REVIEW

Impact of Nutrition on Telomere Health: Systematic Review of Observational Cohort Studies and Randomized Clinical Trials

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ABSTRACT

Diet, physical activity, and other lifestyle factors have been implicated in the pathophysiology of several chronic diseases, but also in a lower total mortality and longer life expectancy. One of the mechanisms in which diet can reduce the risk of disease is with regard to its impact on telomeres. Telomere length (TL) is highly correlated to chronological age and metabolic status. Individuals with shorter telomeres are at higher risk of chronic diseases and mortality. Diet may influence TL by several mechanisms such as regulating oxidative stress and inflammation or modulating epigenetic reactions. The present systematic review aims to examine the results from epidemiologic and clinical trials conducted in humans evaluating the role of nutrients, food groups, and dietary patterns on TL. We also discuss the possible mechanisms of action that influence this process, with the perspective that TL could be a novel biomarker indicating the risk of metabolic disturbances and age-related diseases. The available evidence suggests that some antioxidant nutrients, the consumption of fruits and vegetables, and Mediterranean diet are mainly associated with longer telomeres. However, most of the evidence is based on high heterogenic observational studies and very few randomized clinical trials (RCTs). Therefore, the associations summarized in the present review need to be confirmed with larger prospective cohort studies and better-designed RCTs. *Adv Nutr* 2020;11:576–601.

Keywords: telomerase, telomere length, macronutrients, micronutrients, food, dietary pattern

Introduction

Telomeres are special structures at the end of chromosomes that protect the integrity of DNA information throughout the cell cycle, preventing loss of DNA during cell division (1). After consecutive cellular divisions, telomere length (TL) naturally shortens until a critical size is reached, which causes cellular senescence or apoptosis, also known as the end replication problem (2). In people, telomeres shorten with age in all replicating somatic cells that have been examined, including fibroblasts and leukocytes (3). Thus, TL can serve as a biomarker of a cell's biological (versus chronological) "age" as potential for further cell division. Telomerase, the enzyme with catalytic activity, answers the end replication problem by promoting telomere lengthening (4).

Telomere attrition is a natural phenomenon widely recognized as one of the hallmarks of aging (5). A large number of population-based studies have observed a decrease in leukocyte telomere length (LTL) in parallel with increasing age (6). In this regard, positive relations were established between clinically different pathological conditions, modulated by lifestyle variables through oxidative stress and inflammation, and the accelerated shortening of telomeres (7). Therefore, nutrition, oxidative damage, telomere shortening, and cell senescence represent a sequence of processes, which may play an important role in in vivo aging and longevity.

As stated previously, telomere shortening has been shown to be accelerated by inflammation (7) and oxidative stress (8, 9), but also by metabolic conditions that increase inflammation and oxidative stress such us abdominal obesity, hyperglycemia, and hypertension (10). Prenatal conditions and early adversity contribute to adult TL in addition to current stress and other lifestyle factors. In fact, different studies suggest that telomere attrition is modifiable, as substantial variability exists in the rate of telomere shortening that is independent of chronological age (11). Telomere attrition has also been linked with other potentially modifiable lifestyle factors, such as poor nutrition and physical inactivity (12, 13) indicating the plasticity of TL. In fact, findings from different studies show that a healthy diet, low stress, exercise, and a good sleep pattern are related to longer telomeres (14, 15). Therefore, TL variability may be partially explained by lifestyle practices, including dietary patterns.

Unfortunately, most of the studies relating lifestyle and telomere health are observational and very few randomized

  doi: https://doi.org/10.1093/advances/nmz107.

clinical trials (RCTs) generating high-quality evidence have been conducted. Indeed, some studies have not found such associations, which leads to contradictory results regarding the effect of lifestyle on TL. As far as we know, only 2 systematic reviews have been conducted analyzing the effect of diet on TL (16, 17). However, no one specifically analyzed the association between nutrients, food groups, and dietary patterns using RCTs and observational studies.

Therefore, the aim of this systematic review is to examine the results from epidemiologic and clinical trials conducted in humans evaluating the role of nutrients, food groups, and dietary patterns in TL and telomerase activity. We also discuss the possible mechanisms of action that influence this process, with the perspective that TL could be a novel biomarker, measured from blood samples, that could indicate the risk of suffering age-related diseases.

Although a positive effect of dietary restriction on TL and telomerase activity in rodents has been well documented (18), no clear evidence exists in humans that dietary restriction delays aging related to TL (19). It is important to mention that in the present review, the effect of reduced calorie intake on telomere health is not addressed.

Methods

Protocol registration

The protocol for the systematic review is available in PROSPERO (http://www.crd.york.ac.uk/PROSPERO; identifier: CRD42019139580).

Search strategy

The studies included in this systematic review were identified by a literature search conducted in both MEDLINE-PubMed and Cochrane Library databases as well as a manual search. Published literature from the earliest available online indexing year up to 1 February, 2019 for PubMed and up to 4 February, 2019 for the Cochrane Library was included.

Both searches were conducted by combining 6 separate search subsets of dietary variables with a unique search subset for telomere health. In each database, a list of Medical Subject Headings and keywords was used, in order to obtain a comprehensive vision of all the published literature available for the purpose of this review (**Supplemental Tables 1** and **2**).

Eligibility criteria and study selection was used

The search included case-control studies, cross-sectional studies, prospective cohort studies, and RCTs. We considered studies involving males or females, healthy adults or patients affected by some major disease, such as cancer, diabetes, hypertension, or overweight and obesity. We excluded studies conducted in pregnant women, children, or infants.

After a primary screening, the full texts of the selected articles were obtained. Using a standardized model, 2 independent researchers analyzed the full text of the articles that passed the first screening. Finally, a third author evaluated eventual discrepancies in the selected articles. This systematic review includes 59 observational studies and 11 RCTs (**Supplemental Figure 1**).

Study Quality Assessment

The quality of all included studies in the present systematic review was assessed by 2 independent researchers. The NIH National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-sectional Studies was used in order to assess the risk of bias in observational studies. The Cochrane Collaboration Tool was used to assess the risk of bias in the included RCTs. Depending on the score assigned, the studies were categorized as either good, fair, or poor quality, according to the Agency for Healthcare Research and Quality standards. Discrepancies between researchers were solved by consensus. After analyzing the quality of all studies, 81.3% of the observational and cross-sectional studies were categorized as good quality, whereas 81.8% of the RCTs were categorized to have low risk of bias.

Results and Discussion

Macronutrients and TL

Total protein and carbohydrates have not been clearly associated with TL (12, 20) (**Table 1**). However, results from 2 cross-sectional studies have shown positive associations between dietary fiber intake and TL (12, 21) suggesting that the quality of carbohydrates, and specially dietary fiber, may have a potential beneficial effect on telomere health in parallel to reducing the risk of chronic diseases (22, 23).

By contrast, the effects of dietary fats with respect to telomeres have been studied in more detail than the other macronutrients. Fat is a key diet component that has been shown to play an important role in inflammation. To date, 2 case-control studies have investigated the association of dietary fat with TL. One cross-sectional

The Physiopathology of Obesity and Nutrition Networking Biomedical Research Center (CIBEROBN) is an initiative of the Carlos III Health Institute(ISCIII) of Spain, which is financed by the European Regional Development Fund (ERDF) (CB06/03). SG is a doctoral fellow from AGAUR no. 2018FI_B_00444, Generalitat de Catalunya. SC is supported by an RYC-2013-12598 grant by the Spanish Ministry of Science, Innovation and Universities; JM is a doctoral fellow funded by the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement no. 713679 and from the Rovira i Virgili University (URV); JG-G received a PFIS grant no. FI17/00255 into the AES program from the Carlos III Health Institute (ISCIII), Spanish Ministry of Health .
Author disclosures: The authors report no conflicts of interest.
Supplemental Tables 1 and 2 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: BSDS, Baltic Sea Diet Score; CVD, cardiovascular disease; DII, Dietary Inflammatory Index; FA, fatty acid; HBCS, Helsinki Birth Cohort Study; HEI-2010, Healthy Eating Index; KGES, Korean Genome Epidemiology Study; LA, linoleic acid; LTL, leukocyte telomere length; MedDiet, Mediterranean diet; MESA, Multi-Ethnic Study of Atherosclerosis; NHS, Nurses' Health Study; PBMC, peripheral blood mononuclear cell; PREDIMED, Prevention with Mediterranean Diet Study; RCT, randomized clinical trial; SFA, short-chain fatty acid; SMSFA, short-to-medium-chain fatty acid; TFA, *trans*-fatty acid; TL, telomere length; WHI, Women's Health Initiative; WHICAP, Washington Heights-Inwood Community Aging Project; 1,25(OH)D3, 1,25 dihydroxyvitamin D.

TABLE 1 Epidemiologic studies evaluating the effect of dietary macronutrients on telomere length[1]

Reference	Design	Population	Method	Factor	Results
Tucker AL et al., 2018 (21)	Cross-sectional	5674 healthy participants from the NHANES study	PCR	Dietary fibers	Fiber intake per 1000 kcal was positively associated with TL (linear association)
Cassidy A et al., 2010 (12)	Cross-sectional	2284 women from the Nurses' Health Study	PCR	Dietary fiber, fats, protein	Fiber intake was positively associated with LTL, whereas protein intake was not associated to LTL. PUFA (specifically, Linoleic acid) intake were significantly inversely associated with LTL
Zhou M et al., 2016 (20)	Cross-sectional	Chinese population with normal glucose tolerance ($n = 200$), pre-diabetes ($n = 197$) and newly diagnosed diabetes ($n = 159$)	PCR	Dietary carbohydrate, protein and fat intake	No correlation between daily carbohydrate, protein and fat intake and LTL was reported
Mirabello L et al., 2009 (24)	Case-control	612 advanced prostate cancer cases and 1049 age matched cancer free controls from the PLCO Cancer Screening Trial	PCR	Dietary fat intake	Prostate cancer cases and controls did not differ with respect to mean relative TL. Non-significant trends for fat intake related to relative TL was found
Song Y et al., 2013 (25)	Case-control	4029 women from the WHI-OS with and without diabetes	PCR	Different types of fat intake	Women with SFA intake in the lowest compared to highest quartile had significantly longer TL. MUFAs and PUFAs were not significantly associated with TL in the fully adjusted models. SMSFA had an inverse association with TL
Tiainen A-MK et al., 2012 (26)	Cross-sectional	1942 Healthy subjects from the Helsinki birth cohort	PCR	Dietary fats	In men, high total fat, SFA, and butter intake was inversely associated with LTL
Kark D J et al., 2012 (27)	Prospective cohort	609 Healthy subjects from the Jerusalem LRC study	SB	Daily carbohydrate, protein and fat intake	In men, PUFA and MUFA as a percentage of total energy showed significant inverse associations with LTL in bivariate models. This significance was maintained only in MUFAs in the multivariable backward stepwise regression
Kielcot-Glaser et al., 2013 (28)	RCT	106 Healthy subjects treated with: *a*) 2.5 g/day n-3 PUFA; *b*) 1.25 g/day n-3 PUFA; *c*) placebo capsule constituted by a mixture of oils representative of dietary fat content in American diet for 4 months	PCR; TRAP	n-3 PUFA supplementation, n-6:n-3 PUFA ration	No significant differences in TL between the three groups were noted. Decrease in one unit of n-6: n-3 PUFA was associated with an increase in TL by 20 bp
O'Callaghan N et al., 2014 (30)	RCT	33 adults with mild cognitive impairment with supplemented either: *a*)n-3 PUFAs as EPA (1.67 g EPA+ 0.16 g DHA/day) *b*) n-3 PUFAs as DHA (1.55 g DHA+ 0.40g EPA/day) *c*) n-6 PUFA as linoleic acid (2.2g LA) for 6 months	PCR	n-3 supplementation	Changes in erythrocyte DHA group were inversely significantly associated with TL. No differences between intervention groups were observed in changes of TL

(*Continued*)

TABLE 1 (*Continued*)

Reference	Design	Population	Method	Factor	Results
Pawelczyk T et al., 2018 (31)	RCT	71 Schizophrenic patients treated with: *a*) 2.2 g/day of n-3 PUFA ($n = 36$); *b*) Placebo (Olive oil, $n = 35$) for 26 weeks	PCR	n-3 supplementation	Significant increase in the telomerase activity in both groups were observed and the increase in the n-3 PUFA group were significantly higher than placebo
Pavanello S et al., 2011 (34)	Case-control	457 Healthy participants (controls = 257, cases of alcohol abusers = 200)	PCR	Alcohol consumption (units of drink/day, each unit = 10–12 g of alcohol)	Abusive intake of alcohol was negatively associated with TL. Participants consuming >4 drink units per day compared with <4 drink units per day had a significantly shorter TL
Bekaert S et al., 2007 (35)	Cross-sectional	2509 Healthy participants from Asklepios study	PCR	Alcohol consumption (units alcohol per week)	Alcohol consumption in both men and women were inversely associated with TL

[1] LTL, leukocyte telomere length; PLCOCST, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; TL, telomere length.

study involving prostate cancer participants indicated no associations ($P = 0.77$) (24), whereas Song et al. (25) showed a positive cross-sectional association with certain classes of fatty acids (FAs). In this case-control study among postmenopausal women, MUFAs and PUFAs showed no associations ($P = 0.33$ and $P = 0.55$, respectively), whereas short-to-medium-chain fatty acids (SMSFAs) were inversely associated with LTL. Replacing 1% of energy intake from SMSFAs with other energy sources was associated with longer telomeres. In the same cross-sectional analysis, no association was observed for total fat ($P = 0.09$). By contrast, in a cross-sectional analysis of the Helsinki Birth cohort, high total fat intake was associated with shorter LTL in men, but not in women ($P = 0.26$) (26). Similar inverse correlations between dietary total fat, short-chain fatty acids (SFAs), and LTL were seen in a prospective study conducted amongst 609 participants from the Jerusalem Lipid Research Clinic (LRC) cohort (27). In that study, along with SFAs, MUFAs and PUFAs (expressed as percentage of total energy) showed significant inverse associations in the bivariate models. Interestingly, these associations were seen only in men, but the significance was maintained only in the case of MUFA intake after multivariable backward stepwise regression (27). PUFA intake, specifically linoleic acid (LA), was also inversely associated with LTL in another cross-sectional study (12).

An RCT investigating the effect of ω-3 (n–3) supplementation on telomerase activity or LTL showed no significant effects of supplementation. The participants in this placebo-controlled RCT took ω-3 supplements at different concentrations (2.5 g/d or 1.25 g/d) or placebo (FAs in the typical American diet) for a period of 4 mo. Even though no significant differences in TL between the 3 groups were noted ($P = 0.39$), they found a significant inverse association between changes in the ω-6:ω-3 PUFA ratio in plasma and LTL (28). It is worth mentioning that the ratio of ω-6:ω-3 has been an interesting topic of study as these 2 FAs regulate several inflammatory pathways by competing for enzymes and receptors (29). Consequently, ω-6 compared with ω-3 supplementation was investigated in another 6-mo RCT in adults with mild cognitive impairment. Dietary supplementation with both ω-3 FAs, DHA and EPA, or ω-6 LA FA showed a trend towards telomere shortening in the LA-supplemented group and a protective effect on TL in the DHA group (30). In another ω-3 supplementation study with concentrated fish oil (enriched in EPA + DHA) or placebo (olive oil, rich in MUFA), amongst schizophrenia patients, a significant increase in the peripheral blood mononuclear cell (PBMC) telomerase concentration was reported in the fish oil–supplemented group (31). Unfortunately, most of the RCTs are of short duration, preventing determination of the effects on telomere shortening.

Taking into account all the aforementioned studies we can conclude that even though most studies have demonstrated a positive relation between ω-3 FA and LTL, the overall relation of MUFAs and PUFAs with LTL is inconsistent, as these studies demonstrated either no significant association ($P > 0.05$) (25, 26) or an inverse association (27) between MUFAs or PUFAs and LTL. Hence, this requires further investigation in the future by means of longer RCTs conducted in large samples of individuals.

Alcohol has been related to all-cause mortality in a J-shaped curve, although debated for different disease associations (32, 33). However, its relation with TL is controversial. A case-control study and a cross-sectional study have investigated the association between alcohol intake and TL. The case-control study conducted by Pavanello et al. (34) showed that among 457 participants (200 alcohol abusers, 257 controls), subjects drinking more than 40 g of alcohol per day (drink units) had significantly shorter TL compared with those that drink less. Similar results were seen in a cross-sectional analysis of the Asklepios study, where alcohol consumption was negatively associated with TL in both men and women (35). In the following section, alcohol beverage intake as a food group will be further discussed in order to give a wider perspective.

TABLE 2 Epidemiologic studies and RCTs evaluating the effect of dietary micronutrients on telomere length[1]

Reference	Design	Population	Method	Factor	Results
Borras et al. 2012 (42)	Case-control	62 hemodialysis patients, 55 sex-matched controls. 24 hemodialysis patients received vitamin D supplements for 28.8 mo	SB	Vitamin D	Hemodialysis patients had shorter TL compared with the controls. Significant associations between phosphorous concentrations, active vitamin D treatment, and LTL were observed
Mirabello et al. 2009 (24)	Case-control	612 prostate cancer cases and 1049 age-matched cancer-free controls from the PLCOCST	PCR	Vitamins and minerals	No significant baseline associations were found between the intake of vitamin E, lycopene, β-carotene, vitamin D, selenium, and LTL
Xu et al. 2009 (43)	Cross- sectional	586 participants with breast cancer from the Sisters Study	PCR	Multivitamin supplementation in diet	Multivitamin supplementation was associated with longer TL. Compared with the nonusers, daily users had an average 5.1% longer TL. With adjustment for multivitamin use, the total intake of micronutrients remained significant only for vitamins C and E
Marcon et al. 2012 (44)	Cross- sectional	56 healthy subjects	TRF	Thiamin, riboflavin, niacin, vitamin B-6, folate, vitamins A, C, D, E, and β-carotene	Vitamins A, C, E, folic acid, and β-carotene were positively correlated with LTL. After adjustments, only β-carotene show a significant correlation
Cassidy et al. 2010 (12)	Cross- sectional	2284 female participants from the Nurses' Health Study	PCR	Vitamin D	No significant associations between vitamin D and TL were reported
Lee et al. 2017 (45)	Cross- sectional	1958 men and women from the Korean Genome Epidemiology Study	PCR	Vitamins A, C, E, thiamin, riboflavin, vitamin B6, niacin, retinol, carotene, folate, calcium, phosphorous, iron, zinc	After adjusting for potential confounders, vitamin C and potassium were significantly positively associated with LTL. Folate showed a trend for positive association
Lin et al. 2018 (46)	Cross- sectional	7324 participants from the NHANES study	PCR	Dietary copper intake	One unit of log-transformed dietary copper intake was significantly associated with longer telomeres
Zhu et al. 2012 (47)	RCT (parallel)	37 African Americans randomly assigned to: *1*) experimental group ($n = 19$, 2000 IU vitamin D/d); *2*) control group ($n = 18$, placebo) for 16 wk	TRAP	Vitamin D supplementation	Significant differences in changes of telomerase activity were observed between groups. A significant increase in the PBMC telomerase activity from baseline to postintervention was noted in the vitamin D-supplemented group
Balcerczyk et al. 2014 (48)	RCT (parallel)	Healthy subjects supplemented with either: *1*) NucleVital Q10 Complex ($n = 66$ women) containing various micronutrients and ω-3 PUFA; *2*) control group ($n = 34$ women) for 12 wk	PCR	NucleVital Q10 Complex supplementation	A significant increase in telomerase concentration but not in TL was seen in the supplementation group. However, differences in changes between intervention groups were not checked
Sharif et al. 2015 (49)	RCT (parallel)	90 elderly participants with Zn deficiency were randomly assigned to: *1*) Zn supplementation group ($n = 45$; 20 mg/d Zn tablets); *2*) placebo group ($n = 45$; 100% maltodextrin tablets) for 12 wk	PCR	Zinc supplementation	Telomeres were shorter in the Zn group compared with placebo after intervention; however, this difference was not significant. Significant increase in TL within groups was observed

[1] LTL, leukocyte telomere length; PBMC, peripheral blood mononuclear cell; PLCOCST, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RCT, randomized clinical trial; SB, Southern blotting; TL, telomere length; TRAP, telomerase repeated amplification protocol; TRF, telomere restriction fragment; Zn, zinc.

Dietary micronutrients and TL

TL has also been associated with the intake of micronutrients (**Table 2**). Various classes of micronutrients such as vitamins, minerals, and other bioactive compounds have been shown to play a protective role against oxidative stress and DNA damage (36–38). Folate and vitamin B-12, in particular, have been of interest in many studies due to their essential role in purine and pyrimidine synthesis (39). Vitamin D, a fat

soluble vitamin, was inversely associated with low all-cause mortality, type 2 diabetes, and inflammation in some studies (40, 41).

A retrospective case-control study analyzing the effect of vitamin D supplementation in hemodialysis participants showed that patients not receiving vitamin D treatment had shorter telomeres (42). This association between vitamin D and TL, however, was not seen in another case-control study with prostate cancer participants ($P = 0.77$) (24).

The intake of vitamins C and E have also been shown to play important biological roles. Amongst the 3 cross-sectional studies reported in the present review, 1 of the studies showed a positive association between vitamins C or E and TLs (43). The cross-sectional study by Marcon et al. showed significant correlations for vitamins C and E, which vanished after adjustments. In fact, among all the micronutrients analyzed, β-carotenes showed significant correlations after adjustment for potential confounders (44). The third study reported a similar positive trend for vitamin E and TL (12). In the cross-sectional Sisters Study, women taking daily multivitamin supplements had 5.1% longer telomeres compared with the nonusers (43). With respect to the consumption of vitamin C, similar positive associations to the cross-sectional studies mentioned above were seen in a prospective cohort with 10 y of follow-up among older and middle-aged Korean men, where vitamin C was positively associated with changes in LTL (50). This study also reported a positive association between folate and potassium intake with changes in LTL. Age stratification in this study showed that all these associations remained significant only among men that were aged <50 y. The authors suggested that a higher fruit and vegetable intake at earlier ages would help delay biological aging (50). Amongst the cross-sectional studies evaluating the effects of micronutrients on TL, the epidemiological data from the NHANES study indicated a significant positive correlation between TL and dietary copper intake (46), whereas a case-control study found a positive correlation between phosphorous and TL (42).

Three RCTs exploring the effects of different vitamins and minerals have been published. A double-blind RCT conducted amongst 37 African Americans showed that oral vitamin D supplementation for 16 wk significantly increased PBMC telomerase activity in the intervention group. Even though age and sex are important factors altering TL and telomerase activity, this effect persisted after adjusting for these variables (47).

In another RCT, supplementation with a commercial compound containing different antioxidants and ω-3 FA for 12 wk was tested in 66 healthy women. In this study, a significant increase in telomerase activity was noted, even if no changes were observed in TL, after supplementation. In the same study, significant changes in the expression of sirtuin family members *SIRT1*and *2* in PBMCs were noted (48). Finally, zinc supplementation in an elderly population in Southern Australia increased from baseline to week 12 of supplementation, but no differences in TL changes between the placebo and the supplemented group were observed ($P > 0.05$) (49). In summary, because of the heterogeneity between the studies (in terms of design, type of subjects studied, and length), it is extremely difficult to establish beneficial effects of micronutrients and vitamins on telomere health. Therefore, larger and longer studies are required in the future to understand the effect of these nutrients and the beneficial amounts on telomere biology.

Food groups and TL

Several epidemiological studies and clinical trials have analyzed the relation between food groups and telomere health under the hypothesis they may influence the aging process via antioxidative and anti-inflammatory effects (**Table 3**). Vegetables, fruits, legumes, and nuts are sources of polyphenols, unsaturated FAs (in the case of nuts), and fiber. Their consumption has been associated with positive effects on markers of inflammation and oxidative stress, but also with insulin resistance or other cardiovascular risk factors (51, 52) in parallel with longer telomeres. By contrast, processed meats, alcoholic beverages, or sweetened carbonated beverages, and other foods rich in saturated FAs, alcohol, and sugar, have frequently been related to inflammation and oxidative stress in parallel with shorter telomeres.

Nuts, oils, and other dietary fats.

Eight observation studies and 1 RCT analyzed the effect of nut consumption (20, 45, 56–58, 60, 64, 67, 71) on telomere health with contradictory conclusions. The effect of walnut consumption on TL has been evaluated only in the context of a clinical trial (the Walnuts and Healthy Aging Study) (71). The authors evaluated the effect of a supplement of 30–60 g/d of walnuts in the context of a typical diet (equivalent to 15% estimated energy requirements) in comparison to the usual diet without walnuts (71). After 2 y, the participants in the control group had significantly shorter telomeres expressed as percentage of telomeres with a length <3 kb.

Eight cross-sectional studies evaluated the association between nut consumption and TL, and only 3 of them reported positive associations after adjusting for multiple confounding factors (20, 45, 64). In cohorts such as the NHANES (64) or the Korean Genome Epidemiology Study (KGES) (45) carried out in US and Korean populations, respectively, nut consumption was cross-sectionally associated with longer telomeres, whereas no association was found in the Nurses' Health Study (NHS) ($P = 0.91$) (58) or the Washington Heights-Inwood Community Aging Project (WHICAP) ($P = 0.13$) (60). Only Karimi et al. (67) found a negative association between nut and seed consumption with the T/S ratio [telomere (T) to single-copy gene (S) sequence] in a waste recyclers healthy Iranian group.

TABLE 3 Epidemiologic studies and RCTs evaluating the effect of food groups on telomere length[1]

Reference	Design	Population	Method	Food groups	Results
Hou et al. 2009 (53)	Case-control	716 Polish participants (300 cases of GC and 416 controls; 65.4% men and 34.6% women)	PCR	Fruit, vegetables	Controls consuming fruit several times per month or more have a higher TL mean compared with those who rarely or never consume. This association was not observed in the case of vegetables
Mirabello et al. 2009 (24)	Case-control	612 advanced prostate cancer cases and 1049 healthy US men from the PLCOCST, 55–74 y	PCR	Fruits, vegetables	No significant associations between TL and fruits and vegetables in all participants combined was reported
Lian et al. 2015 (54)	Case-control	271 hypertensive and 455 normotensive Chinese men and women participants, 40–70 y	PCR	Vegetables, fruit, meat, fish or seafood, poultry, milk, soya milk, egg, fried food, dessert	Higher vegetable intake was associated with longer aged-adjusted relative telomeres. Regular fried food and soya milk intake were associated with short aged-adjusted relative telomeres. No other significant associations were observed
Kahl et al. 2016 (55)	Case-control	124 healthy Brazilian participants (18.5% nonexposed-pesticide men, 31.5% nonexposed-pesticide women, 29.8% exposed-pesticide men, and 20.2% exposed-pesticide women), 17–78 y	PCR	Drinking status, fruit, and vegetables	Farmers not exposed to pesticide mixtures and consuming fruits and vegetables 3–4 d/wk or daily showed longer telomeres than farmers who were exposed to pesticides
Bekaert et al. 2007 (35)	Cross-sectional	2509 Belgian adults (48.5% men and 51.5% women) from the Asklepios study cohort, aged 35–55 y	SB	Fruit and vegetables	Fruit and vegetable consumption was not associated with TL
Nettleton et al. 2008 (56)	Cross-sectional	840 white, black, and Hispanic US adults from the MESA study, 45–84 y	PCR	Whole and refined grains, fruit, vegetables, low-fat and high-fat dairy, seeds or nuts, nonfried fish, red meat, processed meat, fried foods, coffee, nondiet soda	Nonfried fish and processed meat consumption was associated with shorter telomeres after adjusting for age and energy. Only processed meat consumption was associated with shorter telomeres after multivariate adjustment including other food groups. Participants in the highest quartile of processed meat intake had a lower T/S ratio. In the case of the food group including ham, hot dogs, salami, and other lunchmeats, an inverse association was reported with TL
Cassidy et al. 2010 (12)	Cross-sectional	2284 US females from the NHS	PCR	Whole grains, fruit, and vegetables	Participants in the highest quintile of whole grains consumption had significantly higher TL (as changes of z score) than participants in the lowest quintile. Fruit and vegetable intake were not significantly associated

(*Continued*)

TABLE 3 (*Continued*)

Reference	Design	Population	Method	Food groups	Results
Chan et al. 2010 (57)	Cross-sectional	2006 elderly Chinese (48.6% men and 51.4% women)	PCR	Cereals, meat and poultry, egg and egg products, fish, milk and milk products, fruit and nuts, vegetables, legumes/seeds and nuts, pickled vegetables, dim sum, fast food, fats and oils for cooking, tea	Chinese tea was positively associated in men with TL. Fats and oils for cooking in women were negatively associated with TL. No other associations were noted
Marcon et al. 2012 (44)	Cross-sectional	56 Italian subjects (44.6% male and 55.4% female)	TRF	Cereals, vegetables, fruits, eggs, dairy, oils and butter, meat, fish	Only the vegetable food group was positively associated with TL. The amount of fruit, vegetables, peppers, carrots, and spinach was correlated with longer TL inside of this food group
Tiainen et al. 2012 (26)	Cross-sectional	1942 Finnish men and women from the HBCS, 57–70 y	PCR	Fats (total, butter, margarine, oil), vegetables, roots, legumes, fruits (total, berries, fruit juice)	Butter intake was significantly associated with shorter telomeres in men. Vegetable intake was associated with longer telomeres in women. Men with the highest butter intake and the lowest fruit intake had shorter telomeres. In the analysis stratified by BMI, margarine intake was associated with longer telomeres in overweight and obese men; and higher vegetable intake was associated with longer telomeres in overweight/obese women. No other food group associations were found
Song et al. 2013 (25)	Cross-sectional	4029 white, black, Hispanic, and Asian healthy US postmenopausal women from the WHI observational study	PCR	Fat added on bread, butter use only, use of other fat only, cheese, low-/no-fat cheese, other cheeses	The use or consumption of total milk, nonskim milk, butter for cooking, total fat added on bread, total cheese, and high-fat cheese were inversely associated with TL in the model adjusted for age. Nonskim milk (whole milk and reduced-fat milk), and high-fat cheese intake were inversely associated with TL in the fully adjusted model
Crous-Bou et al. 2014 (58)	Cross-sectional	4676 healthy US women from the NHS, 42–70 y	PCR	Vegetables, fruit, whole grains, fish, meats, legumes, nuts	There were no differences in TL between quartiles of food groups consumption
Leung et al. 2014 (59)	Cross-sectional	5309 white, black, Hispanic, and other ethnic US adults (46.6% men and 53.4% women) from the NES, 20–65 y	PCR	Sugar-sweetened soda, noncarbonated sugar-sweetened beverages, diet soda, fruit juice	Sugar-sweetened soda consumption was associated with shorter telomeres; consumption of 100% fruit juice was marginally associated with longer telomeres. No significant associations were observed between the consumption of diet sodas or noncarbonated sugar-sweetened beverages and TL

(*Continued*)

TABLE 3 (*Continued*)

Reference	Design	Population	Method	Food groups	Results
Gu et al. 2015 (60)	Cross-sectional	1743 US elderly individuals (68.3% women and 31.7% men) from the WHICAP, aged ≥65 y	PCR	Fruit and nuts, vegetables, fish, dairy, meat, legumes, cereal, nuts, whole-grain cereals	Vegetable consumption was associated with longer telomeres and cereal intake with shorter telomeres. In non-Hispanic whites, dairy and meat intake was associated with longer telomeres
Lee et al. 2017 (45)	Cross-sectional	1958 Korean adults from the KGES, 40–69 y	PCR	Refined white and mixed rice noodles, dumplings, and flour products, cereal, and snacks, fish and other seafood, red and processed meat, poultry, eggs, legumes, nuts, green and yellow vegetables, seaweed, fruits, dairy products, sweetened carbonated beverages, green tea, coffee, other types of tea or beverages	LTL was negatively associated with red meat and processed meat, and sweetened carbonated beverage consumption. TL was positively associated with legumes, nuts, seaweed, fruit, and dairy products in the full-adjusted models
Fretts et al. 2016 (61)	Cross-sectional	2846 American Indians (60.2% women and 39.8% men) from the SHF	PCR	Processed meat, unprocessed meat	Processed meat intake was negatively associated with TL. However, there was no association with unprocessed red meat intake
Kasielski et al. 2016 (62)	Cross-sectional	28 healthy subjects (25% men and 75% women), 18–65 y	PCR	Cereal, fruit, vegetables, dairy, red meat, poultry, fish, sweets, salty snacks, juices, coffee, tea, mineral water, alcoholic beverages, sweetened carbonated beverages	Red meat consumption was associated with relative higher average TL. There were no associations between other food groups and TL
Liu et al. 2016 (63)	Cross-sectional	4780 US females from the NHS	PCR	Coffee	Those who drank the most coffee had longer telomeres than noncoffee drinkers in the adjusted model. Women who drank 2 or more cups of caffeinated coffee had longer telomeres than noncoffee drinkers. There was no linear association with decaffeinated coffee consumption
Zhou et al. 2016 (20)	Cross-sectional	556 Chinese participants (200 normoglycemic, 197 prediabetic, and 159 incident diabetic. 61.7% women and 38.3% men)	PCR	Cereal and cereal products, tuber crops, legume products, meat, dairy products, seeds or nuts, vegetables, fruit, fish and other seafood, seaweed, sweetened carbonated beverages	The consumption of legumes, nuts, fish, and seaweeds were correlated with longer TL. The consumption of a sweetened carbonated beverage was associated with shorter TL
Tucker 2017 (64)	Cross-sectional	5582 healthy US adults (52.6% women and 47.4% men) from the NHANES	PCR	Nuts and seeds	Nuts and seeds were significantly related to TL in the fully adjusted models

(*Continued*)

TABLE 3 (*Continued*)

Reference	Design	Population	Method	Food groups	Results
Tucker 2017 (65)	Cross-sectional	5826 US adults (55.3% women and 44.7% men) from the NHANES, aged ≥60 y	PCR	Coffee	Coffee intake was associated with longer TL in the total population. When analyzing only coffee drinkers, similar results were obtained. In the analysis by coffee intake categories, adults who consumed high levels of coffee had longer telomeres than moderate or low groups
De Meyer et al. 2018 (66)	Cross-sectional	2509 Belgian subjects (51.5% women and 48.5% men) from the Asklepios study, aged 35–55 y	SB	Beverages, milk and milk products, fruits, sweet and salty biscuits, breakfast cereals, whole wheat bread, white bread, low-fat butter/margarine, whole fat butter/margarine, seafood salad or fish products, meat salad or products, cheese, sweet spreads, eggs, fish/seafood, meat substitution products, meat/poultry/game, whole wheat pasta/whole-grain rice, white pasta or rice, deep-fried potato products, vegetables, sauces	In the total population, sweet and salty biscuits, whole wheat bread, and meat salad were positively associated with TL, whereas deep-fried potato products were negatively associated with TL. In the analysis stratified by sex, in women, a longer TL was associated with sweet and salty biscuits, meat salad and products, and a shorter TL was associated with deep-fried potato products. Regarding men, a longer TL was related to whole wheat bread and cheese, whereas a shorter TL was related to meat/poultry/game and deep-fried potato products
Karimi et al. 2018 (67)	Cross-sectional	300 healthy Iranian men, aged 25–40 y	PCR	Whole grains, refined grains, vegetables and fruit, fish products, dairy products, nuts and seeds, meats, produced meats, liquid oils, solid fats	Processed meats and solid fats were negatively associated with the T/S ratio in the completed study population. Fish products were positively associated only in office workers. Whole grains were positively associated, whereas nuts and seeds, meats, produced meats, and solid fats were negatively associated with this ratio in waste recyclers

(*Continued*)

TABLE 3 (*Continued*)

Reference	Design	Population	Method	Food groups	Results
Bethancourt et al. 2017 (68)	Prospective cohort	1459 Philippine young adults (41.7% women and 58.3% men) from the CLHNS	PCR	Processed meat, grilled/fried meat, nonfried fish, coconut oil, fruit and vegetables, bread and bread products, soft drinks and juice	No associations with food groups were reported
Cardin et al. 2013 (69)	RCT (crossover)	40 participants with chronic hepatitis C	PCR	*1*) 4 cups of coffee/d; *2*) abstinent from coffee for 30 d. After 30 d, they were switched to another group for 30 more days	Compared with the noncoffee consuming period, the coffee consuming period had significantly longer TL at the end of 30 d
Borresen et al. 2016 (70)	RCT (parallel)	29 colorectal cancer survivors (41.4% men and 58.6% women)	PCR	Control snacks + normal diet (placebo group), dry beans + normal diet (intervention group), rice bran + normal diet (intervention group)	No associations with intervention food groups were reported
Pawelcyk et al. 2018 (31)	RCT (parallel)	71 schizophrenia patients, aged 16–35 y	Telomerase ELISA	Olive oil (placebo group), ω-3 (intervention group)	A significantly greater increase in PBMC telomerase levels in the ω-3–supplemented intervention group compared with olive oil–supplemented placebo was observed. In addition, PBMC telomerase concentrations were significantly higher in both groups after 26 wk
Freitas-Simoes et al. 2018 (71)	RCT (parallel)	149 elderly participants (70.5% women and 29.5% men) from the WHAS, 63–79 y	PCR	Normal diet (placebo group), normal diet + walnuts (intervention group)	TL was significantly shorter in the control group after 2-y intervention whereas the walnut group did not have significant changes in TL

[1] CLHNS, Cebu Longitudinal Health and Nutrition Survey; GC, gastric cancer; HBCS, Helsinki Birth Cohort Study; KGES, Korean Genome Epidemiology Study; MESA, Multi-Ethnic Study of Atherosclerosis; NES, National Examination Survey; NHS, Nurses' Health Study; PBMC, peripheral blood mononuclear cell; PLCOCST, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RCT, randomized clinical trial; RTL, relative telomere length; SB, Southern blotting; SHF, Strong Heart Family Study; TL, telomere length; TRF, telomere restriction fragment; T/S, ratio of telomere (T) to single-copy gene (S) sequence; WHAS, Walnuts and Healthy Aging Study; WHI, Women's Health Initiative; WHICAP, Washington Heights-Inwood Community Aging Project.

Six cross-sectional studies and only 1 RCT have analyzed the association between butter or vegetable oil consumption and TL. In 4 cross-sectional studies an inverse association between butter and telomeres (25, 26, 57, 67) was reported, whereas no association was reported in the remaining 2 food groups ($P > 0.05$) (44, 66). In elderly Chinese women a negative association was found between the intake of fats and oils for cooking and TL but was not found in men ($P = 0.61$) (57). Song et al. (25) obtained similar cross-sectional results in the case of the Women's Health Initiative (WHI) study that included a subsample of 4029 postmenopausal women; whereas in the Helsinki Birth Cohort Study (HBCS) the association was only found in men (26). The consumption of solid fats was also negatively associated with TL in 300 Iranian men (67). However, no associations were reported between fat used for cooking or oil consumption in 2 European studies conducted in Italian ($P = 0.12$) (44) and Belgian participants ($P = 0.91$) (66). Finally, in a double-blind RCT, an increased level of telomerase activity was observed in 35 schizophrenia Polish patients after 26 wk of supplementation with 2.2 g/d of olive oil (31).

Fruits and vegetables.

Current evidence is scarce and inconsistent regarding fruit and vegetable intake and their relation with telomeres. Three case-control (53–55) and 4 cross-sectional studies (26, 44, 60, 45) found a positive association between fruit and vegetable consumption and longer telomeres, whereas another 10 cross-sectional studies did not find any association (all, $P > 0.05$) (12, 20, 24, 35, 56–58, 66–68).

In a gastric cancer case-control study, fruit but not vegetable consumption was associated with longer TL only among controls (53). In another case-control study with 271 hypertensive and 455 normotensive Chinese participants, vegetable but not fruit intake was associated with longer telomeres (54). By contrast, in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCOCST; $n = 1661$, US participants) no significant associations between fruit ($P = 0.44$) or vegetables ($P = 0.28$) and TL were reported (24). Kahl et al. (55) only found beneficial associations for fruit and vegetable consumption in those participants who were not exposed to pesticides in a sample of 124 healthy Brazilian farmers, but not in those exposed.

In 4 cross-sectional studies (44, 45, 51, 60) a positive association was observed between fruit or vegetable consumption and TL. In the first 3 studies conducted in occidental populations, only positive associations between the consumption of vegetables and longer telomeres were observed, whereas in the Lee et al. study, a positive association with fruits, but not vegetables was reported in full-adjusted models. Several cross-sectional studies did not find a significant association between fruit and vegetable consumption and TL (all, $P > 0.05$) (12, 20, 24, 35, 56–58, 66–68). For example, in a large sample of 2509 Belgian adults from the Asklepios study, neither fruit nor vegetable intake was associated with TL ($P = 0.53$) (35) and the same results were observed both in a subsample ($P = 0.75$) (12) and in the total population (58) of NHS.

Cereals and legumes.

A total of 5 cross-sectional studies have found positive associations either with cereals (12, 66, 67) or legumes (20, 45) intake. In 2284 US women (12), 2509 Belgian subjects (66), and 100 Iranian males (67), whole grains or whole-grain products were positively associated with longer TL. However, these studies did not take into consideration the type of legumes in their analyses. In 2 different Asian populations (20, 45), legumes but not cereal consumption ($P > 0.05$) was positively related to TL. Legumes contain folic acid, antioxidants, and other phytochemicals that may be involved in DNA integrity. In the WHICAP study, a negative association between total cereal consumption and TL (60) was reported, even though a secondary analysis with only whole-grain cereals reported no significant association ($P = 0.85$). Some studies failed to show the significant benefits of consuming cereals (44, 56–58, 62, 68), legumes (26, 57, 58, 60), or both aforementioned food groups (58) on TL, including the single clinical trial that compared both food groups (70) (all, $P > 0.05$).

Meat, poultry, and derivatives.

Thirteen publications have analyzed meat consumption and telomere health (20, 44, 45, 54, 56–58, 60–62, 66–68). Processed meat contains high concentrations of advanced glycation end products and nitrosamines that may promote inflammation and oxidative stress. Results from 5 cross-sectional studies have shown negative associations between red meat or processed meat and TL (45, 58, 61, 62, 66). In addition, De Meyer et al. (66) found a negative association between poultry consumption and TL in 1218 Belgian men. In a subsample of participants from the Multi-Ethnic Study of Atherosclerosis (MESA), those in the highest quartile of processed meat consumption showed shorter TL compared with those in the first quartile (56). In the Strong Heart Family Study ($n = 2846$) a lineal inverse association between processed meat consumption and TL was also observed (61). A similar inverse association was seen in 2 other studies including an Asiatic population (45, 67). Only 2 studies included in this review have reported a positive association between red meat consumption and TL. One of these studies showed a significant positive correlation in a sample of 28 healthy people aged 18–65 y (62). The second study (60) reported a comparable association in a non-Hispanic white population ($n = 506$) but not in the African-American ($n = 536$; $P = 0.88$) and Hispanic groups ($n = 679$; $P = 0.32$). In a prospective evaluation of 1459 Philippine adults, an association between processed or grilled/fried meat consumption and TL was shown after 12 y of follow-up (68). Similarly, no associations between any meat subgroup and TL (20, 44, 54, 57, 58) (all, $P > 0.05$) were reported in 5 other cross-sectional studies.

Fish.
Zhou et al. (20) and Karimi et al. (67) reported a positive correlation between fish intake and TL in normoglycemic or altered-glycemic Chinese and healthy Iranian individuals, respectively. However, 1 case-control study (54), 1 prospective cohort (68), and 7 cross-sectional studies (44, 45, 57, 58, 60, 62, 66) that investigated the relation between fish intake and TL showed no associations (all, $P > 0.05$). Similar to the above-mentioned prospective cohort (68), no associations (44, 58) have been reported between fish consumption and TL in Italian ($n = 56$) and US healthy participants ($n = 4676$; $P > 0.05$). In the MESA (56) nonfried fish consumption was associated with shorter TL in an adjusted model including age and energy intake, but this association was lost after additional adjustments.

Milk and other dairy products.
In the KGES (45) a significant positive association between total dairy product consumption and TL was reported, whereas in the WHI observational study (25) including 4029 healthy postmenopausal US women, the association was inverse and significantly stronger only when skimmed milk and low-/no-fat cheese were not considered. De Meyer et al. (66) observed a positive association only between cheese intake and TL in men, but not in women ($P = 0.51$) or the total population ($P = 0.33$) with other dairy products. Similar results were reported in 8 other cross-sectional studies (20, 26, 44, 54, 56, 57, 60, 62).

Beverages.
Numerous epidemiological studies have analyzed the effect of beverage consumption on TL (20, 45, 54–57, 59, 62, 63, 65, 66). In 2 cross-sectional studies with a total of 2741 US men and 7865 US women from NHANES and NHS, respectively, those participants who drank coffee had longer telomeres than noncoffee drinkers (63, 65). In another study evaluating this association in an elderly Chinese population, only tea consumption was related to TL in men, but not in women ($P = 0.50$) (57). In line with the above 2 studies, the results of a crossover intervention study with 40 chronic hepatitis C patients showed that the consumption of coffee for 30 d lowered oxidative damage and increased TL by 40% in 89% of the participants (69). Caffeine, the main component of tea and coffee, was also associated with longer telomeres.

Leung et al. (59) analyzed the effect of several beverages on TL in 5309 US adults from the NHANES and reported a marginal association between natural fruit juice consumption and longer telomeres, whereas sugar-sweetened beverage consumption was associated with shorter telomeres. Two studies conducted in Asiatic populations also showed inverse associations between the intake of sweetened carbonated beverages and TL (20, 45). Although soy has a high content of polyphenols and antioxidants, Lian et al. (54) found that individuals who regularly consumed soymilk had shorter telomeres. Four studies (55, 56, 62, 66) did not find any association between any of the beverage groups considered and TL, including sweetened beverages, alcoholic beverages, nonsweetened beverages, coffee, and juices ($P > 0.05$).

Taking into account all the studies analyzed in this section, we can conclude that, in general, associations between food groups and TL are inconsistent. Even if several studies have shown significant positive associations in the case of the consumption of nuts, vegetables, coffee, and legumes, and negative associations for butter, processed meat, and sweetened carbonated beverages, other studies were not able to confirm them. However, it is important to mention that most of these studies were cross-sectional, thus more prospective observations and especially RCTs are needed in order to elucidate any possible causal associations, as only this type of study enables establishing cause–effect relations.

Dietary patterns and TL

Dietary pattern analysis has received considerable attention in nutritional epidemiologic studies during recent years, in relation to their emerging influence on the prevention of chronic diseases. Conceptually, dietary patterns describe the overall diet and eating routines of a population, and may thus be more predictive of disease risk than individual foods or nutrients. Increasing evidence suggests that the health benefits of foods are attributed to the additive and synergistic interactions of nutrients and other phytochemicals on different biological mechanisms which are also involved in telomere maintenance, as we will see in the last section of this review. Special dietary quality indices have been proposed to evaluate the adherence to a certain dietary pattern (e.g., Mediterranean diet, Western diet, vegetarian diet, vegan diet, and others). Dietary patterns also reflect adherence to formal dietary guidelines recommended for disease prevention (72).

Several epidemiological studies showed that adherence to specific dietary patterns may be related to changes in telomere attrition. Of the 70 articles selected in this systematic review, 16 evaluated the effect of dietary patterns on TL (45, 56, 58, 60, 66, 67, 73–82) (**Table 4**).

A priori food patterns.
Related to food a priori patterns, 11 cross-sectional (58, 60, 66, 73–76, 78–81), 3 prospective cohort (75, 76, 81) studies, one of them RCT (76), were included in this systematic review (Table 4).

The Mediterranean diet (MedDiet) is one of the best dietary patterns analyzed in relation to cardiovascular disease (CVD) risk and other health outcomes (83) including reduction of overall mortality (84–87) and increased likelihood of healthy aging (88). Some key foods of the Mediterranean diet, such as, vegetables, seeds, fruits, olive oil, nuts, and wine, are especially rich in antioxidant and anti-inflammatory components and their consumption has been broadly associated with an improvement of several inflammatory and oxidant biomarkers (see the food and nutrient sections), which have been implicated in the maintenance of TL. However, it is

TABLE 4 Epidemiologic studies and RCTs evaluating the effect of dietary patterns on telomere length[1]

Reference	Study design	Population	Method	Dietary pattern/factor	Results
Nettleton et al. 2008 (56)	Cross-sectional	840 white, black, and Hispanic US adults from the MESA, 45–84 y	PBL/qPCR	Food groups and dietary patterns derived from principal component analysis	Processed meat intake was inversely associated with TL Neither the derived dietary pattern for fats and processed meat nor the dietary pattern for whole grains and fruit were significantly associated with telomere length after adjustment for demographic and lifestyle factors
Sun et al. 2012 (73)	Cross-sectional	5862 US women from the NHS aged 30–55 y	PBL/qPCR	AHEI	No association between the AHEI score and TL was observed
Boccardi et al. 2013 (74)	Cross-sectional	217 elderly Italian subjects (102 females and 115 males)	PBL/qPCR	MedDiet	High adherence to MedDiet showed longer leukocyte TL ($P = 0.003$) and higher telomerase activity ($P = 0.013$) compared with the group with lower adherence to MedDiet
Crous-Bou et al. 2014 (58)	Cross-sectional	4676 healthy American women within the NHS, 35–55 y	PBL/qPCR	MedDiet	Greater adherence to the MedDiet was associated with longer telomeres after adjustment for potential confounders
Gu et al. 2015 (60)	Cross-sectional	1743 US multiethnic individuals (WHICAP), >65 y	PBL/qPCR	MedDiet	MedDiet score was not associated with LTL in the overall study population after adjusting for age, sex, education, ethnicity, caloric intake, smoking, and physical and leisure activities. A significant association between MedDiet and LTL among non-Hispanic whites was reported
García-Calzón et al. 2015 (75)	Cross-sectional	520 Spanish individuals at high cardiovascular disease risk-PREDIMED-NAVARRA, 55–80 y	Buffy coat/qPCR	DII	Longer telomeres at baseline were found in participants who had a more anti-inflammatory diet (lowest DII score)
García-Calzón et al. 2016 (76)	Cross-sectional	520 females and males at high cardiovascular disease risk from the PREDIMED-NAVARRA center, 55–80 y	Buffy coat/qPCR	MedDiet	A greater baseline adherence to a MedDiet pattern was associated with longer telomeres only in women in a cross-sectional setting
Mazidi et al. 2017 (77)	Cross-sectional	10,568 participants from NHANES, USA, 48% ($n = 5020$ were men). Mean age was 44.1 y	PBL/qPCR	Dietary patterns determined by principal component analysis and food components "a posteriori"	Three food patterns together explaining 56.8% of the variance of the dietary nutrient consumption were identified. A food pattern, which was a representative of minerals and vitamins, increased across TL quarters and had a positive association with TL. Mean (adjusted for sex, age, and race) dietary intakes of carbohydrate, dietary fiber, total folate, vitamin B-6, magnesium, iron, copper, PUFAs 22:5, and vitamin C increased across TL quarters whereas total fat and caffeine decreased across TL quarters

(*Continued*)

TABLE 4 (*Continued*)

Reference	Study design	Population	Method	Dietary pattern/factor	Results
Shivappa et al. 2017 (78)	Cross-sectional	7215 adults aged >19 y in the NHANES program, USA	Whole blood/qPCR	DII	After multivariable adjustment, higher DII scores (i.e., relatively more proinflammatory) were associated with shorter LTL
Leung et al. 2018 (79)	Cross-sectional	4758 healthy US adults, NHANES, 20–65 y	Whole blood/qPCR	HEI AHEI MedDiet DASH	HEI-2010, AHEI-2010, MedDiet, and DASH scores were each positively associated with longer LTL
De Meyer et al. 2018 (66)	Cross-sectional	2509 Belgian males and females aged 35–55 y (Asklepios population)	Whole blood/SB	Dietary patterns and individual food components (DII)	Upon adjustment for confounders, no significant associations could be identified between LTL and holistic dietary patterns, i.e., overall dietary score, dietary quality, dietary diversity, and dietary equilibrium. Additionally, the association between LTL and other general dietary characteristics, i.e., total daily energy, fiber intake, as well as the DII were evaluated, without significant results. A higher daily intake of deep-fried potato, sweets, and meat was associated with shorter telomeres in both sexes
Karimi et al. 2018 (67)	Cross-sectional	300 healthy Iranian men 25–40 y	Whole blood/qPCR	Healthy dietary pattern; Western dietary pattern; traditional dietary pattern "a posteriori"	A positive relation was reported between the healthy dietary pattern (with consumption of whole grains, refined grains, dairy, and cereals) and traditional dietary pattern (with increased consumption of fruit, vegetables, and whole grains, fish and dairy products) with TL Negative association was identified with the Western pattern and TL
Milte et al. 2018 (80)	Cross-sectional	679 (females and males) participants at WELL study in Victoria, Australia, 57–68 y	Whole blood/qPCR	Dietary Guideline Index Recommended food score MedDiet score	After adjustment for age, sex, education, smoking, physical activity, and BMI, there were no significant associations between diet quality and relative telomere length
Meinilä et al. 2019 (81)	Cross-sectional	1046 females and males from the HBCS, Helsinki, Finland, 56–70 y	Whole blood/qPCR	BSDS Modified MedDiet score DII	BSDS, mMED, and DII were not associated with TL in the cross-sectional analysis in men or women
Gong et al. 2018 (82)	Cross-sectional	553 Chinese adults (50.8% men), 25–65 y	Whole blood/TRF; SB	Dietary pattern determined by principal component analysis "a posteriori"	Vegetable-rich pattern characterized by higher intake of fruit, whole grains, various vegetable groups, dairy products, nuts, eggs, and tea, was positively related to TL in women
Meinilä et al. 2019 (81)	Prospective cohort	1046 females and males from the HBCS, Helsinky, Finland, 56–70 y	Whole blood/qPCR	BSDS Modified MedDiet score, DII	No association between mMED and LTL change was found in men. In women, mMED was associated with faster LTL shortening Adherence to BSDS and DII did not associate with LTL change in men or women

(*Continued*)

TABLE 4 (*Continued*)

Reference	Study design	Population	Method	Dietary pattern/factor	Results
García-Calzón et al. 2015 (75)	Prospective cohort	520 Spanish individuals at high cardiovascular disease risk-PREDIMED-NAVARRA, 55–80 y	Buffy coat/qPCR	DII	A greater anti-inflammatory potential of the diet (i.e., a decrease in the DII) could significantly slow down the rate of telomere shortening
Lee et al. 2015 (45)	Prospective cohort	1958 Korean adults, 40–69 y, 10-y follow-up	PBL/qPCR	Dietary patterns determined by factor analysis "a posteriori"	The first factor labeled "prudent dietary pattern" characterized by high intake of whole grains, seafood, legumes, vegetables, and seaweed was positively associated with leukocyte TL. In the analysis of particular food items, higher consumption of legumes, nuts, seaweed, fruit, and dairy products and lower consumption of red meat or processed meat and sweetened carbonated beverages were associated with longer leukocyte TL
García-Calzón et al. 2016 (76)	RCT	520 Spanish individuals at high cardiovascular disease risk from the PREDIMED-NAVARRA center, 55–80 y	Buffy coat/qPCR	Two MedDiets, 1 supplemented with extra-virgin olive oil and the other with mixed nuts compared with a low-fat diet	No beneficial effect of the intervention with the MedDiet for the prevention of telomere shortening in comparison with a low-fat diet was observed after 5 y of intervention

[1] AHEI, Alternate Healthy Eating Index; BSDS, Baltic Sea Diet Score; DASH, Dietary Approaches to Stop Hypertension; DII, Dietary Inflammatory Index; HBCS, Helsinki Birth Cohort Study; HEI, Healthy Eating Index; LTL, leukocyte telomere length; MedDiet, Mediterranean diet; mMED, modified Mediterranean diet; MESA, Multi-Ethnic Study of Atherosclerosis; NES, National Examination Survey; NHS, Nurses' Health Study; PBL, peripheral blood leukocytes; PLCOCST, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PREDIMED-NAVARRA, Prevention with Mediterranean Diet, center of Navarra; RCT, randomized clinical trial; SB, Southern blotting; TL, telomere length; TRF, telomere restriction fragment; WELL, Wellbeing, Eating, and Exercise for a Long Life Study.

unclear whether the protective effects on TL provided by the MedDiet result from its individual constituents or the combination of these.

A total of 8 studies (58, 60, 74, 76, 78–81) focused on analyzing the relation between adherence of MedDiet and TL and their conclusions are controversial. Most of the studies are cross-sectional. Crous-Bou et al. (58), in a cohort of 4676 healthy American women, showed that greater adherence to the MedDiet was significantly associated with longer TL. However, in that study, no association between any of the individual Mediterranean food items analyzed and TL was demonstrated, which supports the concept of the dietary pattern as a powerful tool to detect health benefits. In a similar way (74), adherence to the MedDiet was positively associated with telomerase activity, and accordingly with longer TL. These findings were confirmed by another study conducted in 1743 individuals from the WHICAP study (60), where a significant association between the MedDiet and TL among a non-Hispanic white population was reported, even though no association was found in the total population studied ($P = 0.15$). This positive association between baseline adherence to the Mediterranean diet and TL was also reported in a population of women at high cardiovascular risk [Prevention with Mediterranean Diet study (PREDIMED)] (76) and in the NHANES study (79).

Four cross-sectional studies (66, 75, 78, 81) have analyzed the relation between the Dietary Inflammatory Index (DII) and TL. In 2 of them, respectively, conducted in healthy US adults and Spanish people at high CVD risk, a high DII score was associated with shorter TL after adjusting by potential confounders (75, 78), whereas no association was reported in the HBCS study ($P = 0.24$ in women and $P = 0.36$ in men) (81) and in 2509 Belgian males and females from the Asklepios population ($P = 0.95$) (66).

Few other studies have been conducted on other a priori dietary patterns that have also demonstrated beneficial effects on health (73, 79–81). Leung et al. (79) showed in the NHANES cohort that not only MedDiet, but also the Healthy Eating Index (HEI-2010), the Alternate Healthy Eating Index (AHEI-2010), and the Dietary Approaches to Stop Hypertension (DASH) scores were each positively associated with TL at baseline. On the contrary, no association between TL and the Baltic Sea Diet Score (BSDS; $P = 0.41$) (81) or other a priori healthy dietary index have been shown in 2 other studies (73, 80) ($P > 0.05$ in both).

Only 2 studies have prospectively examined the association between a priori dietary patterns and changes in TL (75, 81). In a population of 1046 females and males from the HBCS aged 56–70 y, no association was reported between the Mediterranean diet score ($P > 0.05$), BSDS, and anti-inflammatory dietary index with changes in TL after 10 y of follow-up ($P > 0.05$) (81). In that study a positive association between MedDiet adherence and telomere shortening was reported only in women. In contrast, in the context of the PREDIMED study, a greater anti-inflammatory potential of the diet (i.e., a decrease in the DII) was associated with increased TL. After 5 y of follow-up, participants with a high proinflammatory diet index had a 2-fold higher risk of accelerated telomere attrition compared with participants with an anti-inflammatory diet (75).

To the best of our knowledge, the effect of a dietary pattern has only been tested in 1 RCT. In the context of the PREDIMED trial, no beneficial effects on changes in TL were reported in those participants allocated to the 2 Mediterranean intervention arms compared with those allocated to the control group after 5 y of intervention ($P = 0.58$) (76).

A posteriori food patterns.

Two main approaches to characterize dietary patterns are those that are determined a priori (i.e., HEI-2010, MedDiet, DII) and those that are derived a posteriori (e.g., principal component or cluster or factor analyses). The key advantage of a posteriori–derived food patterns is that they take into account many aspects of the diet rather than focusing on a few hypothesized key food or nutrient groups. On the other hand, a posteriori dietary patterns do not build on previous research and thus do not appraise current diet–disease paradigms.

Four cross-sectional (56, 67, 77, 82) and 1 prospective a posteriori food-derived dietary patterns (45) have been related to TL. In the context of the MESA study including 840 white, African-American and Hispanic adults, neither a dietary pattern characterized by the high consumption of fats and processed meat, nor a dietary pattern composed of whole grains and fruit were associated with TL after adjustment for potential confounders. These results were unexpected in light of the observed association between the intake of processed meat and TL in the same study (56). On the other hand, 3 food patterns (FAs, minerals and vitamins, and PUFAs), together explaining 56.8% of the variance of the dietary nutrient consumption, were identified in the NHANES study (77). A food pattern, which was representative of minerals and vitamins, was positively associated with TL in adjusted models. Moreover, the intake of dietary fiber, total folate, vitamin B-6, magnesium, iron, copper, and vitamin C also increased across the quartiles of TL whereas total fat and caffeine decreased across TL quarters.

Karimi et al. (67) found a positive relation between adherence to a healthy lifestyle and TL in a cross-sectional study of healthy male residents of Tehran and a negative association with the Western pattern. Adherence to a healthy lifestyle and a dietary pattern with an increased consumption of fruit, vegetables, whole grains, fish, and dairy products appears to be necessary to prevent TL attrition.

A similar dietary pattern, also including nuts, eggs, and tea, was cross-sectionally related to TL in women but not in men from a Chinese cohort (82). In a Korean population followed for 10 y, a posteriori–derived food pattern so-called "prudent dietary pattern" characterized by a high intake of whole grains, seafood, legumes, vegetables, and seaweed was prospectively associated with leukocyte TL in contrast to a "Western dietary pattern" characterized by the high intake of refined grain, red or processed meat, and sweetened carbonated beverages. In the analysis of particular food items, the higher consumption of legumes, nuts, seaweed, fruit, and dairy products and lower consumption of red meat or processed meat and sweetened carbonated beverages were associated with longer TL. These results suggest that diet in the remote past, that is, 10 y earlier, may affect the degree of biological aging in middle-aged and older adults (45).

However, current evidence regarding dietary intake and TL is still scarce and there are also inconsistencies. More studies are needed to better understand the relation between diet and TL. Further large prospective and RCTs are warranted in the future to establish a causal relation between food or dietary patterns and telomere attrition.

Blood concentrations of selected nutrients and TL

Despite an increasing interest in studying the relation between diet and telomere health, it is sometimes difficult to directly correlate dietary intake of certain macro- and micronutrients with a specific response at the molecular level. Therefore, we will present a separate section, where we have included all those studies in which plasma or serum concentrations of macro- and micronutrients (in some cases reflecting the status of this nutrient) have been measured and analyzed in association with telomere attrition and maintenance (**Table 5**).

FAs.

Multiple epidemiologic studies have demonstrated greater survival rates among individuals with a higher dietary intake of marine ω-3 FA (86, 87). Therefore, considering TL as a potential biomarker for biological aging, the association between ω-3 FA intake and TL is gaining more and more attention in the scientific community. Farzaneh-Far et al. (14) found a significant inverse association of baseline concentrations of ω-3 FA in whole blood with telomere shortening after 5 y of follow-up in a prospective cohort study of 608 outpatients with stable coronary artery disease from California. Previous findings suggested that deceleration of telomere attrition could be a potentially novel pathway for

TABLE 5 Epidemiologic studies evaluating the effect of blood nutrients on telomere length[1]

Reference	Design	Population	Method	Factor	Results
Boccardi et al. 2019 (89)	Cross-sectional	68 subjects from the Geriatric Unit of Ospedale Maggiore Policlinico of Milan (2009–2016)	PCR-ELISA and qPCR	Plasma β-carotene	In all populations, β-carotene was significantly and positively correlated with telomerase activity, independent of gender. Subjects affected by AD had significantly lower concentrations of β-carotene and LTL compared with healthy controls
Julin et al. 2017 (90)	Cross-sectional	2483 men from a multiple nested case-control subcohort of the HPFS	PCR	Plasma vitamin D	Neither plasma 25(OH)D3 or 1,25(OH)2D3 were associated with LTL
Min and Min, 2016 (91)	Cross-sectional	3660 healthy subjects from the NHANES study (1999–2002)	PCR	Serum carotenoids	A doubling of blood α-carotene, β-carotene (*trans* + *cis*), and β-cryptoxanthin was associated with ∼2% longer telomeres. Compared with the lowest carotenoid quartile of α-carotene, β-carotene (*trans* + *cis*), and β-cryptoxanthin, telomere length for adults with the highest quartiles was significantly increased by 5–8%
Pusceddu et al. 2017 (92)	Cross-sectional	65 healthy subjects	PCR	Serum vitamin B-12, total serum folate	Age and gender-adjusted RTL correlated with total serum folate and 5-methyltetrahydrofolate
Richards et al. 2007 (93)	Cross-sectional	2160 healthy women	PCR	Serum vitamin D	Serum vitamin D concentrations were positively associated with LTL, and this relation persisted after adjustment for age and other covariates (age, season of vitamin D measurement, menopausal status, use of hormone replacement therapy, and physical activity). The difference in LTL between the highest and lowest tertiles of vitamin D was 107 bp, which is equivalent to 5.0 y of telomeric aging. This difference was further accentuated by increased concentrations of CRP
O'Callaghan et al. 2014 (30)	Cross-sectional	89 healthy South Australian adults	PCR	Plasma magnesium and calcium	A negative association between telomere length and both plasma calcium and magnesium concentrations were reported in older females. These relations were not observed in the younger adults, nor in the older males
Sen et al. 2014 (94)	Cross-sectional	786 healthy subjects from the Austrian Stroke Prevention Study, a population-based cohort study on brain aging	PCR	Plasma lutein, zeaxanthin, and vitamin C concentrations	Of all micronutrients, the combination of lutein and zeaxanthin (Lu∼Zx) and vitamin C remained significantly and independently associated with LTL when adjusted for age and sex. After additional adjustment the relation between Lu and Zx and LTL became stronger, whereas the association between vitamin C and LTL remained virtually unchanged

(*Continued*)

TABLE 5 (*Continued*)

Reference	Design	Population	Method	Factor	Results
Paul et al. 2015 (95)	Cross-sectional	1044 healthy subjects from the Framingham Offspring Study	PCR	Plasma folate	There was no significant positive association between plasma folate and leukocyte telomere length
Liu et al. 2016 (96)	Cross-sectional	1154 healthy subjects from the USRT study	PCR	Plasma 25(OH)D3	No significant association between continuous 25(OH)D3 and long LTL in all participants, nor in white females, white males, black females, or black males were reported. Vitamin D deficiency (defined as 25(OH)D3 <30 nmol/L), was significantly associated with shorter telomeres in whites, but not in other groups
Shin and Baik, 2016 (97)	Cross-sectional	798 healthy subjects	PCR	Serum vitamin B-12 and folate	In multiple adjusted models, no association was observed between LTL and serum folate and vitamin B-12
Williams et al. 2016 (98)	Cross-sectional	5096 healthy subjects from the Northern Finland Birth Cohort 1966	PCR	Plasma 25(OH)D3	No evident association between plasma 25(OH)D3 and telomere length was observed
Nomura et al. 2017 (99)	Cross-sectional	7826 healthy subjects from NHANES cohort data (1999–2002)	PCR	Serum folate, vitamin B-12, vitamin A, γ-tocopherol, α-tocopherol, and carotenoids	Serum vitamin A was positively associated and γ-tocopherol was inversely associated with LTL. Serum folate and α-tocopherol were marginally positively associated with LTL, whereas vitamin B-12 was not associated with LTL. Serum carotenoids were generally positively associated with LTL
Tucker 2017 (100)	Cross-sectional	5768 healthy subjects from NHANES cohort data (1999–2002)	PCR	Blood γ-tocopherol, blood α-tocopherol, dietary vitamin E, dietary supplements	An inverse association between serum concentrations of γ-tocopherol and TL was observed. Telomeres were approximately 1 y shorter (15.6 bp) for each increment of 47.3 to 55.7 g/dL of γ-tocopherol in the blood, depending on the variables controlled
Liu et al. 2019 (101)	Cross-sectional	7336 healthy subjects from NHANES cohort data (1999–2002)	PCR	Serum ferritin	Low ferritin concentrations (iron deficiency) were not significantly associated with telomere length compared with normal ferritin concentrations
Mazidi et al. 2018 (102)	Cross-sectional	5446 healthy subjects from NHANES cohort data (1999–2000)	PCR	Plasma *trans*-fatty acids like palmitelaidic acid, elaidic acid, vaccenic acid, and linolelaidic acid	After adjusting for age, sex, ethnicity, education, marital status, subclinical inflammation, BMI, and smoking, only palmitelaidic acid and linolelaidic acid were negatively associated with TL
Farzaneh-Far et al. 2010 (14)	Prospective cohort	608 patients from the Heart and Soul Study	PCR	Serum marine ω-3 fatty acids	Those participants in the highest quartile of DHA3EPA experienced the slowest rate of telomere shortening

[1] AD, Alzheimer's disease; CRP, C-reactive protein; DHA3EPA, docosahexaenoic acid eicosapentaenoic ω-3 fatty acid; HPFS, Health Professionals Follow-Up Study; LTL leukocyte telomere length; RTL, relative telomere length; TL, telomere length; USRT, US Radiologic Technologists Study; 1,25(OH)2D3,1,25-dihydroxyvitamin D; 25(OH)D3, 25 hydroxy-vitamin D.

ω-3 FAs to exert their known antiaging properties (103, 104). Nonetheless, a specific mechanism is still missing; for instance, the oxidative stress could be a powerful driver for telomere shortening, such as ω-3 FA reshaping the FA composition of cell membranes in order to reduce oxidative damage. Furthermore, a higher telomerase activity had been previously correlated with ω-3 FA supplementation in PBMCs (105).

At the same time, *trans*-fatty acids (TFAs) have also been differently correlated with TL in NHANES, the periodic cross-sectional surveys conducted in US adults. Palmitelaidic and linolelaidic acids detected in plasma were positively associated with an increasing telomere shortening over time (102). In fact, a diet rich in TFAs had already been correlated with a lower antioxidant effect on DNA damage in animal models, in a way that these findings confirm the hypothesized relation between telomere attrition and oxidative DNA damage.

Vitamins.

Telomere attrition is accelerated in oxidative stress and chronic inflammatory conditions. In this regard, it will be relevant to investigate the potential associations between dietary intake of anti-inflammatory agents and TL, which is detailed in the following paragraphs.

Vitamin D is a known potent inhibitor of the proinflammatory response and thereby diminishes the turnover of leukocytes, with a consequent decrease in LTL. Nonetheless, dietary intake of vitamin D is not a good indicator of its authentic metabolically active form. Rather, the hydrolyzed form, 1,25-dihydroxyvitamin D [1,25(OH)D3] is the biologically active form (106).

Correlations between this biologically active 1,25(OH)D3 with TL were evaluated in the Health Professionals Follow-Up Study (HPFS), among 2843 men. The cross-sectional analysis showed no associations between vitamin D and LTL (107). Similarly, no associations were found in the Northern Finland Birth Cohort, with 5096 participants ($P = 0.97$) (98).

Instead, another cross-sectional study conducted with 2160 adult women from a large population-based cohort of twins in the UK, observed a positive association between the serum concentration of 1,25(OH)D3 and TL. In addition, a similar trend of association has been observed in this study between serum concentrations of vitamin D and C-reactive protein (CRP) concentrations (105). Pusceddu et al. (92) evaluated the effects of folate treatment against vitamin D supplementation in an elderly population. The results obtained from a cross-sectional analysis of baseline values revealed that subjects with TL above the median had higher concentrations of total folate.

When examining TL correlations in a representative population of US Radiologic Technologists Study (USRT) the results are contradictory. In fact, no association was found in either of the different race subsets of the analyzed population ($P = 0.87$) except for vitamin D deficiency, which was significantly correlated with shorter telomeres, at least in the white population of the cohort (96). Vitamin B-12, folate, α- and γ-tocopherols all exert beneficial effects on brain aging other than contributing to telomere maintenance, at least in in vitro models (108). Nonetheless, results obtained from different studies about their relations with TL are inconsistent, as can be observed from the studies included in this review.

For instance, no direct association has been found between folate, vitamin B-12, and telomere shortening in adults aged 55 y involved in a cross-sectional study embedded within the population-based KGES cohort (97). Furthermore, no significant association has been found in the Framingham Offspring Study between plasma folate concentrations and TL, after 4 y of folic acid supplementation even if a positive trend has been observed in participants with a higher plasma concentration of folic acid (95).

Two cross-sectional studies from the NHANES population showed contrasting results for analysis with bioactive compounds, micronutrients in serum, and TL. One study showed no association between TL and any of the analyzed micronutrients. Nomura et al. (99) did not find any significant association with TL for any of the nutrients analyzed; whereas another study reported an inverse association between γ-tocopherol and TL (100).

Carotenoids.

Various epidemiological studies have explored the antioxidative effect of both dietary and serum concentrations of carotenoids with different health and aging-related diseases in which oxidative stress plays a major role. In a representative population of 3660 US adults from the NHANES study, TL was positively associated with serum concentrations of different carotenoids, like α-carotene, β-carotene (*trans* + *cis*), β-cryptoxanthin, combined lutein/zeaxanthin, and *trans*-lycopene (91). The same population was also examined by Nomura et al. (99) in order to evaluate the potential association between serum concentrations of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene and TL in 7458 participants of the NHANES study. However, no association between carotenoids and leukocytes TL were reported ($P > 0.05$) (109). Nonetheless, the opposite results were obtained in an older population of Italians, in which telomerase activity has been significantly and positively correlated with β-carotene plasma concentrations (89).

Minerals.

The plasma or serum concentrations of certain minerals have been correlated with diseases in which telomere shortening also plays an important role, such as CVD and cancer. Therefore, new emerging studies have explored these associations in cohort studies (49).

O'Callaghan and colleagues (110) reported several relations between plasma minerals (calcium, magnesium, potassium, selenium, and zinc) and TL, which was strictly dependent on age and sex. In particular, a significant negative association between TL and plasma concentrations of magnesium and calcium was observed only in older females.

Body iron status has also been inversely associated with TL in US adults aged ≥65 y belonging to a NHANES cohort population. The association between high body iron status and shorter TL is biologically plausible, as it is a powerful pro-oxidant and hydroxyl radical promoting agent. Even so, the detailed molecular mechanisms, which explain this relation, remain unclear (101).

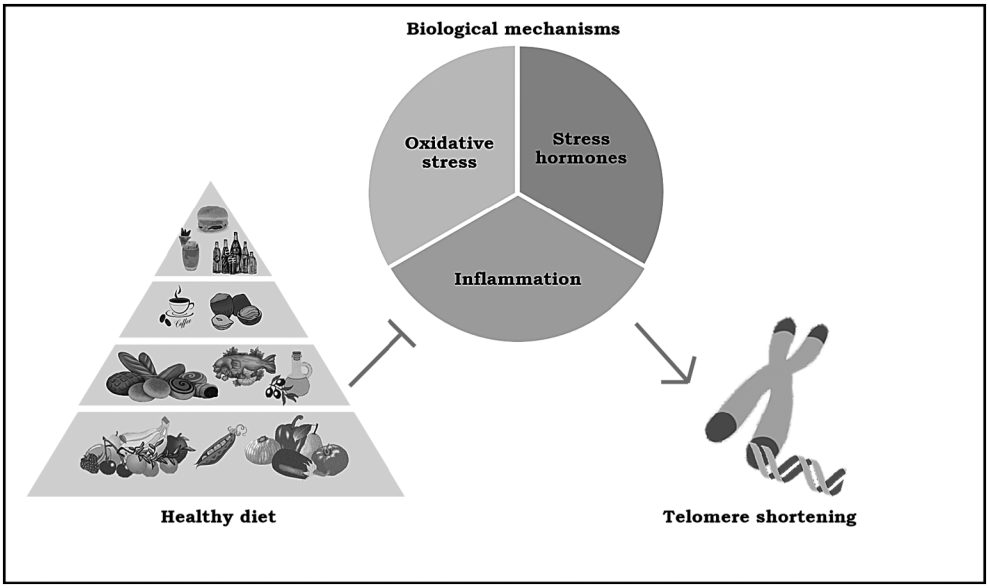

FIGURE 1 Schematic representation of the biological mechanisms by which diet is involved in preventing telomere shortening.

In conclusion, although in many cases blood concentrations of some nutrients better reflect the nutrient status of the individual, no clear associations have been systematically reported between blood concentrations of FAs, vitamins, or minerals and telomere length.

Potential mechanisms implicated in nutrition regulation of telomere maintenance

Telomere maintenance has been shown to be positively associated with nutrition status. As has been shown, various nutrients influence TL probably through mechanisms involved in cellular functions embracing inflammation, oxidative stress, DNA methylation, DNA integrity, and telomerase activity.

Even if the biochemical pathways that explain the relation between environmental impact and telomere maintenance remain unclear, there are 3 main potential mechanisms involved in this association: stress hormones, inflammation, and oxidative stress (**Figure 1**). First, it is important to state that the production of reactive oxygen species could potentially increment telomere erosion. In fact, telomere sequences are highly prone to oxidation into 8-oxoG because of the high content of guanine residues, as has been observed in different in vitro studies (111). When present in telomeres, 8-oxoG residues are likely to decrease both the affinity of shelterin proteins for telomeric DNA and disrupt G-quadruplex structures of telomeres that play an important protective role in avoiding telomere shortening (112). In addition, oxidative damage of telomeres inhibits telomerase, leading to telomere shortening, giving rise to premature cell senescence (113).

Therefore, whatever molecular mechanism is involved in increasing oxidative stress, it could potentially be related to dysregulation of telomere maintenance, such as during chronic inflammatory status. In fact, IL-6 and TNF seem to influence and directly modulate telomerase activity (114). Insulin resistance is also a chronic state related to both oxidative stress and inflammation that has a great role in promoting telomere shortening, as has been observed in type 2 diabetes populations (114). At the same time, chronic stress seems to exert a critical function in telomere maintenance, both by direct exposure or mother transmission in early life (115). Even if biological mechanisms are still unclear, the dysregulation of the hypothalamic-pituitary-adrenal axis and anomalous secretion of cortisol during a chronic stress condition may increase telomere shortening (116) and reduce telomerase activity (117) in humans.

Obviously, different environmental factors, such as diet and lifestyle, could modulate these biological mechanisms of telomere maintenance by promoting or preventing cellular oxidative stress and inflammation.

Other than promoting an antioxidative environment, diet could also play a great epigenetic role in telomere maintenance, by means of the acetylation and/or methylation of histones, which are directly related to telomere recombination and regulation of TL (118).

Conclusions

In this systematic review, an overall understanding of the relation between diet and telomere maintenance has been discussed. Generally, it could be observed that adherence to healthy dietary patterns, such as MedDiet, and more specifically the introduction of certain micronutrients in the diet, could have a protective effect on telomere shortening. The same positive tendency has also been found for certain food groups like fruit and vegetables or coffee, even if results remain inconsistent (**Tables 6** and **7**). In addition, potential

TABLE 6 Schematic representation of the influence of diet on telomere length in adults[1]

Dietary exposure factors	Cross-sectional studies	Case-control studies	RCTs
Macronutrients			
Dietary fiber	O O	—	—
Dietary fats	/ X	/ X	—
PUFA	X	/	// O
Proteins	//	—	—
Carbohydrates	/	—	—
Alcohol	X	X	—
Micronutrients			
Vitamin D	/ /	O /	O
Vitamin C	O O O /	—	—
Vitamin E	O O //	/	—
Vitamin A	O /	—	—
β-carotene	O	/	—
Niacin	/	—	—
Folate	/	—	—
Iron	/	—	—
Zinc	/	—	/
Dietary copper intake	O	—	/
Food groups			
Fruit	O O /////////	O O //	—
Vegetables	O O O ////////	O O //	—
Whole and refined grains	O O O /////// X	—	/
Meat	O O O //// X X X X X	/	—
Fish or seafood	O O /////// X	/	—
Fried food	/ X	X	
Seeds or Nuts	O O O //// X	—	O
Legumes	O O ///	—	/
Sweetened beverages	/// X X X	—	—
Coffee	O O ///	—	O
Animal fats	// X X X	—	—
Vegetable oils	/	—	O
Milk and dairy products	O O ///// X	/	—
Dietary patterns *a priori*			
Mediterranean diet	O O O O ///	—	/
Alternate Healthy Eating Index	O /	—	—
Dietary Inflammatory Index	X X //	—	—
Baltic Sea Diet Score	/	—	—
Dietary Approaches to Stop Hypertension	O	—	—

[1] Circles indicate a protective effect on telomere length, the slash a neutral effect, and the cross a potential risk factor for telomere length. RCT, randomized clinical trial.

common risk factors have been identified in these studies. Among them, there are some known proinflammatory food groups such as processed meat and sweetened beverages. Confirming their negative contribution on telomere health, the same negative association has been observed with a high inflammatory dietary pattern.

However, it is important to note that the studies in this review are mainly cross-sectional observations, which depict

TABLE 7 Schematic representation of blood nutrients on telomere length in adults[1]

Blood nutrients	Cross-sectional studies	Case-control studies	RCTs
Macronutrients			
Plasma *trans*-fatty acids	X	—	—
Serum ω3-fatty acids	O	—	—
Micronutrients		—	—
Serum vitamin D	O ///	—	—
Serum vitamin A	X	—	—
Serum vitamin C	O	—	—
Serum vitamin B-12	///	—	—
Serum vitamin E	/	—	—
Serum carotenoids	O	—	—
Serum folate	O ///	—	—
Serum ferritin	/	—	—
Plasma magnesium and calcium	X	—	—
Whole blood γ-tocopherol	X X	—	—

[1] Circles indicate a protective effect on telomere length, the slash a neutral effect, and the cross a potential risk factor for telomere length. RCT, randomized clinical trial.

temporal conditions of defined populations. More clinical trials are needed in order to have a deeper comprehension of the influence of diet on telomere attrition.

Protective or detrimental effects of diet on telomere maintenance must be considered in relation to certain lifestyles and cultures; such a unidirectional causality is not the purpose of this review.

Acknowledgments

The authors' responsibilities were as follows—SC, MB, JS-S: initiated the idea of this review and designed it; SG, SC: performed the screening procedure in order to collect the selected articles. SG, SC, JM, JG-G: wrote the manuscript; SG, SC, JM, JG-G: critically reviewed the article for important intellectual content; JS-S: assessed the articles and helped to draft and critically review the article for important intellectual content; and all authors: read and approved the final manuscript.

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