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Systematic Review

Lifestyle effects on telomeric shortening as a factor associated with biological aging: A systematic review

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Abstract.
BACKGROUND: Telomeres are structures located at the chromosome ends, whose function is protecting DNA from attrition caused during cell division. Telomeric length serves as a mitotic clock, activating senescence and cellular cycle arrest when it reaches a shortening limit, which causes aging. Lifestyle is a factor that can affect telomeric shortening. Unhealthy habits have been linked to accelerated telomeric shortening, while healthy lifestyles are known to reduce this process and slow down aging. Current community has expressed an interest in improving lifestyle choices; however, an increase in unhealthy habits and chronic stressors have been seen.
OBJECTIVE: This review aims to show the influence that different lifestyles have on telomeric length.
METHODS: The review was carried out following the PRISMA statement in three databases. Twenty-eight research articles and nine review articles were reviewed, identifying six main lifestyles habits.
RESULTS: Regular moderate-vigorous physical activity, dietary patterns rich in vegetables and antioxidants, and the stress control techniques were related to greater telomeric lengths and improvements in the oxidative response by reducing the levels of oxidative stress markers. On the contrary, stress, obesity, smoking, and alcoholism showed a negative effect of shorter telomeres, which can be a factor of early aging.
CONCLUSION: The previous demonstrates the influences of lifestyles on telomere shortening rates and aging, therefore they should be considered as areas of interest for future research, and personal and community health improvement.

Keywords: Telomere, telomeric shortening, aging, lifestyle

Abbreviations

ACEs	Adverse childhood experiences
AGEs	Advanced Glycation End-products
DNA	Deoxyribonucleic Acid
ESTHER	Epidemiological Study on the Chances of Prevention, Early Recognition, and Optimized Treatment of Chronic Diseases in the Older Population
HPA	Hypothalamic-Pituitary -Adrenal Axis
HPFS	Health Professionals Follow-up Study

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LTL Leukocyte Telomere Length
MDD Major Depressive Disorder
NHANES National Health and Nutrition Examination Survey
NO Nitrogen Oxides
PBMC Peripheral Blood Mononuclear Cells
bp Base pairs
PCR Polymerase Chain Reaction Technique
PRISMA Preferred Reporting Items for Systematic reviews and Meta-Analyses
rLTL relative Leukocyte Telomere Length
SAM Sympathetic-Adrenal-Medullary System
SOD Superoxide Dismutase

1. Introduction

Telomeres are nucleoprotein structures located at the ends of every chromosome. They are made of non-coding DNA, which are responsible for the recognition and protection of this part of the chromosome [1, 2]. They consist of a sequence of DNA tandem repeats (TTAGGG) and are associated with Shelterin complex proteins. These proteins form a loop-shaped structure known as the telomeric loop at the end of the chromosome, which helps prevent erroneous DNA damage pathway activation [3, 4]. Telomeres also act as a mitotic clock that determines the replicative capacity of the cell. With each division, cell life erosion can occur [5, 6]. This erosion is caused by the inability of DNA-polymerase to fully replicate linear DNA, which is called end replication problem [7]. Once the telomere reaches a critical shortening point, the Hayflick limit, the senescence and cell cycle arrest pathways are activated. The proliferative cell capacity and tissue recovery are limited, which causes aging [3, 8, 9]. Likewise, telomeres have mechanisms to lengthen themselves and reduce erosion effects caused by cell division; the main one is the telomerase enzyme [1]. This reverse transcriptase enzyme is responsible for adding de-novo telomeric repeats using a homologous RNA template, which compensates for erosion caused by terminal replication problems [1, 2]. However, this enzyme is expressed primarily during embryonic development and after birth. It is active in the male germ line, stem cell, and certain types of cancer [4, 10].

In addition to erosion caused by cell division, both genetic and environmental factors can affect the length of the telomere. Telomere shortening is evident in different degrees, and they are indicative of biological aging [6, 10]. Oxidative stress, for example, accelerates telomere shortening due to telomeric DNA guanine oxidation, which activates DNA damage response by cleavage. Consequently, telomere segments are lost in a greater amount than in cell division [3, 4]. Another main factor to telomere shortening has been lifestyle choices [11]. Unhealthy habits and chronic stressors have been linked to an accelerated shortening of telomeres [6]. On the other hand, healthy lifestyles have been shown to delay shortening and even lengthen the telomere, which is reflected in slower biological aging [12, 13].

PBMC (peripheral blood mononuclear cells) are a type of proliferating cells in which replication leads to constant telomere wear, which allows good correlations between telomere length and aging, in addition PBMC present a high correlation with the telomere length in other tissues, for this reason they are a useful cell type for the analysis of the rate of aging in humans [14, 15]. However, the effect of specific diseases, a specific tissue aging, or cell-specific adaptations can be better reflected by the telomeric lengths of different cell types. Regarding the analysis of the aging rate in humans, PBMC (peripheral blood mononuclear cells) allow obtaining good correlations between telomere length and aging, because it is an easily accessible sample (peripheral venipuncture). Furthermore, blood is a tissue that is in contact with all the other tissues of the body, essential for the transport of oxygen, nutrients and metabolic waste, and it has been described that there is a correlation between the telomeric length of peripheral lymphocytes and the telomeric length of various types of tissues. PBMC are a type of proliferating cells in which replication leads to a constant shortening of telomeres; however, the telomeric lengths of different cell types may better reflect the effect of specific diseases, the aging of a specific tissue, or specific adaptations of the cell. [14].

Currently, there has been a growing interest in improving the quality of life and slowing down aging. Telomere shortening and its role in aging has gained recognition since the 1990s [15]. Nonetheless, the increase in unhealthy lifestyles and other chronic stressors, such as living in big cities, have raised the need to improve the overall health of the community. Because of this, the objective of this review is to demonstrate the influence that current healthy and unhealthy lifestyles have on telomeric length since it is a biological aging factor.

2. Methodology

The review was carried out following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement, taking into account five inclusion criteria: (1) research or review articles in Spanish or English; (2) studies carried out among healthy patients or those suffering from pathologies related to lifestyle or aging; (3) works related to the effect of lifestyles or lifestyle intervention tests on telomeric length; (4) articles with information on telomeric length as an effector of cell aging; (5) publications between the years 2008-2018. Based on the criteria, articles were searched for on PubMed (NCBI), ScienceDirect, and Scielo databases, using key descriptors: telomere length, aging, and lifestyle. Once the articles were selected, according to the screening and selection process proposed in the PRISMA statement, the information relevant to criteria 3 and 4 was extracted in order to develop this review. Additionally, we tabulated the information based in the year of publication, applicability to everyday life, and the journal ranking.

A total of 1,596 records were found in the three databases (142 from PubMed, 1,432 from ScienceDirect, and 22 from Scielo). Only 830 of the records were published between 2008–2018. Furthermore, 125 articles (51 from PubMed, 71 from ScienceDirect, and 3 from Scielo) that met criteria (1) and (2) indicated the information we were looking for in the title. Of the previous 125 articles, 67 were chosen after reading the abstract (37 from PubMed, 28 from ScienceDirect, and 2 from Scielo), which fulfilled criteria (2), (3) and (4). Finally, 36 research articles were chosen after reading the full text. We finally decided on 28 articles that included all of the criteria (18 from PubMed, 9 from ScienceDirect, and 1 from Scielo). Additionally, 9 review articles (2 from PubMed, 6 from ScienceDirect, and 1 from Scielo) were taken into account for theoretical support (Fig. 1).

3. Results and discussion

The research articles were grouped according to lifestyle. In all of the articles that took into account

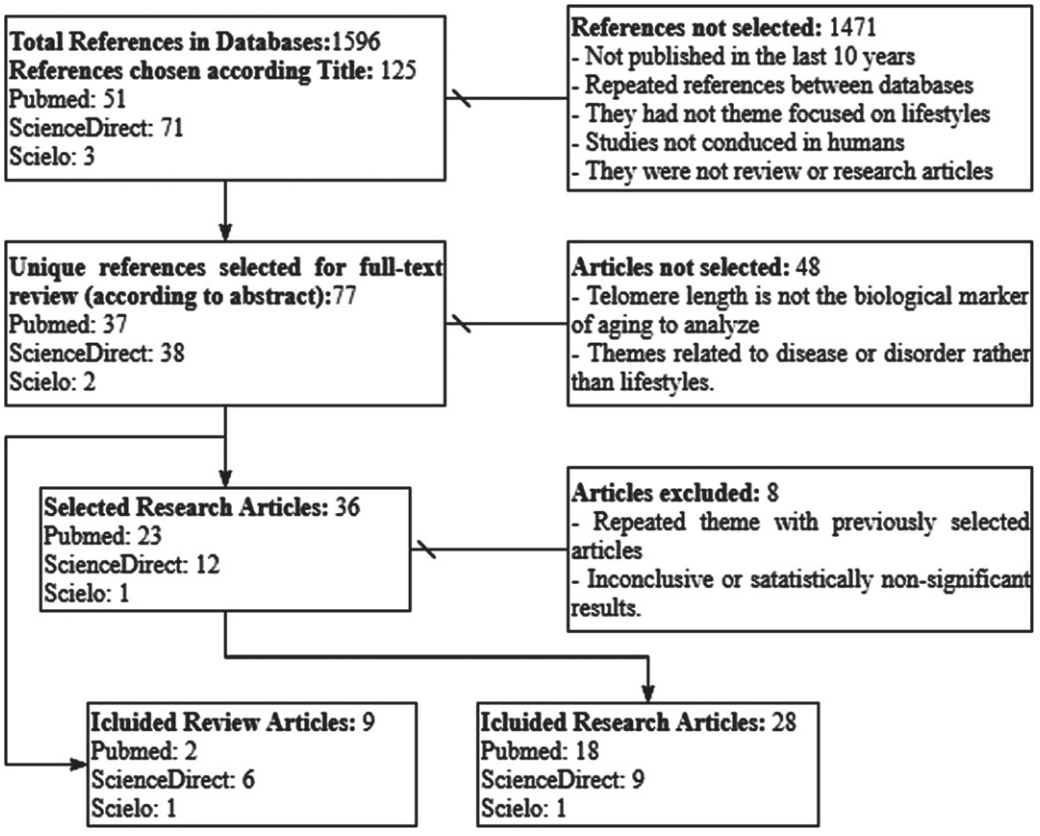

Fig. 1. Flowchart of the article selection process.

age and/or a follow-up, a negative relationship between age and telomere length was reported with varying effects according to lifestyle. Nineteen of the articles focused on the effect of healthy lifestyles on telomere length, which included physical activity (7 articles), diet and nutrient consumption (5 articles), and psychological stress control (7 articles). The previous habits had a positive correlation with telomere length and, in some cases, lengthened the telomeres over time (Supplementary Tables 1, 2 and 3). Likewise, one of these articles demonstrated a significant effect on telomere length through a comprehensive lifestyle intervention based on physical activity, diet, stress control, and social support. In comparison to the control group, the lifestyle changes yielded increased telomerase activity and lengthening over time [13]. On the other hand, 6 of the articles focused on unhealthy lifestyle habits, such as smoking, alcohol consumption, and sedentarism. Only 3 of the articles focused on psychological stress regarding adverse events and/or psychological syndromes, and they showed a negative effect on telomeres (telomere shortening) in comparison to healthy controls (Supplementary Table 4).

4. Healthy lifestyles and their effect on the telomere

4.1. Physical activity

Regular physical activity has been shown to have a positive effect on telomere length. Moderate levels of physical activity have been studied extensively and are most closely related to longer telomere lengths independent of other possible confounding factors such as: Body Mass Index, diseases, and demographic characteristics, among others [16, 17]. In a study conducted by Du et al. [5], older women (average age of 59 years old) who had moderate or high physical activity showed a significantly longer leukocyte telomere length (LTL) than less active women. For this study, this difference in telomere length is calculated as an average of 4.4 years of aging among participating women. In another study, Tucker [18] found that participants in NHANES (National Health and Nutrition Examination Survey) with high physical activity had significantly longer telomeres. On average, the participants' telomeres were 140 bp (base pairs) longer than sedentary people, which is equivalent to being an average of 9 years younger [18].

In addition to moderate or vigorous physical activity, higher intensity exercise levels also showed a positive correlation to telomere length. This may include resistance training, triathlon training at a competitive level, or almost any sport at a professional or elite level. The positive impact of this level of exercise is mainly due to the physiological processes activated by these levels of physical activity. Colon, et al. [19] found greater telomere lengths in competitive level triathletes in comparison to recreationally active people. This demonstrates a positive relationship between telomere length and athlete development parameters, such as VO2max or greater aerobic capacity in triathletes. The previous allows for greater performance, as well as reliance on oxidative metabolism pathways. These characteristics are part of the same phenotype as longer telomere lengths [19]. The relationship between telomere length and high intensity exercises is mainly due to the capacity of redox balance (oxidation-reduction) caused by the effects of this level of exercise on the body [20]. For example, resistance training has been shown to generate a higher availability of nitric oxide (NO) and an increase in the activity of SOD (superoxide dismutase enzyme), indicating a greater regulation of the levels of nitrogen free radicals (produced by the reaction NO with O2) and ROS, which is associated with an improvement in the oxidative response and a reduction in oxidative stress markers [20]. Likewise, an adaptation of specific antioxidants/oxidative stress markers, an improvement in the maintenance of LTL and a reduction in DNA methylation levels has been observed in resistance training practitioners, indicating a greater antioxidant capacity in the cell. which can provide better telomere maintenance and prevent DNA damage from oxidative stress [14]. Taking into account these effects on redox homeostasis and telomere length, maintaining regular physical activity at a moderate to intense level can be considered as a factor that helps reduce telomeric shortening, improving the oxidative response, thus contributing to prevent accelerated aging.

4.2. Diet

Diet has shown to have different effects on telomere length depending primarily on the type of food consumed. Foods with unhealthy characteristics have been linked to shorter telomeres. In a study conducted by Fretts, et al. [9], American Indians of the Strong Heart Family tested the relationship between

the consumption of processed and unprocessed red meat with LTL. They found that the consumption of processed red meat is related to shorter LTL. For each serving of meat consumed, telomere length shortened by approximately 4 years; however, no relationship was found regarding the consumption of unprocessed red meat [9]. Telomere shortening due to the consumption of processed red meat may be linked to high protein, fat, and AGE (Advanced Glycation End-products) contained within the meat. These substances cause oxidative stress and trigger an inflammatory response, which promotes the oxidation of DNA and the accelerated shortening of telomeres [9, 21].

Healthy foods and supplements have been shown to have a positive effect on telomere length. Tucker [22], for example, investigated the relationship between dietary fiber consumption (self-reported) and leukocyte telomere length (LTL) in participants of the NHANES study (National Health and Nutrition Examination Survey, USA). They found that a higher consumption of dietary fiber results in longer telomeres. For every 10g of fiber (per 1000 kcal) consumed, telomeres were 67 base pairs longer equivalent to 4.3 years less of aging [22]. Another study by Nonino, et al. [23] found a positive relationship between telomere length and drinking green tea in obese women. After an 8-week period of drinking green tea, obese women showed a significant increase in telomere length compared to telomere length before the intervention; effect that can be explained due to the antioxidant components present in green tea, such as flavonoids and mainly epigallocatechin-3-gallate (EGCG) [23].

Some nutrients have also been shown to increase telomere length, notably omega-3 fatty acids, vitamins, and minerals. This is due to their antioxidant capability (Omega 3, Vitamins C and E), oxidative stress control, inflammatory and immune response (Vitamins D, A, and B12), or DNA damage response action (Folate and Nicotinamide) which can control telomere length and aging [21, 24].

Diets rich in fruits and vegetables, such as the Mediterranean diet, have also been shown to have a positive effect on telomere length, thereby, decreasing the aging process [25, 26]. A study conducted by Gong et al. [27] found among 4 dietary patterns that only the 'rich in vegetables' pattern that was characterized by a major intake of fruits, whole grains, various groups of vegetables, dairy products, nuts, eggs and tea, was positively related to TL in women, while the other patterns did not show a statistical relationship with TL [27]. This positive effect of the dietary pattern on LT is largely due to the antioxidant capacity of these foods, which contributes to the reduction of oxidative stress, which has been related to the maintenance of telomeres [28]. In this way, it is advisable to increase the consumption of fruits and vegetables and other foods with antioxidant potential, in order to help regulate the length of telomeres, improve the response of cells to oxidative stress, and reduce damage to DNA that causes aging.

4.3. Techniques for the control of psychological stress

Controlling psychological stress has been shown to have a positive effect on the maintenance of telomeres. Different techniques to control stress have shown an effect on reducing the length of telomeres over time, as well as improving complications from disease and age. Duan, et al. [29] found that Tai Chi has been related to increased telomerase activity in peripheral blood mononuclear cells after 6 months in middle-aged adults (55–65 years). This increase in telomerase activity may act as a contributing factor to the maintenance of telomeres [29]. Krishna, et al. [30] compared healthy and active yoga practitioners (30–40 years) to healthy non-yoga practitioners and found that regular practitioners of yoga had longer telomere lengths, a reduction in systemic oxidative stress markers (total antioxidant status), and lower Malondialdehyde and homocysteine levels [30].

Meditation and other techniques have been shown to maintain the length of telomeres and control the factors involved in their shortening. A follow-up study conducted by Ornish, et al. [13] found that a comprehensive 5-year lifestyle intervention, which included meditation, was associated with longer telomeres, and an increase (at 3 months of intervention) and subsequent reduction (at 5 years of intervention) in telomerase activity among men diagnosed with low-risk prostate cancer through an active surveillance (biopsy). Dada, et al. [31] and Tolahunase, et al. [32] found that meditation during yoga practice resulted in longer telomeres, a reduction in oxidative stress markers, and lower DNA damage in sperm cells [13, 31, 32]. Meditation techniques alone have also demonstrated an effect on telomere length. Hoge, et al. [33] conducted a study on people (ages 18 or older) practicing Metta Meditation or love-kindness (which focuses on positive intention, kindness, and human warmth) in comparison to non-practitioners

of yoga or meditation. They found a significantly higher leukocyte telomere length only in the women practicing this meditation technique [33]. In another study conducted by Conklin, et al. [34], the participants engaged in a month of Insight Meditation (a vipassana practice, based on meditative withdrawal and focus on deep and isolated concentration) showed an average increase in telomeric length of 104.2 bp in peripheral blood mononuclear cells (equivalent to a 4-year decrease in aging), in addition to presenting slightly higher patterns of telomerase activity and gene expression related to telomere biology, (mainly *Atrip, Cct1, Cct6, Gar1 and Hnrnpa1*) in meditating practitioners after 3-weeks of Insight meditative withdrawal [34].

The capability of these practices on telomere maintenance is mainly linked to both physical and psychological qualities. Since these practices are mind-body interventions, they have moderate to intense levels and utilize various breathing techniques that contribute to the improvement of conditions related to lifestyle (Body Mass Index and glucose levels), inflammatory response, and the reduction of oxidative stress levels in the body. Therefore, cell damage is decreased, and telomere maintenance mechanism are activated. This contributes to the cell's longevity and improves the health of the cell at the somatic and reproductive level. The appearance of aging in relation to diseases like cancer is reduced both at and early and future age [29–34]. Different stress management techniques have an important role in both psychological and physical health, which also contribute to the regulation of oxidative stress levels and telomere shortening. Thus, it is advisable to regularly practice these techniques and reduce the effects of psychological stress as a means to slow down one's aging.

5. Unhealthy lifestyles and their effect on telomeres

5.1. Smoking and alcoholism

Although cigarette and alcohol consumption have been linked to other diseases (including cancer), their effect on telomere length is still unclear. While some studies generally report these factors as being negatively related to telomeric length, other studies report an insignificant or null relationship. For example, Latifovic et al. [35] conducted a cross-sectional study among men and women (20–50 years) to determine the influence of alcohol, cigarette consumption, and physical activity (self-reported) on the relative Length of Leukocyte Telomere (rLTL) measured by quantitative PCR. The findings showed that daily cigarette consumption was related to shorter rLTL (on average 0.096 relative units shorter than in non-smokers). However, they found no relationship between alcohol consumption (self-reported as moderate by the participants) and telomere length compared to other research studies [35]. Likewise, Muezzinler, et al. [36] studied a subsample of men and women (50–75 years) from the ESTHER study (Epidemiological Study on the Chances of Prevention, Early Recognition, and Optimized Treatment of Chronic Diseases in the Older Population). They found an inverse relationship between smoking and LTL, where current smokers had shorter telomeres than non-smokers. In addition, the intensity of the habit was related to lower LTL, but they found that smoking was associated with lower rates of telomere shortening during the 8-year follow-up. As a secondary result, shorter telomeres were found in association to increased alcohol consumption [36].

Although alcohol consumption is a major risk factor for morbidity and mortality, its link to telomere length is still unknown. Some studies have shown telomere shortening when alcohol consumption is increased, while others have reported beneficial health benefits with moderate consumption [24]. In the case of smoking, the intensity of consumption has been linked to telomere shortening [37]. Revesz et al. [38] found that smoking was associated with shorter telomeres, along with other factors. Huzen, et al. [39] found smoking as a factor related to telomeric length change, where active smokers had an annual shortening rate of three times over non-smokers. Moreover, people who quit smoking had an annual telomere shortening rate comparable to people who had never smoked. The negative effect of smoking on telomere length may be due to the free radicals it produces, which induce oxidative stress. This results in an accelerated shortening of the telomeres [37]. Even though the effect of these lifestyle factors on telomeric length may not be entirely clear, they can be considered as potential accelerators of telomeric shortening. Because of this, a reduction in their consumption is recommended in order to improve one's health and slow down biological aging.

5.2. Sedentary lifestyle and obesity

Sedentary behavior and obesity have also been associated with a negative effect on telomere length

and aging [23, 40]. Sedentary behavior has been related to reduced mitochondrial activity (an important determinant of biological aging). It is also a predictor for conditions like obesity, which has been directly related to shorter telomeres [5, 40].

Joshu, et al. [41] conducted a study on 596 men (40–75 years) participating in the HPFS (Health Professionals Follow-up Study), who were surgically treated for prostate cancer. Prostatectomy tissue samples were measured, taking into account cell type and telomeric length. They found that the men with increased anthropometric measures (adiposity, hip circumference, and weight gain starting at 21 years of age) and lower amounts of physical activity had shorter telomeres only in stromal prostate cells. Additionally, they found that overweight or obese men, who were less active, had telomeres 20.7% shorter in stromal cells than active and normal-weight men. This ratio can be translated into a 29% increase of having fatal prostate cancer [41]. Likewise, another study conducted by Grun, et al. [42] in adults aged 18–65 discovered shorter telomeres in patients with severe or morbid obesity, as well as an increase in macromolecule oxidative damage (lipid peroxidation and protein oxidation) and antioxidant response systems non-enzymatic levels (total reactive antioxidant potential and total antioxidant reactivity). Also, they found increased levels of Shelterin complex (*TRF1, TRF2, POT1* and *DKC1*) expression, where *TRF1* levels were the main contributor to telomeric shortening in people with obesity [42]. The increase in Shelterin components expression indicated an adaptive antioxidant response insufficiency. Together with metabolic dysfunction and chronic inflammation, Shelterin components expression contributes to an increase in oxidative stress levels, accelerated telomeric shortening, and premature biological aging [23, 42]. In this way, it is crucial to control Body Mass Index, prevent obesity, and reduce sedentary habits. Therefore, accelerated aging and pathologies could be prevented early on.

6. Conclusion

Biological aging is a complex process specifically linked to telomeric shortening. This shortening, limits the proliferative capacity of cells, which over time reduces the capacity of tissue recovery and accelerates aging. Environmental factors can influence the rate at which this process occurs. Environmental factors can influence the speed at which this process occurs, of which lifestyles have been related as the main factors involved in the acceleration or deceleration of this process. The studies presented in this review show that different lifestyles can have a certain influence on the length of telomeres, showing an apparent reduction or increase in telomere length depending on the nature of the lifestyle.

Unhealthy lifestyles (sedentary lifestyles, obesity, smoking, and alcohol) have negative effects on telomeric length, which is reflected in an accelerated shortening of the telomere and development of premature aging. On the other hand, healthy lifestyles (physical activity, stress management, and antioxidant-rich diets) show telomere maintenance and even a lengthening effect. In this way, different lifestyles have an apparent impact on the biological aging rate, which is why it is advisable to control habits that negatively impact telomere length and support those that contribute to maintenance and/or lengthening of these.

Different lifestyles have an apparent impact on the rate of biological aging, which is why it is advisable to control habits that negatively impact telomere length and support those habits that contribute to the maintenance and/or lengthening of telomere. Although the different studies presented show the influence of different lifestyle habits on telomere length and implicitly on aging, they are mostly carried out on a type of cell that, although it reflects globally the telomeric shortening in the body (such as PBMC are), do not allow to generate estimations towards a total aging process of the organism, both chronological and biological, this because the possible relationship of the effects of lifestyle on specific tissues or the adaptive response of some cells types to the lifestyles changes can't be reflected. For this reason, lifestyles should be considered an area of interest for future research, taking into account in turn different types of cells, this in order to obtain better estimates of an aging process and the effects of different styles of life on telomere length in the body, with a view to improving physical and psychological health and general life expectancy at the individual and community level.

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Conflict of interest

The authors declare no conflict of interest.

Author Contributions

REEO and JMS wrote the paper and edited the manuscript; REEO, JMS, JFV, MFC, and CIEP studied the concepts; REEO, JMS, JFV, MFC, and CIEP prepared the manuscript; all authors participated in discussions and critically reviewed the manuscript; JMS and MFC approved the final version of the manuscript.

Supplementary material

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