

Effects of Diet on Telomere Length: Systematic Review and Meta-Analysis

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Keywords

Age · Diet · Telomere

Abstract

Background: The goal of this systematic review and meta-analysis is to determine the effect of diet on telomere length. **Methods:** We searched the following databases: MEDLINE, Embase, LILACS, CINAHL, ISI Web of Science, and Scopus, as well as the Cochrane Central Register of Controlled Trials and the National Institutes of Health, from inception to December 2016. Articles that assessed effects of diet on telomere length were included. **Results:** A total of 2,128 studies were identified, 30 were read in full, and 7 were systematically reviewed. Five RCTs were included in the meta-analysis, covering 9 diets; a total of 533 participants were included. Study heterogeneity (I^2) was 89%, and differences were not identified regarding average telomere lengths (mean difference 1.06; 95% CI –1.53 to 3.65). **Conclusion:** The available evidence suggests that there is no effect of diet on telomere length, but the strong heterogeneity in the type and duration of dietary interventions does not allow any final statement on the absence of an effect of diet on telomere length.

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Introduction

The accumulation of time-dependent cellular damage is currently considered the main cause of aging [1]. Cellular senescence or the state of irreversible cell cycle arrest [2] induces dramatic changes in cell phenotype, resulting in changes to nuclear structure, gene expression, protein processing and metabolism, and resistance to apoptosis [3]. Senescent cells release bioactive molecules as inflammatory mediators (cytokines and chemokines), proteases, and reactive species [3]. In this environment, the pro-inflammatory milieu associated with reactive species induces friction in the DNA that occurs randomly in the chromosomes and impacts mostly their more susceptible regions, called telomeres [4].

Shortening of telomeres is a physiological process that occurs with each cell division in somatic cells and varies with age, progressing with the aging process [5]. However, several studies have linked telomere length, and premature or accelerated telomere shortening, with premature aging [6]. In recent years, positive relationships were established between clinically different pathological conditions, modulated by oxidative stress, inflammation, and lifestyle variables [7], and accelerated shortening of telo-

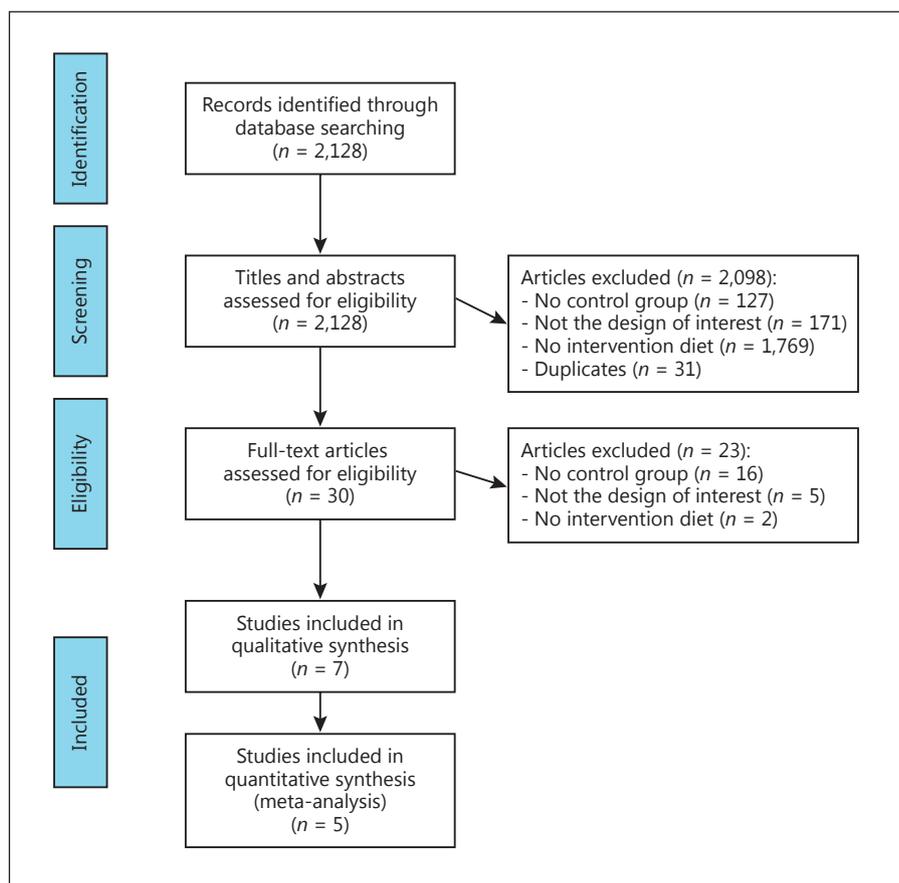


Fig. 1. Study selection flowchart.

meres. Among them, we can highlight cancer [8], tobacco use [9], oxidative stress, psychological conditions [10], poor living conditions, diabetes, cardiovascular diseases [11], radiation exposure, and, finally, diet [12].

The association between diet and shortening of telomeres is currently under scrutiny. A number of studies have reported both a decrease and an increase in telomere length process as a result of the diet to which an individual is exposed. Several factors may influence this relationship [13]. Currently, there are a significant number of diets, such as those with calorie restriction; diets rich in fats, carbohydrates, proteins, or modified fibers; micronutrient supplementation; liquid diets; and low-calorie diets [14].

Factors that may explain the association between diet and telomere length include increased oxidative stress and inflammation [15]. Oxidative stress promotes telomere erosion during cell replication, as well as the synthesis of proinflammatory cytokines. The so-called cardio-protective diets (Mediterranean, unsaturated fatty acid supplementation, hypocholesterolemic, and antihypertensive) [16] have constituents that may interfere by

blocking or hindering the main stages of cancer development and cardiovascular diseases, including DNA damage repair and blocked telomerase activity. It is likely that blood polyunsaturated fatty acid levels are involved in preventing telomere shortening over time [17].

Accelerated shortening of telomeres can induce a premature phenotype of cellular and systemic aging with concomitant failure of the body. Therefore, telomere length and its shortening may be associated with a lower life expectancy [18]. Diet exposure is considered a complex process inherent to the human condition, in which time is a relevant factor. Diet is believed to be either a protective or a detrimental factor for telomere length, depending on its composition. Thus, this study will systematically review the effect of diet on telomere length.

Methods

This review followed the PRISMA guidelines [19]; its protocol was based on the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015019193).

Table 1. Characteristics of the studies and diets analyzed

Autors [Ref.], year	Design	Country	Telomere length assessment method	Fluid analyzed	Intervention	Control diet	Subjects' age, years	Sex	Total, <i>n</i>
Mason et al. [23], 2013	RCT	USA	qPCR	Blood	Low-weight diet	Subject's pre-study diet	50–75	Female	321
Marin et al. [22], 2012a	RCT	Spain	Q-FISH	Blood	Saturated fatty acids	Subject's pre-study diet	>65	Male and female	20
Marin et al. [22], 2012b	RCT	Spain	Q-FISH	Blood	Mediterranean diet	Subject's pre-study diet	>65	Male and female	20
Marin et al. [22], 2012c	RCT	Spain	Q-FISH	Blood	CHO-ALA-PUFA	Subject's pre-study diet	>65	Male and female	20
Kiecolt-Glaser et al. [17], 2013a	RCT	USA	qPCR	Blood	Omega-3 supplement (1.25 g/day)	Placebo	40–85	Male and female	106
Kiecolt-Glaser et al. [17], 2013b	RCT	USA	qPCR	Blood	Omega-3 supplement (2.5 g/day)	Placebo	40–85	Male and female	106
O'Callaghan et al. [21], 2014a	RCT	Spain	qPCR	Blood	Omega-3 PUFA (EPA)	Omega-6 PUFA (LA)	>65	Male and female	33
O'Callaghan et al. [21], 2014b	RCT	Spain	PCR	Blood	Omega-3 PUFA (DHA)	Omega-6 PUFA (LA)	>65	Male and female	33
Tosevska et al. [24], 2016	RCT	USA	qPCR	Blood	Hyperproteic, whey-based, supplemented diet	Subject's pre-study diet	65–98	Male and female	105
Borresen et al. [25], 2016a	RCT	USA	qPCR	Blood	Navy bean powder supplemented	Not navy bean powder supplemented	47–78	Male and female	37
Borresen et al. [25], 2016b	RCT	USA	qPCR	Blood	Rice bran supplemented	Not rice bran supplemented	47–78	Male and female	37
Thomson et al. [26], 2016	RCT	USA	NS	Blood	Cruciferous vegetables	Subject's pre-study diet	≥18	Female	781

qPCR, quantitative polymerase chain reaction; Q-FISH, quantitative fluorescence in situ hybridization; CHO-ALA-PUFA, low-fat and high-carbohydrate diet enriched with *n*-3 polyunsaturated fatty acids; PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linolenic acid; NS, not stated.

This review included RCTs that evaluated the effects on telomere length of the following diets: calorie restriction, high-fat diet, Mediterranean diet, micronutrient supplementation, or combinations of different interventions. We included all published studies without restrictions on time, language, and participant race or age.

Excluded were (a) studies that did not evaluate the type of diet in relation to telomeres, (b) duplicate studies or nonspecific diets, (c) systematic reviews and meta-analyses, (d) studies that did not have a diet as a control group, and (e) studies with animals. Initially, two reviewers, working independently, checked all the titles and abstracts to identify studies that met the eligibility criteria. Following this step, the same reviewers read those meeting the eligibility criteria in full; a third reviewer solved divergences. All eligible papers were extracted using a standardized data collection form.

Search Strategy

For this review, an electronic search was conducted on the following databases: MEDLINE, Embase, LILACS, CINAHL, ISI Web of Science, Scopus, and LILACS. The following websites for online registration of clinical trials were also used: Cochrane Central Register of Controlled Trials (<http://www.cochrane.org>) and National Institutes of Health (<http://www.clinicaltrials.gov>), from inception to December 2016. The MEDLINE search strategy was as follows: (((Telomere) OR Telomeres)) AND (((((((((((((((((((((((((((((((Diet) OR Diets) OR Caloric Restriction) OR Restriction, Caloric) OR Low-Calorie Diet) OR Diet, Low-Calorie) OR Diets, Low-Calorie) OR Low Calorie Diet) OR Low-Calorie Diets) OR Nutrition) OR (Diet, Food, and Nutrition)) OR Dietary Advice) OR Dietary Intervention) OR Diet Therapy) OR Therapy, Diet) OR Diet Therapies) OR Therapies, Diet) OR Dietary Modification) OR Dietary Modifications) OR Modification, Dietary) OR Modifications, Dietary) OR Diet Modification) OR Diet Modifications) OR Modification, Diet) OR Modifications, Diet) OR Liquid Diet) OR Food) OR Foods) OR Nutrients). The titles of all references listed in the included studies were also reviewed to identify relevant additional material that could be included. We also conducted searches in print journals and the gray literature.

We used the recommendations of the Cochrane Collaboration [20] for evaluation of bias risk in the included studies and for heterogeneity analysis. Heterogeneity was considered using the I^2 test; publication bias was assessed by funnel plot. The investigators used standardized methods to evaluate the individual results; the final values and standard deviation (SD) of the results of interest were extracted to estimate the difference between treatment groups.

To evaluate the association between dependent and independent variables, the mean difference (MD) was applied by RevMan 5.3.

Sensitivity Analysis

Meta-analyses were performed more than once, removing studies one at a time to check whether heterogeneity was caused by individual studies.

Results

Study Selection

A total of 2,128 studies were identified through electronic searches; 2,098 of these were excluded after reading their titles and abstracts, and 30 articles were read in full.

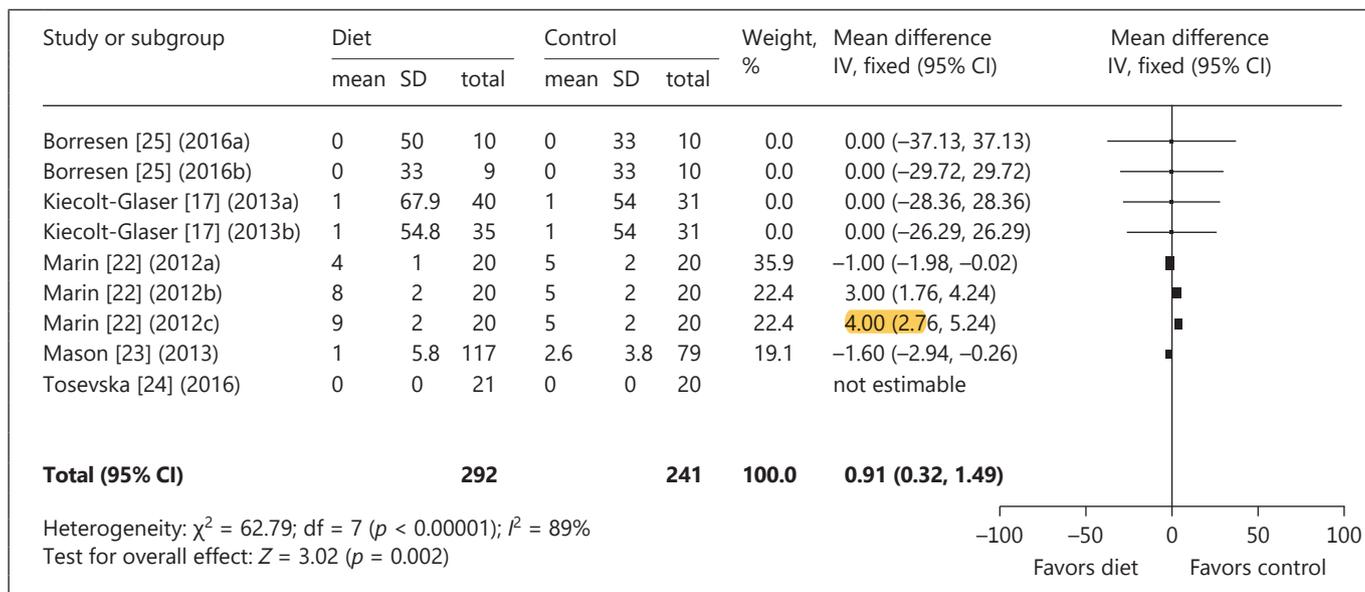


Fig. 2. Forest plot of telomere length comparison between diet and control groups.

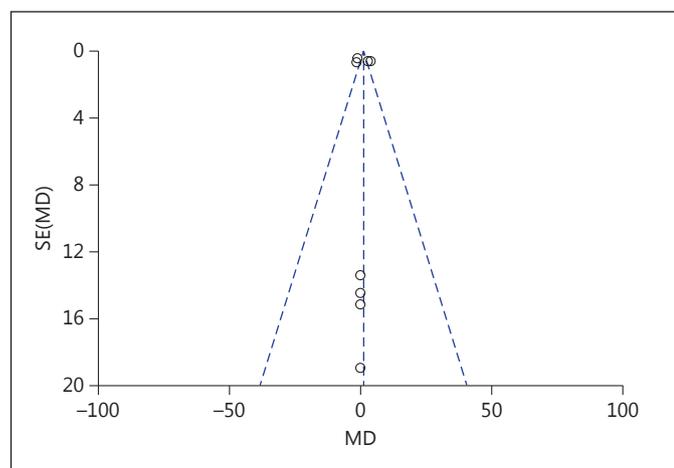


Fig. 3. Funnel plot of risk of publication bias.

Of these 30 articles, 23 were excluded for the following reasons: 16 articles had no control group, 4 were systematic reviews, 2 did not have a diet as an intervention, and 1 was an editorial. Finally, 7 articles were included in the review. The whole process is detailed in Figure 1.

The characteristics of the 7 included articles are summarized in Table 1 [17, 21–26]. The included studies involved 12 types of dietary intervention: a calorie-reduced diet; a Mediterranean diet; a saturated fatty acid-rich diet; a low-fat and high-carbohydrate diet enriched with *n*-3

polyunsaturated fatty acids; 4 alternatives of omega-3-based diets; a hyperproteic, whey-based, nutritionally supplemented diet; 2 types of diet with the addition of vegetable-based products; and a low-fat diet rich in cruciferous vegetables.

The sample size ranged from 20 to 781 subjects per study, aged 18–98 years. In most RCTs, the control diet was the diet the subjects had had prior to enrollment. The follow-up time in the included studies ranged from 4 weeks to 2 years. Quantitative polymerase chain reaction was the preferred method for measuring telomeres, and 1 study used fluorescence in situ hybridization.

Meta-Analysis

For the meta-analysis, 5 clinical trials were assessed [17, 22–25], which covered 9 diets (Fig. 2). A total of 533 participants were included (292 in the diet group and 241 in the control group). Study heterogeneity was high ($I^2 = 89\%$; $\tau^2 = 6.82$; $\chi^2 = 62.79$). The MD in telomere lengths between the groups was not significant (MD 1.06; 95% CI -1.53 to 3.65). In the sensitivity analysis, exclusion of data from each of the studies did not reduce heterogeneity ($I^2 = 89\%$), and the difference between means remained nonsignificant. The funnel plot analysis did not indicate any risk of publication bias between the studies reporting MDs (Fig. 3).

Risk of bias is also included in Figures 4 and 5. According to the GRADE system [27], the included studies only

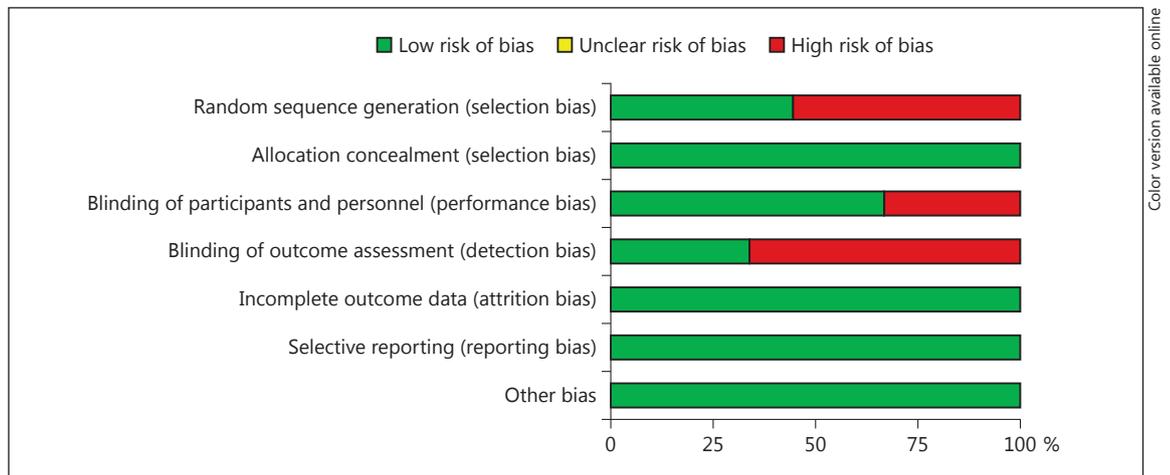


Fig. 4. Risk of bias with various study design processes.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Borresen 2016a	+	+	+	-	+	+	+
Borresen 2016b	+	+	+	-	+	+	+
Kiecolt-Glaser 2013a	-	+	+	+	+	+	+
Kiecolt-Glaser 2013b	-	+	+	+	+	+	+
Marin 2012a	-	+	-	-	+	+	+
Marin 2012b	-	+	-	-	+	+	+
Marin 2012c	-	+	-	-	+	+	+
Mason 2013	+	+	+	-	+	+	+
Tosevska 2016	+	+	+	+	+	+	+

Fig. 5. Risk of bias summary. Review authors' judgements about each risk of bias item for each included study.

had a high risk of bias in random sequence generation (60%), blinding of participants and personnel (30%), and blinding of outcome assessment (70%).

Discussion

This meta-analysis did not identify any significant effect of diet on telomere length. In addition to these findings, the results indicate a high heterogeneity in the available/included studies. Previous narrative reviews have reported a positive association between diet and telomere length; however, this is the first meta-analysis that evaluated the influence of diet on telomere length [28]. A recent systematic review [29] analyzed telomerase activity in association with psychological stress, mental disorders, and lifestyle interventions. Among lifestyle interventions, the micronutrient supplementation diet was analyzed, and telomerase activity was found to be increased in individuals who did not have any other lifestyle intervention.

A narrative review [28] highlighted the influence of the intake of saturated fats, refined sugars, grains, and alcohol on telomere shortening and the protective effect of the Mediterranean diet on telomere maintenance. They also stressed the lack of evidence from an intervention using fish that are rich in omega-3, which has antioxidant properties. However, our study intended to conduct a more thorough analysis of the evidence through a systematic and statistical evaluation.

The diets that are shown in these studies vary in duration from 4 weeks to 2 years, and they could interfere with

telomere length due to the dynamic structure that continuously changes with every cell division. Thus, the diet that is given to these persons should modify and decrease oxidative stress, which constantly changes the status of the cell [30].

In vitro modeling experiments may provide some insight into how micronutrient deficiencies or excess may affect telomere integrity. Deficiencies in micronutrients such as vitamin C, vitamin E, zinc, and selenium may lead to increased susceptibility to oxidative radicals, which can either oxidize guanine in the telomere sequence or cause single- or double-stranded breaks in telomeric or subtelomeric sequences [31].

In many of these studies, the quantitative polymerase chain reaction technique was used to measure telomere length, and despite the different techniques that can be used with this method, it is the most established and precise one. Even then, there are issues with precision measures that may have interfered with the final result. These facts should lead to more studies in order to improve measurement [23].

This systematic review and meta-analysis has some limitations: the high heterogeneity among the included studies, the variability in time of exposure and diet, and the loss of subjects in 60% of the included studies. However, when we performed a sensitivity analysis, removing

studies one by one, the I^2 test result did not change, that is, it remained nonsignificant, therefore suggesting that the interpretation of the results of our meta-analysis is consistent. This study did not exclude any particular population (i.e., according to health status, age, race, sex, and type of diet), a generalization of the search protocol that may have contributed to the increased heterogeneity. Considering the lack of specific information regarding telomere length by sex and age, we did not adjust the analyses for these variables. Only one study included patients younger than 65 years, and all studies included both sexes.

Conclusion

The available evidence suggests that there is no effect of diet on telomere length, but the strong heterogeneity in the type and duration of dietary interventions does not allow any final statement on the absence of an effect of diet on telomere length.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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