Risk of Bias

According to the AXIS tool, overall, most studies demonstrated moderate risk of bias when scores were aggregated from the 20 criteria (28.86 ± 2.61 out of 60). All studies had clear aims, used appropriate and valid outcome measures to address their aims, provided sufficient methodologies and basic data, and presented and discussed all analyses appropriately. One study had a modest number of participants, which made the statistical power questionable, another had a possible conflict of interest (funding), 2 did not discuss limitations of their work, 3 may not have included participants representative of their target cohort, and the internal consistency of another 3 studies were questionable, as it appeared that several participants were not included in some analyses (Figure 2).

Longer Telomeres in Individuals With Superior Cardiorespiratory Fitness

Relative to unfit individuals with relative VO_{2max} below the 50th percentile based on age- and sex-based norms (n = 98) (41), fit participants with relative VO_{2max} in the 70th percentile or higher (n = 336) possessed longer telomeres in all tissues (SMD [95% CI]: 0.36 [0.14–0.59], I^2 = 0%, p = .002, Figure 3), with no obvious signs of publication bias (Supplementary Figure 1). Similar findings were observed in separate subgroup analyses on skeletal muscle (n = 21 vs 64, 0.57 [0.07–1.07], I^2 = 0%, p = .03) and leukocytes (n = 71 vs 255, 0.28 [0.02–0.55], I^2 = 0%, p = .04). No clear signs of publication bias were observed for subgroup analyses (data not shown).

To determine if VO_{2max} had a linear association with telomere length, extremely fit participants were compared to unfit and fit individuals (≥90th vs ≤50th and 70th–90th percentiles, respectively). Relative to the unfit controls (n = 98), extremely fit individuals (n = 192) possessed longer telomeres in all tissues (0.28 [0.03–0.53], I^2 = 0%, p = .03, Figure 4). No statistically significant differences were observed in subgroup analyses (data not shown). Again, the funnel plot did not demonstrate clear signs of publication bias (Supplementary Figure 2). A comparison between extremely fit and fit

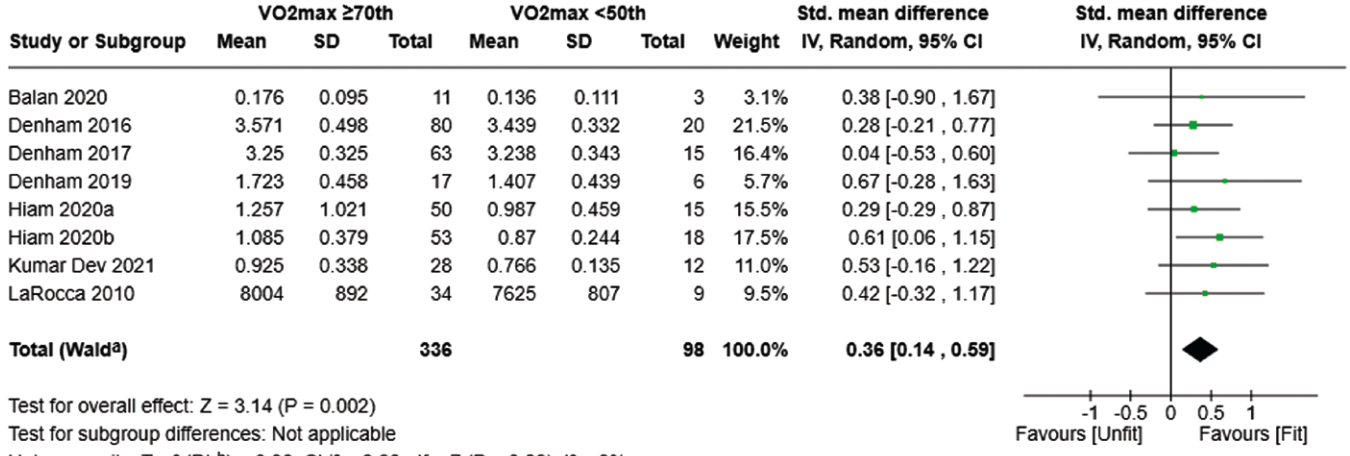

Figure 3. Telomere length differences in unfit and fit individuals.

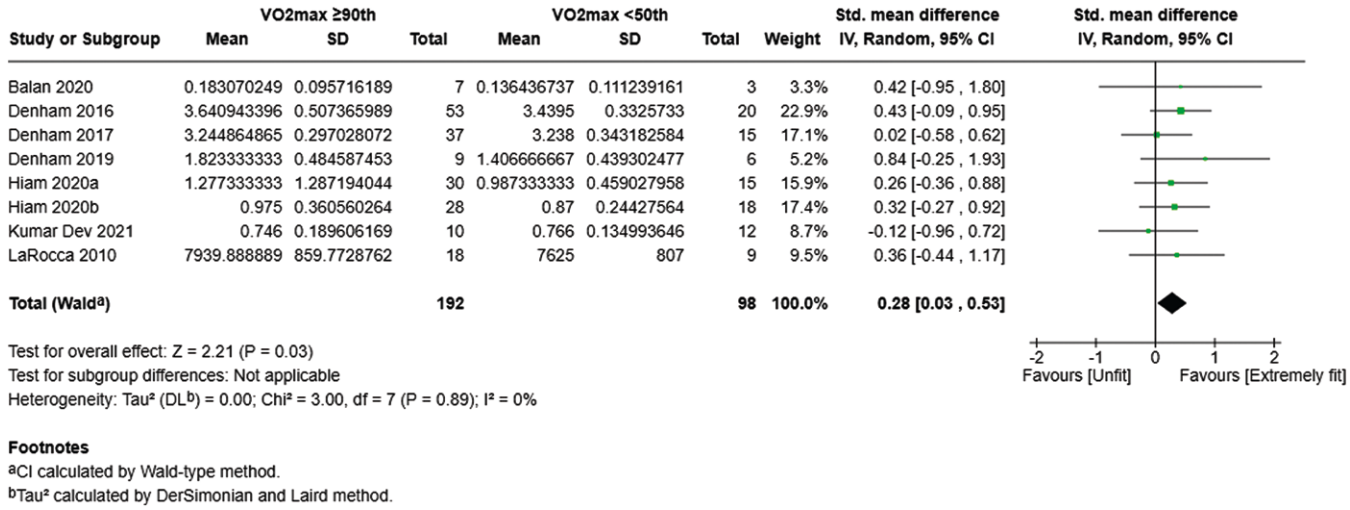

Figure 4. Telomere length differences in unfit and extremely fit individuals.

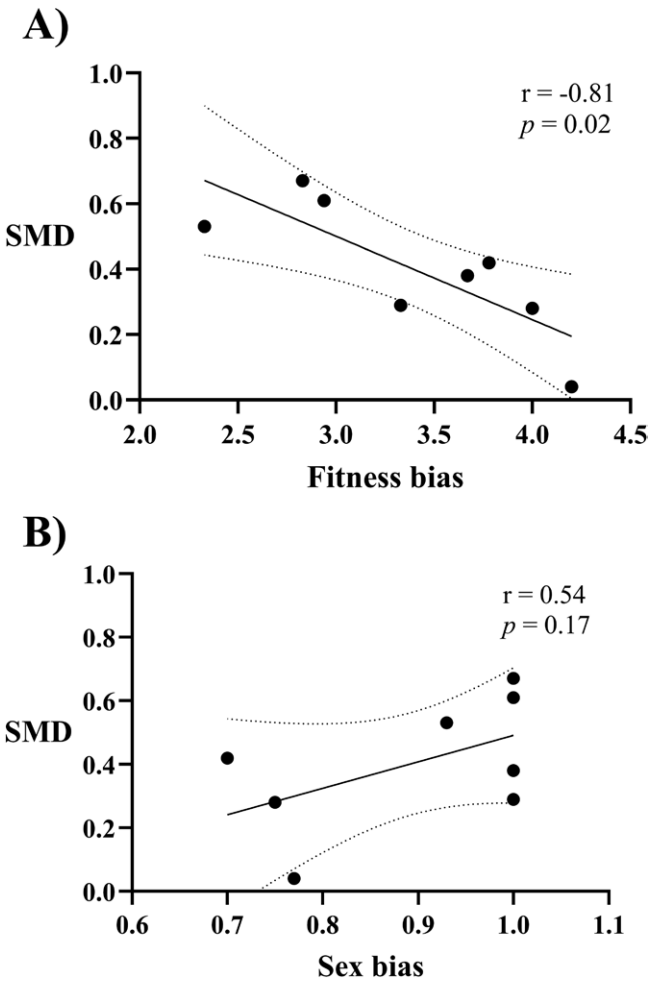

Figure 5. The influence of fitness bias and sex bias on telomere length differences between unfit and fit individuals. A) Strong inverse correlation between fitness bias and standardized mean difference (SMD). Data are expressed as fit relative to unfit individuals. B) A correlation between sex bias (% male) and SMD that was not statistically significant. Data are from Pearson's correlation.

individuals was performed (n = 192 and 144, respectively), yet a statistically significant overall effect was not observed (−0.08 [−0.40 to 0.24], I^2 = 47%, p = .62, Supplementary Figure 3). Further, no statistically significant differences were observed in subgroup analyses, and publication bias did not appear to be present (Supplementary Figure 4).

Linear Correlations Between Observed Effects, and Sex and Fitness Bias

Females, on average, possess longer telomeres than males (48,49), and participant bias in the exercise science literature remains problematic (50,51). An estimate of sex and fitness bias was calculated by determining the ratios between the number of males and females, as well as fit and unfit individuals from each study, and a correlation was performed between these ratios and the effect sizes (≤50th percentile vs ≥70th). A strong inverse correlation was observed between fitness bias and the observed effects from each comparison included in the meta-analysis (r = −.81, p = .02, Figure 5A), whereas the positive correlation between the standardized mean difference and sex bias did not reach statistical significance (r = .54, Figure 5B).

Discussion

Excessive telomere shortening culminates in cell senescence or apoptosis, which accelerates biological aging. Although physical activity, endurance athlete status, and exercise training are associated with telomere maintenance (33–35), the link between cardiorespiratory fitness and telomere length remained unclear. This systematic review and meta-analysis on individual participant data aimed to investigate the association between telomere length and VO_{2max}, as cardiorespiratory fitness is a highly trainable metric of health and endurance performance, linked to human longevity (5,6,17). The major findings from the present work suggests that individuals who are relatively fit with a VO_{2max} in the 70th percentile, based on age- and sex-adjusted normative data, possess longer telomeres in several types of cells (eg, skeletal muscle, sperm, and leukocytes) compared to unfit individuals with below-average fitness (41). Further, relative to the unfit individuals, extremely fit participants with VO_{2max} above the 90th percentile had longer telomeres, yet they were similar and not statistically different from their fit peers (i.e., those in the 70th to 90th percentile). These novel findings are highly translatable and have clinical utility, such that everyone should be encouraged to engage in sufficient aerobic training to improve their VO_{2max} to, at least, the 70th percentile based on their age and sex, to enhance healthy biological aging.

Despite the large heterogeneity in relative VO_{2max} in untrained individuals, it is highly trainable through regular endurance exercise (11–13,52). Previous work has suggested that endurance training and physical activity are associated with telomere maintenance, possibly through the temporary upregulation of telomerase after each bout of endurance exercise and following long-term training (53). Exercise training is known to prevent and manage the symptoms of many aging-related ailments associated with short telomeres (eg, heart disease, dementia, and cancer), and exercise-associated telomere maintenance may play a role in primary prevention. Indeed, endurance athletes have exhibited increased telomerase at the levels of enzyme activity and gene expression in PBMCs and leukocytes (53). Moreover, a single bout of moderate- to high-intensity endurance exercise increases *TERT* expression and telomerase activity in human leukocytes and PBMCs, at least for 24 hours after the cessation of training (54). Exercise-induced telomerase may also support angiogenesis and other physiological adaptations conferred by endurance training that influence VO_{2max} (54). However, human skeletal muscle telomerase activity is either absent or only detectable in certain cases (55,56), most likely due to the terminally differentiated nature of skeletal myocytes and the relatively minute number of satellite cells that divide slowly (ie, in response to stress). Given that telomerase is detectable in human skeletal muscle at the protein level (TERT) in healthy individuals (56) and the noncanonical functions of TERT (54), these, along with antioxidant mechanisms in skeletal muscle that would increase with long-term exercise training, could ultimately lead to less age-related telomere shortening. Unlike most somatic cells, the testes express relatively high levels of telomerase that support age-related telomere lengthening in sperm (27). Thus, regular exercise training could repeatedly lead to temporary increases in TERT and/or telomerase activity—in cells that are almost telomerase deficient (ie, skeletal muscle and leukocytes)—which may attenuate age-associated telomere shortening and support healthy biological aging.

They also suggest a systemic mechanism for telomere maintenance conferred by exercise that remains to be established. Possible explanations may also involve other hallmarks of aging (eg, mitochondrial dysfunction, chronic inflammation, genome instability, perturbed epigenetic landscape, etc.) that are intricately linked to telomere biology (25). Regardless, the meta-analytical findings suggest extensive endurance training aimed at maximizing VO_{2max} may not be necessary to facilitate healthy biological aging, reflected by telomere length and the rate of shortening.

Cardiorespiratory fitness demonstrates an inverse linear relationship with mortality risk (6), yet the benefits of physical activity show signs of diminishing returns with higher training volumes and modest regression at the upper end (57,58). For instance, in a large prospective cohort study, a dose-dependent decrease in mortality risk was observed when moderate to vigorous intensity physical activity was performed from 0–7.5 metabolic equivalent of task (MET)-hours·week^{-1} (20%) to 10 MET-hours·week^{-1} (39%), when the benefits on mortality risk began to subside (31% for those performing ≥10 MET-hours·week^{-1}) (58). It is important to note that endurance athletes above the 90th percentile (41) for VO_{2max} in the present study would presumably perform considerably more exercise each week compared to most participants. A 35-year-old male with a VO_{2max} of 56 ml·kg^{-1}·min^{-1} would quickly achieve 11 MET-hours of physical activity per week jogging at a relatively easy pace of 8.8 METs or ~9 kph—2 training session lasting 37.5 min·week^{-1}, and it is reasonable to suggest that elite athletes would exceed over 10 MET-hours in as little as one session. One of the strengths of the present meta-analytical findings is that relative VO_{2max} is an objective physiological measure and the gold-standard assessment of cardiorespiratory fitness that lacks inherent issues with common methods used to assess physical activity (eg, Hawthorne effect, response bias, recall bias, etc.). It also has more precision than estimated VO_{2max} values obtained from submaximal exercise tests and maximal tests without pulmonary analysis. One's VO_{2max} is impacted by exercise, physical activity, and sedentary behavior, all of which may influence telomere dynamics (34). VO_{2max} also reflects overtraining, as endurance athletes with overtraining syndrome possess shorter mean and minimum skeletal muscle telomeres and decreases in VO_{2max} relative to their healthy athletic peers—albeit still superior to most individuals (80th–90th vs >90th percentile, respectively) (59). Together, these findings are consistent with concepts of diminishing returns and that excessive exercise training outside of physiological limits may be detrimental to telomere maintenance.

Notably, a strong inverse correlation was observed between the effect size and fitness bias, such that larger effects were observed when the numbers of fit and unfit participants in studies were more balanced. It was not the focus of the review, yet it is an interesting observation that may help explain previous negative findings. For example, some case–control and cross-sectional studies examining physical activity or endurance athlete status with telomere length have included groups with similar VO_{2max} values when considered according to age- and sex-based percentiles (Supplementary Table 2). This raises a key point for future studies to address the fitness bias by including appropriate untrained and/or unfit controls. From birth, telomere length is heterogenous within and between participants (up to 4.59 kb difference when measured by Southern blot) (60), which emphasizes the need to ensure adequate statistical power measured a priori. Furthermore, it is unlikely that exercise training can prevent age-related telomere attrition by extending the telomeres, rather it is probably limited to slowing this process (61). As such, it has been suggested that telomere length differences between fit and unfit or exercise-trained and untrained individuals may only become detectable in adulthood or middle age once sufficient age-related telomere shortening and the influence of chronic exercise training have been completed (61). This should be acknowledged when statistical power is lacking (ie, small sample size) and participant (fitness) bias maybe present.

If one aspires to optimize healthy aging, it may be prudent to focus on other lifestyle factors linked to health and lifespan (eg, calorie restriction, meditation, belonging/engagement, etc.) once a sufficient VO_{2max} is achieved from exercise training. Meditation also appears to attenuate telomere shortening (62) and increase telomerase activity (63), through signaling pathways possibly complementary and separate to exercise (64). Given that obesity is associated with short telomeres (65), it is worth noting that calorie restriction-induced weight loss will also inflate relative VO_{2max} if physical activity remains consistent, as VO_{2max} is expressed relative to body weight—ml·kg^{-1}·min^{-1}. Furthermore, calorie-restricted transgenic mice overexpressing *TERT* demonstrate less age-related telomere attrition, as well as longer health and lifespans (66). Thus, weight management should also be encouraged for telomere length maintenance, especially when obesity is associated with short telomeres (65), increased inflammation (67), and several age-related diseases associated with telomere dysfunction (31). Additional benefits to healthy aging could also be achieved from maximizing VO_{2max} with endurance exercise via molecular mechanisms other than telomere maintenance that should be examined in future studies.

There are limitations associated with this review. Despite genuine attempts, not all data were available for inclusion (n = 11 studies). The meta-analysis was limited to 7 studies and 8 comparisons. It is, however, unlikely that the 11 studies would undermine the major finding of this work, as most demonstrated positive associations between VO_{2max} and telomere length (see Supplementary Table 2). Due to the relatively modest number of participants and heterogeneity in telomere length, it was inappropriate to perform additional subgroup analyses (ie, all VO_{2max} percentiles, age groups, biological sex, etc.). However, sufficient statistical power was obtained to address the major goal of the systematic review and meta-analysis, and highlight important considerations for future research. Despite a lack of statistical significance, the sex bias (favoring men) appeared to indicate that a larger effect was observed in studies that focused solely on men (Figure 5B) that should be considered in future investigations. Most studies included in the systematic review used quantitative PCR (ie, telomere-to-single-copy gene ratio) to measure telomere length in arbitrary units (5 out of the 7). One used FISH, which is highly precise, yet expresses telomere length in arbitrary units. Another group measured telomere length in kilobase pairs (kbp) using Southern blot, but this method includes part of the subtelomeric sequence. Although we could not identify any noticeable effects, telomere length assessment method may have had subtle impacts on the SMDs from each study. Since more precise measures of telomere length are now available (eg, TESLA and STELA), others are encouraged to employ these techniques and analyze not only mean telomere

length, but also the percentage of short and long telomeres with aging, exercise training, and aerobic fitness.

Conclusion

The optimal dose of exercise training required to maximize health and lifespan remains unclear. The novel findings from this work have crucial clinical implications and should encourage sedentary individuals to become active or engage exercise professionals to design training programs aimed at increasing VO_{2max} to support healthy biological aging. They also highlight the need for those with acceptable cardiorespiratory fitness to maintain a relatively high VO_{2max} throughout their lifespan. Ultimately, these translatable findings offer achievable cardiorespiratory fitness targets associated with telomere maintenance and healthy biological aging. Cardiorespiratory fitness is highly trainable through regular engagement in an accessible and inexpensive lifestyle factor, endurance exercise.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

None.

Conflict of Interest

None.

Data Availability

The data will be made available upon reasonable request.

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Authors Contributions

J.D. conceived the review. C.R. and J.D. created the review protocol, participated in data analysis and interpretation, and drafted, reviewed, and approved the final version of the paper.

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