Associations between diet, lifestyle factors, and telomere length in women[1–3]

Aedín Cassidy, Immaculata De Vivo, Yan Liu, Jiali Han, Jennifer Prescott, David J Hunter, and Eric B Rimm

ABSTRACT

Background: Leukocyte telomere length is associated with diseases of aging, but there is limited knowledge of diet and lifestyle determinants

Objective: The objective was to examine cross-sectionally the association between diet, body composition, and lifestyle factors on leukocyte telomere length in women.

Design: Leukocyte telomere length was measured by quantitative polymerase chain reaction in 2284 female participants from the Nurses' Health Study, who were selected as controls for an investigation of biological predictors of cancer. Diet, lifestyle, and anthropometric data were assessed by questionnaire.

Results: After multivariate adjustment, dietary fiber intake was positively associated with telomere length (z score), specifically cereal fiber, with an increase of 0.19 units between the lowest and highest quintiles ($P = 0.007$, P for trend = 0.03). Although total fat intake was not associated with telomere length, polyunsaturated fatty acid intake (−0.26 units, quintile 5 compared with quintile 1: $P = 0.002$, P for trend = 0.02), specifically linoleic intake, was inversely associated with telomere length after multivariate adjustment (−0.32 units; $P = 0.001$, P for trend = 0.05). Waist circumference was inversely associated with telomere length [0.15-unit difference in z score in a comparison of the highest ($\geq$32 in, 81.28 cm) with the lowest ($\leq$28 in, 71.12 cm) category ($P = 0.01$, P for trend = 0.02) in the multivariate model]. We found no association between telomere length and smoking, physical activity, or postmenopausal hormone use.

Conclusions: Although the strength of the associations was modest in this population of middle- and older-age women, our results support the hypothesis that body composition and dietary factors are related to leukocyte telomere length, which is a potential biomarker of chronic disease risk. *Am J Clin Nutr* doi: 10.3945/ajcn.2009.28947.

INTRODUCTION

Telomeres are critical in maintaining the structural integrity of the genome and in protecting chromosomes from degradation and end-to-end fusion (1). They undergo erosion with each cycle of replication, and this shortening may trigger cellular senescence or apoptosis (2, 3), a process that is accelerated by oxidative stress and inflammation both in vitro (2–8) and in vivo (9–12). Telomere length progressively shortens with age in various mitotic tissues and cell types (2, 13–17). Leukocyte telomere length (LTL) may serve as a potential biomarker of biological age, reflecting the cumulative burden of oxidative stress and inflammation (18).

A growing body of epidemiologic and clinical data suggest that accelerated telomere attrition is associated with diseases of aging (19–21), including an increased risk of bladder cancer (22, 23), osteoporosis (24), coronary heart disease, diabetes, and heart failure (12, 25–32). Telomere length is a complex trait that is shaped by a combination of genetic, epigenetic, and environmental determinants (33–36); however, the range of factors that influence telomere dynamics is not fully established. Of the biological factors, a growing body of evidence suggest that heredity plays an important role. Several genes influence telomere length (37–39), and the reported heritability ranges from 36% to 90% (40, 41). Furthermore, genome-wide linkage studies provide evidence of linkage to autosomal regions (40, 41). Environmental and lifestyle factors may also play a key role, and shortened telomere length has been associated with, psychological stress (11), low physical activity levels (42), and equivocal data on the effects of body size (43, 44), smoking (43, 45), and socioeconomic status (46, 47) have been reported. However, to date, limited studies have investigated the relative importance of dietary intake on LTL (48, 49). Given that telomere shortening is accelerated by oxidative stress and inflammation and that diet affects both of these processes, the objective of our study was to determine the potential relation between dietary factors and LTL and also to further examine the importance of other lifestyle factors. Although this was a cross-sectional study, and therefore exploratory in nature, we hypothesized that *1*) a diet high in fruit and vegetables and rich in dietary fiber and whole grains would be associated with longer LTL because these dietary factors exert antioxidant and antiinflammatory effects, and *2*) a diet high in polyunsaturated and *trans* fatty acids, which are associated

[1] From the School of Medicine, University of East Anglia, Norwich, United Kingdom (AC); Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (IDV, JH, JP, DJH, and EBR); the Departments of Epidemiology (IDV, JH, JP, DJH, and EBR) and Nutrition (YL and EBR), Harvard School of Public Health, Boston, MA; and the Clinical Research Program, Department of Dermatology, Brigham and Women's Hospital, Boston, MA (JH).

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[3] Address correspondence to EB Rimm, Departments of Nutrition and Epidemiology, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115. E-mail: erimm@hsph.harvard.edu.

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with inflammation and oxidative stress, may accelerate the biological aging process and be associated with shorter LTL.

SUBJECTS AND METHODS

The study population comprised 2284 female participants from the Nurses' Health Study who were selected as control subjects in nested case-control studies of biological predictors of breast, skin and endometrial cancer (50, 51). The Nurses' Health Study is a prospective cohort investigation involving 121,700 female US nurses who were 30–55 y of age at baseline in 1976. Information about health and disease is assessed biennially, and dietary information was obtained every 4 y through self-administered questionnaires (52, 53). From 1989 to 1990, a blood sample was requested from all participants and was provided by 32,826 women. Women who provided blood samples were similar to those who did not (54), and the controls who participated in the current study were randomly selected by using a risk-set sampling (55) at a ratio of 1:1 to 1:3. Controls were matched to cases on age, menopausal status, blood collection variables (time of day, season, year of blood collection, and fasting status), and recent (<3 mo) postmenopausal hormone use from the subgroup of participants who were free of diagnosed cancer at the time cancer was diagnosed in the cases. We did not include cancer cases in our analyses because case status may be related to telomere length and also to specific lifestyle characteristics that predict cancer and, thus, lead to biased results from the oversampling of women with cancer.

Anthropometric, lifestyle, self-reported blood pressure measurements, and dietary data were derived from the questionnaire administered in 1990, with missing information substituted from previous questionnaires. Body mass index (BMI) was calculated as weight (in kg) divided by the square of the height (in m). Average nutrient intakes were computed by using a validated semiquantitative food-frequency questionnaire (52, 53, 56). Physical activity, expressed in terms of metabolic equivalent task (MET) hours, was assessed by using a previously validated questionnaire (57).

Measurement of LTL

A quantitative real-time polymerase chain reaction method was used to measure relative telomere length in genomic DNA extracted from peripheral blood leukocytes (50), and the ratio of telomere repeat copy number to a single gene copy number (T:S) was determined as previously described (50). Each sample was analyzed in triplicate, and the relative telomere length was calculated as the exponentiated T:S ratio. CVs of the telomere and single-gene assay ranged from 0.57% to 3.07% and 0.56% to 2.07%, respectively. The CVs for the exponentiated T:S ratio of quality control samples ranged from 14% to 16% (50, 51).

Statistical analyses

Control subjects were derived from 3 ongoing nested case-control studies examining the relation between LTL and skin, breast, and endometrial cancer (50, 51). Given the interrun differences in assessment of relative LTL, we derived the log relative telomere length for each set of controls separately after deleting extremes (1%). We then derived a z score for each set of controls, and, after excluding participants with missing covariates, the z scores were pooled for all subsequent analyses (n = 2284).

We calculated age-adjusted participant demographic and lifestyle characteristics and age- and energy- adjusted nutrient intake data across quintiles of the LTL z score. Spearman's age-adjusted partial correlation coefficients were derived to examine the correlation of LTL with all variables. To evaluate the associations between diet and lifestyle variables and LTL we used 2 multivariable linear regression models with robust variance estimates (52). In model 1 we adjusted for age (5-y categories) and smoking status (never, past, nonsmoker with unknown past history, current smoker, and unknown), and in model 2 we additionally adjusted for postmenopausal hormone use (never, past <5 y, past ≥5 y, current <5 y, and current ≥5 y), physical activity (quintiles), and BMI (in kg/m^2: <25, 25–29, 30–34, and ≥35). We also included total energy intake and energy-adjusted protein, individual fatty acids [polyunsaturated (PUFA), saturated, *trans*, and monounsaturated], cereal fiber (for carbohydrate analysis protein was removed from the model) in model 2. We calculated P trends across categories by including the independent variable as a continuous predictor in the regression models.

To assess the joint and independent effects of PUFAs and age, we created categorical interaction variables by cross-classifying tertiles of PUFA and age (**Figure 1**). Statistical analyses were conducted by using SAS software (version 9; SAS Institute, Cary, NC). All P values are 2-tailed.

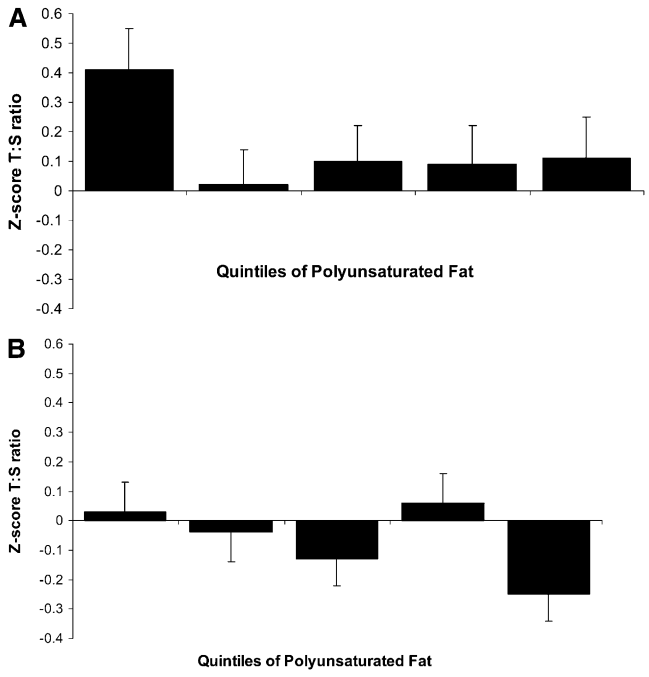

FIGURE 1. Joint associations of age, <60 y (A; n = 922) compared with ≥60 y (B; n = 1362), and polyunsaturated fatty acids on telomere length in the Nurses' Health Study. The median intakes of polyunsaturated fatty acids were 7.4, 9.0, 10.3, 11.8, and 14.1 g/d for quintiles 1–5, respectively. Multivariable linear regression was performed, with adjustment for age, smoking, postmenopausal hormone use, BMI, physical activity, and intakes of polyunsaturated fatty acids, saturated fatty acids, *trans* fatty acids, monounsaturated fatty acids, energy, cereal fiber, and protein. P for interaction = 0.07. T:S, ratio of telomere repeat copy number to a single gene copy number.

RESULTS

Age was inversely correlated with LTL ($r = -0.11$, $P < 0.0001$). Subjects in the lowest quintile of LTL had a higher BMI, higher total fat intake (specifically from monounsaturated fatty acids and PUFAs), and a lower fiber intake, specifically from cereal fiber and whole grains (**Table 1**). The strongest age-adjusted Spearman correlations were for body composition (BMI: $r = -0.06$, $P = 0.009$; waist: $r = -0.06$, $P = 0.01$), total fat intake, polyunsaturated fatty acids and linoleic acid (all $r = -0.06$, $P = 0.004$), and fiber, specifically cereal fiber ($r = 0.06$, $P = 0.004$).

Compared with women in the lowest category of waist circumference (≤28 in, 71.12 cm), women in the top category of waist circumference (≥32 in, 81.28 cm) had a −0.15-unit difference in z score (P for trend = 0.02). In analyses stratified by age, increased waist circumference in the younger age group was negatively associated with LTL (−0.27 change in z score in the group aged <60 y, P for trend = 0.05; −0.07 in the older age group, P for trend = 0.12). The highest compared with lowest BMI category (≥35 compared with <25) was also negatively associated with LTL ($P = 0.03$) (**Table 2**).

Total fat intake was only inversely associated with LTL after adjustment for age and smoking, but this association did not remain statistically significant after multivariate adjustment. However, results from analyses of individual fatty acid intake suggest that a higher PUFA intake (−0.26 z score units, P for trend =0.02), specifically linoleic acid intake, was inversely associated with LTL in the multivariate model (−0.32 z score unit difference, P for trend = 0.05; **Table 3**). As shown in Figure 1, LTL was lowest among the older women in the highest category of PUFA intake ($P = 0.004$, P for interaction = 0.07).

In contrast with PUFAs, dietary fiber intake was positively associated with LTL, specifically cereal fiber, with an increase of 0.19 z score units between the highest and lowest quintiles (quintile 5 compared with quintile 1: P for trend = 0.03), and this was in part explained by whole-grain intake. In our analyses of other factors, there was a trend toward a relation between increased vitamin E intake and LTL, but it was not statistically significant. No significant associations were observed for vitamin D intake, fruit and vegetable intake, smoking, physical activity, or postmenopausal hormone use.

TABLE 1
Characteristics of the 2284 women (controls) who participated in the Nurses' Health Study by quintile of telomere length[1]

	Quintile of z score					P for trend
	1	2	3	4	5	
Age (y)	59.3 ± 6.4	59.7 ± 6.3	59.2 ± 6.5	58.1 ± 6.5	58.0 ± 6.9	—
Postmenopausal (%)	87.6 ± 0.32	85.9 ± 0.32	88.2 ± 0.31	87.7 ± 0.35	87.2 ± 0.37	0.82
HRT use (%)	64.7 ± 0.48	62.3 ± 0.49	65.2 ± 0.48	61.8 ± 0.48	64.4 ± 0.48	0.96
BMI (kg/m^2)	26.0 ± 4.9	25.7 ± 4.8	25.4 ± 4.6	25.3 ± 4.5	25.3 ± 4.3	0.005
Waist (cm)	80.3 ± 11.5	80.0 ± 10.8	79.3 ± 10.3	78.7 ± 9.9	78.7 ± 10.1	0.009
Hip (cm)	101.9 ± 10.2	101.4 ± 9.8	100.8 ± 9.8	101.1 ± 8.9	100.8 ± 9.5	0.1
Waist:hip ratio	0.79 ± 0.12	0.79 ± 0.10	0.79 ± 0.08	0.78 ± 0.06	0.78 ± 0.12	0.14
Weight (kg)	70.2 ± 13.9	68.9 ± 13.1	68.3 ± 13.2	67.4 ± 12.6	68.2 ± 11.2	0.004
Height (cm)	164.1 ± 5.6	163.6 ± 5.8	163.8 ± 6.0	163.3 ± 5.9	164.1 ± 5.8	0.59
Alcohol (g/d)	6.1 ± 10.5	6.4 ± 10.2	6.1 ± 9.2	6.4 ± 11.2	6.4 ± 9.7	0.59
Energy intake (kcal/d)	1795 ± 494	1774 ± 492	1771 ± 488	1789 ± 507	1774 ± 474	0.62
Total fatty acids (g/d)	56.2 ± 10.3	56.0 ± 11.6	54.6 ± 10.2	55.6 ± 10.3	54.1 ± 11.1	0.003
Saturated fatty acids (g/d)	18.8 ± 4.4	18.7 ± 4.4	18.5 ± 4.5	18.6 ± 4.1	18.4 ± 4.5	0.11
Monounsaturated fatty acids (g/d)	21.5 ± 4.8	21.5 ± 5.0	20.7 ± 4.3	21.4 ± 4.8	20.6 ± 4.9	0.006
Polyunsaturated fatty acids (g/d)	10.9 ± 2.9	10.9 ± 3.7	10.5 ± 2.8	10.7 ± 2.8	10.2 ± 2.8	0.0008
trans Fatty acids (g/d)	2.6 ± 1.0	2.7 ± 1.0	2.5 ± 0.93	2.6 ± 0.94	2.5 ± 1.0	0.05
Omega-3, marine (g/d)	0.25 ± 0.19	0.26 ± 0.34	0.25 ± 0.26	0.25 ± 0.25	0.25 ± 0.21	0.96
Linolenic acid (g/d)	0.90 ± 0.30	0.94 ± 0.40	0.90 ± 0.33	0.90 ± 0.30	0.88 ± 0.29	0.13
Linoleic acid (g/d)	9.4 ± 2.7	9.4 ± 3.1	9.0 ± 2.5	9.2 ± 2.7	8.8 ± 2.6	0.0009
Protein (g/d)	75.9 ± 13.3	75.4 ± 13.7	75.1 ± 12.9	76.1 ± 12.8	76.8 ± 13.1	0.19
Carbohydrates (g/d)	200.1 ± 30.7	199.6 ± 35.2	203.4 ± 33.2	201.0 ± 30.9	204.0 ± 33.1	0.06
Fiber (g/d)	18.5 ± 5.3	18.5 ± 6.1	18.8 ± 5.6	18.6 ± 5.2	19.3 ± 5.7	0.03
Cereal fiber (g/d)	5.0 ± 2.7	5.5 ± 4.0	5.5 ± 3.5	5.5 ± 3.2	5.7 ± 3.3	0.006
Whole grains (g/d)	19.9 ± 16.8	21.2 ± 18.6	21.2 ± 15.0	21.5 ± 15.8	22.6 ± 17.5	0.01
Fruit and vegetable intake	6.0 ± 2.5	5.7 ± 2.4	5.9 ± 2.4	5.8 ± 2.6	6.0 ± 2.4	0.77
Vitamin E (IU/ d)	78.7 ± 179.9	84.3 ± 192.6	82.3 ± 175.8	104.7 ± 211.6	93.9 ± 190.3	0.07
Vitamin C (mg/d)	319.0 ± 349.6	310.1 ± 336.7	340.6 ± 392.1	368.5 ± 414.8	324.9 ± 344.2	0.24
Vitamin D (IU/d)	332.1 ± 220.6	350.8 ± 259.7	365.7 ± 252.3	374.0 ± 309.6	367.9 ± 242.9	0.01
Multivitamin users (%)	34.2 ± 0.47	37.6 ± 0.49	39.6 ± 0.49	43.6 ± 0.50	37.7 ± 0.49	0.09
Physical activity (METs/wk)	19.8 ± 20.9	20.2 ± 21.8	19.9 ± 20.0	19.2 ± 21.6	19.6 ± 20.7	0.69
Smoking status						
Never smoker (%)	45.9 ± 0.50	45.2 ± 0.50	48.4 ± 0.50	48.4 ± 0.50	46.8 ± 0.50	0.49
Past smoker (%)	43.5 ± 0.50	41.8 ± 0.49	40.4 ± 0.49	39.6 ± 0.49	42.8 ± 0.50	0.63
Current smoker (%)	10.1 ± 0.30	12.6 ± 0.33	10.5 ± 0.31	11.8 ± 0.32	10.0 ± 0.30	0.76
Pack-years	12.5 ± 19.5	12.6 ± 18.2	12.1 ± 19.2	11.0 ± 17.2	11.7 ± 17.4	0.25

[1] All values (except age) are age-adjusted means ± SDs. METs, metabolic equivalent tasks.

TABLE 2
Lifestyle determinants of telomere length (change in *z* score) in 2284 women from the Nurses' Health Study[1]

	Mean ± SE	*P*	Mean ± SE	*P*	Mean ± SE	*P*	Mean ± SE	*P*	Mean ± SE	*P*	Mean ± SE	*P*	*P* for trend
Pack-years	None: 0.01 ± 0.06	Ref	<10: −0.02 ± 0.07	0.64	10–25: 0.05 ± 0.08	0.58	25–30: −0.09 ± 0.10	0.30	30–35: 0.04 ± 0.13	0.83	>35: −0.004 ± 0.08	0.83	0.77
Smoking (%)	Never: 0.002 ± 0.06	Ref	Past quit <10 y: 0.05 ± 0.07	0.46	Past quit >10 y: −0.007 ± 0.07	0.87	Current 1–14: 0.04 ± 0.11	0.71	Current 15–24: −0.06 ± 0.11	0.58	Current ≥25: 0.005 ± 0.15	0.99	—
Postmenopausal hormone use (%)	Never: 0.05 ± 0.06	Ref	Past <5 y: −0.01 ± 0.07	0.33	Past ≥5 y: 0.09 ± 0.17	0.84	Current <5 y: −0.004 ± 0.06	0.30	Current ≥5 y: −0.06 ± 0.10	0.20	—	—	—
BMI (kg/m^2)	18.5 to <25: 0.10 ± 0.06	Ref	25–29: −0.01 ± 0.06	0.02	30–34: 0.07 ± 0.09	0.66	≥35: −0.14 ± 0.12	0.03	—	—	—	—	0.07
Waist (inches) (n = 1837)	≤28 (71.1 cm): 0.13 ± 0.06	Ref	28–32 (71.1–81.3 cm): 0.06 ± 0.07	0.27	≥32 (81.3 cm): −0.02 ± 0.07	0.01	—	—	—	—	—	—	0.02
Waist:hip ratio (n = 1830)	<0.74: 0.14 ± 0.07	Ref	0.74–0.79: 0.06 ± 0.06	0.20	≥0.80: −0.05 ± 0.07	0.003	—	—	—	—	—	—	0.14
Physical activity (METs/wk)	Q1: −0.03 ± 0.07	Ref	Q2: 0.02 ± 0.07	0.39	Q3: 0.07 ± 0.08	0.13	Q4: 0.05 ± 0.08	0.22	Q5: −0.09 ± 0.07	0.43	—	—	0.13

[1] n = 2284 except for waist (n = 1837) and waist:hip ratio (n = 1830). Multivariable linear regression with adjustment for age, smoking, postmenopausal hormone use, BMI, physical activity, and intakes of polyunsaturated fatty acids, saturated fatty acids, *trans* fatty acids, monounsaturated fatty acids, energy, cereal fiber, and protein. METs, metabolic equivalent tasks; Ref, reference; Q, quintile.

TABLE 3
Dietary determinants of telomere length (change in *z* score) in 2284 women from the Nurses' Health Study[1]

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5		*P* for trend
	Mean ± SE	*P*	Mean ± SE	*P*	Mean ± SE	*P*	Mean ± SE	*P*	Mean ± SE	*P*	
Energy intake (kcal/d)	0.01 ± 0.07	Ref	−0.01 ± 0.07	0.71	−0.02 ± 0.07	0.59	0.03 ± 0.08	0.88	0.02 ± 0.07	0.93	0.76
Total fatty acids (g/d)	0.10 ± 0.08	Ref	0.05 ± 0.07	0.42	−0.02 ± 0.07	0.07	−0.06 ± 0.07	0.02	−0.01 ± 0.07	0.12	0.05
Total protein (g/d)	−0.03 ± 0.08	Ref	0.01 ± 0.08	0.55	−0.04 ± 0.07	0.94	0.07 ± 0.08	0.15	0.02 ± 0.07	0.49	0.34
Carbohydrate (g/d)	−0.01 ± 0.08	Ref	0.03 ± 0.07	0.56	0.00009 ± 0.07	0.84	0.008 ± 0.08	0.79	0.007 ± 0.09	0.82	0.88
Fiber (g/d)	−0.006 ± 0.07	Ref	−0.10 ± 0.08	0.21	−0.03 ± 0.07	0.68	0.007 ± 0.08	0.87	0.12 ± 0.08	0.11	0.03
Cereal fiber (g/d)	−0.08 ± 0.07	Ref	0.03 ± 0.08	0.11	−0.003 ± 0.07	0.22	−0.02 ± 0.08	0.40	0.11 ± 0.08	0.007	0.03
Whole grains (g/d)	−0.08 ± 0.07	Ref	0.02 ± 0.07	0.19	−0.04 ± 0.07	0.65	0.04 ± 0.08	0.11	0.08 ± 0.08	0.04	0.46
Vitamin E (IU/d)	−0.10 ± 0.08	Ref	−0.02 ± 0.07	0.25	0.05 ± 0.07	0.05	0.06 ± 0.08	0.04	0.03 ± 0.07	0.06	0.49
Saturated fatty acids (g/d)	−0.008 ± 0.09	Ref	−0.04 ± 0.08	0.62	−0.005 ± 0.08	0.98	0.004 ± 0.07	0.89	0.08 ± 0.08	0.38	0.29
Polyunsaturated fatty acids (g/d)	0.15 ± 0.08	Ref	−0.04 ± 0.07	0.02	−0.04 ± 0.07	0.01	0.06 ± 0.08	0.28	−0.11 ± 0.08	0.002	0.02
Monounsaturated fatty acids (g/d)	0.04 ± 0.09	Ref	0.05 ± 0.08	0.88	−0.02 ± 0.07	0.48	−0.02 ± 0.08	0.56	−0.03 ± 0.08	0.49	0.42
trans Fatty acids (g/d)	0.02 ± 0.08	Ref	−0.02 ± 0.07	0.52	−0.01 ± 0.08	0.63	0.02 ± 0.07	0.95	0.03 ± 0.08	0.94	0.70
Linolenic acid (g/d)	−0.03 ± 0.08	Ref	0.07 ± 0.08	0.18	−0.08 ± 0.08	0.51	0.01 ± 0.07	0.60	0.10 ± 0.08	0.1	0.23
Linoleic acid (g/d)	0.19 ± 0.08	Ref	0.02 ± 0.07	0.03	−0.04 ± 0.07	0.007	0.04 ± 0.08	0.09	−0.13 ± 0.08	0.001	0.046
Vitamin D (IU)	−0.03 ± 0.08	Ref	0.03 ± 0.07	0.45	−0.05 ± 0.07	0.74	0.03 ± 0.07	0.40	0.04 ± 0.07	0.38	0.11
Fruit and vegetables (g/d)	0.01 ± 0.07	Ref	0.05 ± 0.07	0.60	−0.02 ± 0.08	0.68	−0.04 ± 0.08	0.54	0.03 ± 0.08	0.83	0.75

[1] n = 2284. Multivariable linear regression with adjustment for age, smoking, postmenopausal hormone use, BMI, physical activity, and intakes of polyunsaturated fatty acids, saturated fatty acids, *trans* fatty acids, monounsaturated fatty acids, energy, cereal fiber, and protein (for carbohydrate analyses, protein was removed from model). Ref, reference.

The relative effects of many dietary and anthropometric measures on LTL are summarized in **Figure 2**. These data suggest that the relative magnitude of the association of body composition and diet on LTL are similar; a difference of 0.24 SDs between the average T:S ratio when the extremes of BMI categories were compared and similar effects when the highest and lowest quintiles of PUFA intake were compared.

DISCUSSION

In this cross-sectional study, waist circumference and polyunsaturated fatty acid intake were inversely associated with LTL, whereas a diet high in fiber, specifically cereal fiber, was positively associated with longer LTL. Although the strength of the associations was modest, our results support the hypothesis that body composition and dietary factors are related to LTL in women, a potential mediator of chronic disease risk.

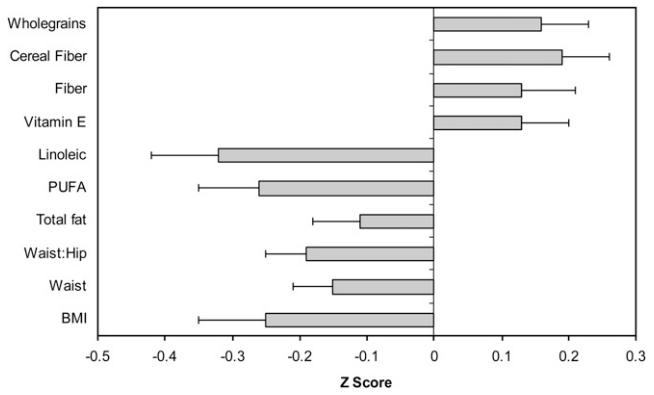

FIGURE 2. Relative effect of body composition and dietary factors on telomere length (change in *z* score) in the Nurses' Health Study (comparison of quintile 5 with quintile 1). Multivariable linear regression was performed, with adjustment for age, smoking, postmenopausal hormone use, BMI, physical activity, and intakes of polyunsaturated fatty acids, saturated fatty acids, *trans* fatty acids, monounsaturated fatty acids, energy, cereal fiber, and protein. n = 2284, except for waist (n = 1837) and waist:hip ratio (n = 1830). PUFA, polyunsaturated fatty acids.

Accelerated telomere attrition is not only associated with diseases of aging (12, 19–32), but telomere shortening may more accurately predict the biological aging process than the chronological age (2). To date, few studies have examined lifestyle determinants of LTL (42–47), and to our knowledge even fewer studies have investigated the relative effect of diet on LTL in humans (48, 49, 63). Our finding that dietary factors and other lifestyle factors are associated with LTL may in part explain potential pathways by which diet and body composition affect the risk of developing type 2 diabetes, cardiovascular disease, and some cancers (58–62).

We observed an inverse association between waist circumference, BMI, and the waist:hip ratio and LTL after adjusting for age and smoking; however, after adjustment for many known lifestyle factors, this relation only remained significant for waist circumference (Table 2). Previous data on the effects of body composition on LTL have been equivocal (43, 44), with one study showing that women with a BMI $>$ 30 had shorter telomeres than those with a BMI $<$ 20 after adjustment for age, but this relation did not remain significant after further adjustment for smoking (43). In the Cardiovascular Health Study, associations between BMI and LTL were observed only in overweight men (BMI $>$ 27) and not in women (BMI $>$ 25) (29). Biologically, an inverse relation between obesity and LTL is plausible given that accumulating adiposity increases oxidative stress and causes deregulation of inflammatory cytokines (64). Compared with genomic DNA, the G-rich telomeric sequence is not only a potential target for acute oxidative damage, but telomeric DNA is relatively less capable of DNA repair, resulting in accelerated telomere loss during the cell cycle and subsequent replicative senescence (4)

To date, there are limited data on the influence of dietary factors on LTL; however, in a recent pilot study, adoption of a healthy lifestyle was associated with an increase in telomerase activity in peripheral blood mononuclear cells—an important finding because telomerase activity is normally low or undetectable in most adult somatic cells (48). The study involved following a 3-mo comprehensive lifestyle change, including dietary change (low-fat, high-plant based), moderate aerobic exercise, stress management, and supplementation with soy, selenium, fish oil, and vitamin C; this intervention resulted in significant reductions in BMI and blood pressure and decreases in LDL cholesterol and psychological stress (48). Although these findings are important, it is difficult to disentangle the relative importance of the individual factors in modifying telomerase activity or to determine whether changes were due specifically to the interventions or to the changes in the clinical characteristics that resulted from the interventions.

Two previous small cross-sectional studies have examined the relation between some dietary components and LTL. In a multiethnic cross-sectional study, the only significant relation between food groups and LTL was an inverse association between consumption of processed meat, which was independent of intake of other food groups (49). In a second study of British women, serum 25-hydroxyvitamin D was significantly related to LTL (63). We were unable to replicate these findings in our large cross-sectional study of women.

In our study, the individual fatty acids were more strongly associated with LTL than with total fat. Specifically, intake of the n−6 PUFA linoleic acid was inversely associated with LTL (Table 2). Available evidence on the effects of n−6 PUFA interventions on cardiovascular disease risk markers suggest that consumption of ≥5–10% energy from omega-6 (n−6) PUFAs has the greatest cardiovascular benefit (65). Furthermore, no association between breast and prostate cancer risk and n−6 PUFAs or linoleic acid has been reported (66–69). n−6 PUFAs are involved in a range of biological pathways, and, although there is evidence suggesting that the mediators formed from n−6 fatty acids may exert proinflammatory and pro-arrhythmic effects (70) and result in modulation of gene expression (71), the modest observed effects of n−6 PUFAs on LTL may be outweighed by the strong inverse association of linoleic acid with LDL cholesterol and other chronic disease risk biomarkers and beneficial metabolic processes (65). Our findings merit further investigation in other studies.

Given that shorter telomeres may represent a potential marker of the cumulative burden of oxidative stress and inflammation, our finding that dietary fiber intake is positively associated with LTL, specifically cereal fiber and whole-grain intake, suggests that a diet high in plant-based foods may favorably influence telomere length via antiinflammatory and antioxidant mechanisms. Growing evidence supports the influence of whole grains and diets high in fruit and vegetables on inflammatory processes (72–75), and a high intake of plant-based diets and whole grains is inversely associated with total mortality and risk factors for chronic disease (76–79). This finding warrants further investigation, particularly to examine the relative importance of specific plant bioactivities such as dietary lignans on telomere biology.

Several previous studies have observed an association between smoking and telomere length (23, 43). In one study, adjusted telomere length was lower in women smokers than in nonsmokers (43) However, in our study and others, smoking status was not associated with LTL (29, 30, 80, 81)—a surprising finding given that telomere attrition is accelerated by oxidative stress (4). In agreement with Nettleton et al (49), we observed no association between physical activity (active leisure time) and telomere length. In one previous study, physical activity was associated with telomere length; however, diet was not included in the multivariate model (42).

Our study had several limitations. The cross-sectional design limits causal inference, and there is the possibility of unmeasured confounding, although we controlled for many lifestyle and dietary factors previously associated with telomere length. Our study relies on a single measure of telomere length; therefore, we cannot examine interindividual variability in telomere length over longer periods of time, and the lack of serial measurements may have limited our ability to detect associations. Our telomere length data were derived from 3 ongoing nested case-control studies and to pool the data z scores were derived. As a result, although we were able to show the magnitude of the associations, we were unable to quantify the T:S ratio or to determine the approximate age-related changes associated with the various lifestyle and dietary factors (Figure 2). We only had data available for healthy, primarily white women; therefore, the findings may not be generalizable to men or other ethnicities. As in any observational study, measurement error in self-reported variables is inevitable; however, misclassification in this prospective study would underestimate the true relation. Although we attempted to control for any potential confounding variables, the possibility of residual confounding remains.

In conclusion, we found that waist circumference and polyunsaturated fatty acid intake were negatively associated, and dietary fiber, specifically cereal fiber, was positively associated with LTL in a large cross-sectional study of middle-aged and older women. Although the strength of the associations was modest, our results support the hypothesis that body composition and dietary factors are related to LTL in women—a potential mediator of chronic disease risk.

The authors' responsibilities were as follows—AC, YL, and EBR: conducted the statistical analysis; AC and EBR: interpreted the data and drafted the manuscript; IDV and JP: performed the telomere length measurements; and DJH, IDV, and JP: critically reviewed the manuscript. All authors contributed to the manuscript and agreed to the final version. None of the authors had a conflict of interest.

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