Mediterranean diet and leukocyte telomere length in a multi-ethnic elderly population

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Abstract Leukocyte telomere length (LTL) is considered as the marker of biological aging and may be related to environmental factors. The current study aimed to examine the relation between Mediterranean-type diet and LTL. We used a cross-sectional study of 1743 multi-ethnic community residents of New York aged 65 years or older. Mediterranean-type diet (MeDi) was calculated from dietary information collected using a food frequency questionnaire. LTL was measured from leukocyte DNA using a real-time PCR method to measure T/S ratio, the ratio of telomere (T) to single-copy gene (S) sequence. Regression analysis showed that the MeDi score was not associated with LTL in the overall study population ($\beta=12.5$; $p=0.32$) after adjusting for age, sex, education, ethnicity, caloric intake, smoking, and physical and leisure activities. However, we found a significant association between MeDi and LTL among non-Hispanic whites ($\beta=48.3$; $p=0.05$), and the results held after excluding dementia subjects ($\beta=49.6$; $p=0.05$). We further found that, in the whole population, vegetable and cereal consumption above the sex-specific population median was associated with longer LTL ($\beta=89.1$, $p=0.04$) and shorter LTL ($\beta=-93.5$; $p=0.03$), respectively. Among non-Hispanic whites, intake of meat or dairy below sex-specific population medians was associated with longer LTL ($\beta=154.7$, $p=0.05$; $\beta=240.5$, $p<0.001$, respectively). We found that higher adherence to a MeDi was associated with longer LTL among whites but not among African Americans and Hispanics. Additionally, a diet high in vegetables but low in cereal, meat, and dairy might be associated with longer LTL among healthy elderly.

Keywords Telomere · Diet · Aging

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Abbreviations

CRP	C-reactive protein
BHS	Bogalusa Heart Study
FHS	Family Heart Study
LA	Leisure activity
LTL	Leukocyte telomere length
MeDi	Mediterranean-type diet
MESA	Multi-Ethnic Study of Atherosclerosis
NHS	Nurses' Health Study
PA	Physical activity
PLCO	Prostate, Lung, Colorectal, and Ovarian
SFFQ	Semiquantitative food frequency questionnaire
WHICAP	Washington Heights-Inwood Community Aging Project

Introduction

Telomeres are highly conserved regions of DNA made up of thousands of repeated 5′-TTAGGG-3′ base pairs located at the ends of each chromosome. Telomeres provide an essential protective role for the genetic material, preventing DNA damage response and repair mechanisms from acting on the chromosomal ends with ensuing genome instability. Because telomere sequences do not fully replicate during DNA replication, they become progressively shorter with each cell division (Blackburn 2001; Blasco 2005). Some cells, such as germline cells, have greater ability to preserve telomere length through the enzymatic activity known as telomerase. Leukocyte telomere length (LTL) has been proposed to be a marker for biological aging, and shortened LTL has been related with higher all-cause mortality (Honig et al. 2012) as well as a variety of age-related conditions such as cardiovascular disease (Estruch et al. 2013; Mainous et al. 2010; Perez-Rivera et al. 2014), diabetes (Zhao et al. 2013), and dementia (Honig et al. 2012).

LTL at birth is likely mainly determined by genetic factors (Andrew et al. 2006; Lee et al. 2014; Matsubara et al. 2006; Slagboom et al. 1994). Although LTL is strongly influenced by genetic factors, telomere attrition might be modulated by environmental and lifestyle factors, including older age, cigarette smoking, gender, ethnicity (Diez Roux et al. 2009), education (Adler et al. 2013) and other indicators of socioeconomic status (Carroll et al. 2013), and diet

(Kiecolt-Glaser et al. 2013). Inflammation (O'Donovan et al. 2011) and oxidative stress (de Vos-Houben et al. 2012; von Zglinicki 2002) may contribute to LTL shortening and may represent pathways for the LTL changes associated with various environmental or lifestyle factors (Kiecolt-Glaser et al. 2013; Wolkowitz et al. 2011).

Dietary factors, as many other lifestyle factors, could potentially prevent or slow down the biological aging process, and this might be manifested in decreased telomere attrition. The Mediterranean-type diet (MeDi) is a healthy dietary pattern (Scarmeas et al. 2006b) that has been associated with lower risk of a wide variety of diseases including cardiovascular diseases (Estruch et al. 2013; Gardener et al. 2011), dementia (Scarmeas et al. 2006b), Parkinson's disease (Alcalay et al. 2012), cancer (Grosso et al. 2013), and others. The MeDi is characterized by high intake of vegetables, legumes, fruits, cereals, fish, monounsaturated fatty acids, low intake of saturated fatty acids, dairy products, meat and poultry, and mild to moderate ethanol use (Scarmeas et al. 2006b). The beneficial effects of MeDi might be related with its antioxidative and antiinflammatory effects. It has been shown that greater adherence to the MeDi, or higher intake of its key components such as olive oil, fruits, and vegetables, is associated with elevated total antioxidant capacity levels (Pitsavos et al. 2005) or increase plasma level of antioxidant carotenoids (Blum et al. 2006). Several observational and interventional studies have found that higher adherence to the MeDi was associated with lower levels of inflammatory biomarkers such as C-reactive protein (CRP) or interleukin (IL)-6 (Casas et al. 2014; Chrysohoou et al. 2004; Fung et al. 2005).

Direct evidence regarding whether MeDi could influence LTL is scarce. One in vitro study showed that MeDi reduced telomere attrition in cultured cells (Marin et al. 2012). To date, only two studies have investigated the relationship between MeDi and LTL in human populations. In one study of elderly (mean age of 77 years) subjects, high adherence to a MeDi was associated with longer LTL and higher telomerase activity (Boccardi et al. 2013). In another study of a US cohort of middle-aged women, higher Alternate Mediterranean Diet scores were associated with higher age-adjusted mean LTL. However, none of the food components of MeDi was associated with LTL in this study (Marta Crous-Bou 2014). These two studies have included participants of European ancestry only (Marta Crous-Bou 2014) (Boccardi et al. 2013); one study was

relatively small with 217 subjects only (Boccardi et al. 2013), and one study included women only (Marta Crous-Bou 2014). Thus, the results may not be generalized to other populations.

In the current study, we investigated the cross-sectional association of LTL with MeDi in a multi-ethnic elderly population. We further examined whether any of the food components of MeDi were associated with LTL.

Materials and methods

Study participants

The Washington Heights-Inwood Community Aging Project (WHICAP) study population has been described previously (Stern et al. 1992). Participants were identified (via ethnicity and age stratification processes) from a probability sample of Medicare beneficiaries aged 65 or older, residing in northern Manhattan. Briefly, at entry, a physician elicited each participant's medical and neurological history, and conducted a standardized physical and neurological examination. Each participant also underwent a structured in-person interview including an assessment of health and function and a neuropsychological battery (Stern et al. 1992). Participants were followed at intervals of approximately 1.5 years, repeating the initial examination and consensus diagnosis. The diagnosis of any type of dementia or its absence was based on standard research criteria, using all available information at a consensus conference of physicians, neurologists, neuropsychologists, and psychiatrists. The diagnosis was made blind to diet or LTL information.

The initial sample for this study included 4308 participants of the ongoing WHICAP cohort. Among these participants, blood samples were obtained from 3106 (72 %), of whom 1976 (64 %) had adequate DNA for LTL measurement. The time of the blood collection was set as the baseline for this study. An additional 211 subjects were excluded because they did not have dietary information, and 22 subjects were excluded due to incomplete dietary information preventing a MeDi calculation. Thus, the analytic sample for the current study was composed of 1743 subjects.

Recruitment, informed consent, and study procedures were reviewed and approved by the Institutional Review Boards of Columbia Presbyterian Medical Center and Columbia University Health Sciences and the New York State Psychiatric Institute. All individuals provided written informed consent.

Telomere measurement

Telomere measurements were performed as previously described (Honig et al. 2012). Coded DNA samples were processed by laboratory personnel, masked to participant characteristics including dietary information. Test DNA samples each underwent two triplicate PCR reactions, with use of calibrator samples for correction of interplate variability. Our assay coefficient of variance ranged from 5 to 8 %. The ratio of telomere sequence to single-copy gene sequence was converted to LTL measured in base pairs (bp) by using the following linear regression formula: $bp = (1585 \times T/S \ ratio) + 3582$ (where T indicates telomere amplification and S, single-copy gene amplification), derived from coanalysis of selected DNA samples using PCR and terminal restriction fragment methods (nonradioactive TeloTAGGG LTL assay, Roche Diagnostics) (correlation coefficient, $r = 0.90$).

Diet and MeDi score

Dietary data regarding average food consumption over the past year were obtained using a 61-item version of Willett's semiquantitative food frequency questionnaire (SFFQ) (Channing Laboratory, Cambridge, MA). (Willett et al. 1985) We selected the dietary assessment on the baseline visit (i.e., the time when blood sample used for LTL measurement was collected) or the closest dietary assessment if no diet was available on the baseline visit. The validity (using two 7-day food records) and reliability (using two 3-month frequency assessments) of various components of the SFFQ in WHIC AP have been previously reported. (Luchsinger et al. 2002, 2003, 2004b) We followed the most commonly described method (Trichopoulou et al. 2003) to calculate the MeDi score as described in our previous reports (Scarmeas et al. 2006a, b, 2009). Individuals were assigned a value of 1 for each beneficial component (fruits and nuts, vegetables, legumes, cereals, and fish) whose caloric-adjusted consumption was at or above the sex-specific population median, for each detrimental component (meat and dairy products) whose caloric-adjusted consumption was below the sex-specific median, for a ratio of monounsaturated fats to saturated fats

above the median, and for mild to moderate alcohol consumption (>0 to <30 g/day). The MeDi score was generated for each participant by adding the scores in the food categories with higher score indicating better adherence to the MeDi.

Covariates

Age (years) and caloric intake (kcal) were used as continuous variables. Education was used as dichotomous variable with ≤12 years of education as reference. Participants were assigned to one of four groups: African American (black non-Hispanic), Hispanic, white (non-Hispanic), or other based on self-report. Ethnicity was used as a dummy variable with non-Hispanic white and other as the reference. We also considered gender (men as reference), smoking status at baseline evaluation (current or past smoker vs. non-smoker). Leisure activity (LA) and physical activity (PA) scores were calculated as described in previous reports (Scarmeas et al. 2001, 2011), and a combined score was used to indicate low (as reference; both low LA and low PA), higher (both high LA and high PA), and middle (other combinations of LA and PA) activities. Heart disease, diabetes mellitus, hypertension, and stroke were defined by self-report and by the use of disease-specific medications (Luchsinger et al. 2004a). A vascular health score (VHS) was constructed by summing the four dichotomous variables, resulting in an integer score in the range 0–4 (Luchsinger et al. 2005). Body mass index (BMI, calculated as weight in kilograms divided by height in meters squared (kg/m^2)) was used as a continuous variable. As previously reported (Manly et al. 2005; Siedlecki et al. 2008) cognition was measured by a mean (average of memory, language, processing speed, and visual-spatial ability domain scores) cognition z-score based on selected neuropsychological tests scores determined using a neuropsychological battery (Stern et al. 1992), with a higher z-score indicates better cognitive performance. We use Activities of Daily Living (ADL) score as a measure of functional status as previously reported (Scarmeas et al. 2011). Self-reported medication use including anti-hyperlipidemics (such as statins) or anti-inflammatory medicines (steroids and nonsteroidal anti-inflammatory drugs) was used as dichotomous variables (yes vs. no).

Statistical analyses

Characteristics of participants by LTL tertiles were compared using ANOVA for continuous variables and χ^2 test for categorical variables. Generalized linear regression models with telomere length as the outcome were used to assess the association between MeDi and LTL. Two models were used, including adjusted for age only (model 1) and adjusted for age, gender, ethnicity, education, caloric intake, smoking status, and leisure/physical activities (model 2). In a fully adjusted model (model 3), we additionally included vascular, cognitive, and functional status in the model. MeDi score was treated as a continuous variable or as a quartile variable in the models. Potential effect modifications by ethnicity and gender were examined by including the interaction terms (potential effect modifier×MeDi) in model 2, followed by stratified analyses based on the effect modifier. Linear regression models were also used to assess the association between the nine food components of MeDi and LTL, with LTL as the outcome and the nine components as independent variables in the model simultaneously.

We excluded subjects who were demented at the time of dietary assessment to limit potential misclassification due to recall bias. We also added a sensitivity analysis by constructing an alternative MeDi which had nuts as a separate food category and replaced cereals with whole grain cereals.

All analyses were conducted using PASW Statistics version 21 (IBM, Chicago, IL, USA). All p values were based on two-sided tests with the significance level set at 0.05.

Results

Clinical and demographic characteristics in relation to LTL

The LTL in the study population ranged from 4103 to 11,447 bp, with an average length of 6409 bp (SD= 873). As previously shown [1], shorter LTL was related to older age at the time of blood draw. Longer LTL was associated with better cognition and functional status. Women represented approximately two thirds of the study population and were older than men (78.8 vs. 76.6 years old on average, ANOVA $p<0.0001$).

Although women seemed to have similar LTL as men (6427 vs. 6370 bp, ANOVA $p=0.21$), linear regression analysis adjusted for age showed that on average, women had 127 bp longer LTL than men (β for being female=127, $p=0.004$). The study population had on average 9.87 years of education, and those in the top tertile of LTL length had more years of education than those in the lowest or middle tertiles. Almost half of the study population were current or past smokers, and they had similar LTL than those who never smoked (6390 vs. 6440 bp, ANOVA $p=0.24$). LTL in Hispanics (6326 bp) was shorter than that of whites (6465 bp, ANOVA $p=0.007$) or African Americans (6451 bp, ANOVA $p=0.01$). There was no difference between whites and African Americans in LTL (ANOVA $p=0.81$) (eTable 1). Subjects with low LA/PA had significantly shorter LTL than those high LA/PA ($p=0.008$). Univariate analysis of individual food groups also showed that LTL was positively associated with vegetable intake but negatively associated with cereal intake (Table 1). Subjects with different LTL had similar vascular status including VHS and BMI (Table 1). LTL was not associated with anti-hyperlipidemics or anti-inflammatory medicine use (Table 1).

MeDi and LTL among all subjects

Examining the entire sample, using MeDi as a continuous variable in the regression models, we found no association between MeDi and LTL. When MeDi was entered into the models as quartiles, we found subjects with the third MeDi score quartile, but not the second or fourth quartile, had longer LTL compared to those with lowest MeDi score quartile in both model 1 and model 2 (Table 2). Additional adjustment of vascular factors attenuated the association in general; however, the 3rd quartile of MeDi, compared to the lowest quartile, was still associated (Table 2, model 2), or marginally associated (Table 2, model 3), with longer LTL.

MeDi and LTL in ethnicity- and gender-stratified analyses

There were significant differences among the three ethnic groups in terms of education, percentage of female participants, percentage of ever smoked, percentage of leisure and physical activity levels, cognitive status, functional status, VHS, and BMI. However, there was no difference between whites and African Americans on

their MeDi score and LTL, although both whites and African Americans had different LTL and MeDi compared to Hispanics (eTable 1). Whites are more likely to use anti-hyperlipidemics than African Americans. No age difference was found among the three groups.

We found a significant interaction between ethnicity and MeDi (Hispanics × MeDi $p=0.02$; African Americans × MeDi $p=0.08$) in the adjusted model, suggesting that the association between MeDi and LTL varied by ethnicity. Stratifying by ethnicity and using MeDi as a continuous variable in the regression models, we found a significant association between MeDi and LTL among whites, with one unit increase in MeDi score corresponding to a 48-bp increase in LTL after adjusted for multiple covariates (Table 2). When MeDi was entered into the models as quartiles, we found that the second, third, and fourth quartiles of MeDi were all associated with longer LTL in whites (p trend=0.02) compared to the lowest quartile, although the results were somehow attenuated in models 2 and 3 (Table 2). MeDi adherence was not associated with LTL among African Americans or Hispanics.

The stratified analyses showed that higher fish intake was also associated with shorter LTL in males, and higher cereal intake was associated with shorter LTL in females (eTable 2). However, in general, there was no interaction between gender and MeDi (p for interaction term gender × MeDi=0.80).

Food components of MeDi and LTL

We explored whether there was any food component of MeDi that might be associated with LTL (Table 3). Intake of vegetable and cereal above the sex-specific population medians were associated with 89 bp ($p=0.04$) longer and 94 bp ($p=0.03$) shorter LTL, respectively, in the whole population. Among whites only, we found similar trend of associations of vegetables and cereal with LTL, although not fulfilling the statistical significance criterion ($p=0.07$ and $p=0.08$, respectively). Additionally, among whites, we found that intake of dairy or meat below sex-specific population medians were associated with 155 bp ($p=0.05$) and 241 bp ($p=0.004$) longer LTL, respectively (Table 3, model 2). Other food components were not associated with LTL among whites. None of the food components was associated with LTL among African Americans or

Table 1 Demographic and clinical characteristics of the study participants by tertiles of telomere length

	All	Shortest LTL tertile	Middle LTL tertile	Longest LTL tertile	p value[b]
Number of subjects	1743	576	583	584	
TL (bp), mean (SD)	6406 (873)	5548 (363)	6312 (196)	7355 (686)	<0.001
range	4103–11447	4103–5983	5983–6665	6667–11447	
Age (years), mean (SD)	78.1 (6.75)	80.0 (6.86)	78.0 (6.47)	76.2 (6.38)	<0.001
Education (years), mean (SD)	9.87 (4.86)	9.62 (4.87)	9.59 (4.90)	10.38 (4.79)	0.007
Race/ethnicity, N (%)					
White	506 (29.0)	170 (29.5)	157 (26.9)	179 (30.7)	0.08
African Americans	536 (30.8)	163 (28.0)	180 (30.9)	193 (33.0)	
Hispanics	679 (39.0)	240 (41.7)	237 (40.7)	202 (34.6)	
Other	22 (1.3)	3 (0.5)	9 (1.5)	10 (1.7)	
Female, N (%)	1191 (68.3)	387 (67.2)	398 (68.3)	406 (69.5)	0.69
LA/PA					
Low, N (%)	638 (36.7)	231 (40.2)	210 (36.1)	197 (33.8)	0.048
Middle, N (%)	816 (47.0)	257 (44.8)	286 (49.2)	273 (46.8)	
High, N (%)	284 (16.3)	86 (15.0)	85 (14.6)	113 (19.4)	
Anti-hyperlipidemics, N (%)	391 (27.1)	127 (28.0)	122 (24.7)	142 (28.6)	0.34
Anti-inflammatory medicines, N (%)	771 (52.8)	252 (55.0)	269 (53.9)	250 (49.7)	0.21
Functional ADL score, mean (SD)	1.47 (2.3)	1.85 (2.6)	1.46 (2.3)	1.12 (1.9)	<0.0001
Mean cognition, mean (SD)	0.13 (0.68)	0.06 (0.7)	0.10 (0.66)	0.23 (0.65)	<0.0001
VHS, mean (SD)	1.70 (1.02)	1.67 (1.08)	1.67 (1.03)	1.75 (0.96)	0.29
Ever smoked, N (%)	845 (49.8)	289 (51.6)	279 (49.5)	277 (48.4)	0.55
BMI (kg/m^2), mean (SD)	27.9 (5.8)	27.9 (5.7)	27.9 (6.2)	27.8 (5.4)	0.99
Dietary intake above sex-specific median					
Fruits and nuts, N (%)	870 (49.9)	289 (50.2)	289 (49.6)	292 (50.0)	0.98
Vegetables, N (%)	860 (49.3)	271 (47.0)	266 (45.6)	323 (55.3)	0.002
Fish, N (%)	871 (50.0)	268 (52.8)	308 (52.8)	295 (50.5)	0.10
Legume, N (%)	867 (49.7)	295 (51.2)	287 (49.2)	285 (48.8)	0.68
Cereal, N (%)	874 (50.1)	322 (55.9)	282 (48.4)	270 (46.2)	0.003
MUFA/SFA, N (%)	876 (50.3)	271 (47.0)	303 (52.0)	302 (51.7)	0.17
Nuts[a], N (%)	865 (50.0)	470 (47.1)	288 (49.8)	307 (53.1)	0.13
Whole grain cereals[a], N (%)	867 (50.1)	275 (47.9)	290 (50)	302 (52.2)	0.34
Dietary intake below sex-specific median					
Dairy, N (%)	873 (50.1)	273 (47.4)	299 (51.3)	301 (51.5)	0.29
Meat, N (%)	877 (50.3)	301 (52.3)	271 (46.5)	305 (52.2)	0.08
Moderate alcohol intake, N (%)	421 (24.2)	121 (21.0)	150 (25.7)	150 (25.7)	0.10
MeDi, mean (SD)	4.24 (1.67)	4.19 (1.75)	4.21 (1.65)	4.32 (1.61)	0.35

bp base pairs, *MeDi* Mediterranean-type diet, *LA/PA* leisure/physical activity, *LTL* leukocyte telomere length, *VHS* vascular health score

[a] Nuts and wholegrain cereals were not separate food components of MeDi by themselves, but included in the food components fruits and cereals, respectively

[b] *p* values from ANOVA for continuous variables and chi-squared for categorical variables

Hispanics. Additional adjustment of vascular, cognitive, and functional status did not change the results (Table 3, model 3).

In general, there seemed to be no association between nuts or whole grain cereal intake and LTL in the study population (Table 3).

Table 2 Association between Mediterranean diet and telomere length

	MeDi	Model 1		Model 2		Model 3	
		β	p	β	p	β	p
All	Continuous	15.47	*0.21*	12.49	*0.32*	10.67	*0.41*
	First quartile	Reference group					
	Second quartile	60.52	*0.31*	59.6	*0.33*	49.97	*0.46*
	Third quartile	**139.31**	***0.02***	**150.23**	***0.01***	**127.93**	***0.04***
	Fourth quartile	67.56	*0.26*	54.08	*0.38*	46.57	*0.47*
	p Trend	27.28	*0.15*	24.04	*0.21*	20.73	*0.30*
Whites	Continuous	**57.78**	***0.02***	**48.32**	***0.05***	42.64	*0.10*
	First quartile	Reference group					
	Second quartile	**244.74**	***0.04***	197.4	*0.10*	211.26	*0.09*
	Third quartile	**371.85**	***0.01***	**324.39**	***0.02***	**284.84**	***0.05***
	Fourth quartile	**316.69**	***0.02***	257.93	*0.06*	254.84	*0.07*
	p Trend	**91.7**	***0.02***	76.03	*0.06*	67.37	*0.11*
African Americans	Continuous	3.52	*0.87*	−2.04	*0.92*	2.21	*0.92*
	First quartile	Reference group					
	Second quartile	160.96	*0.17*	167.3	*0.16*	199.68	*0.10*
	Third quartile	145.04	*0.15*	135.23	*0.19*	147.14	*0.17*
	Fourth quartile	68.28	*0.55*	51.7	*0.65*	72.64	*0.55*
	p Trend	19.07	*0.59*	11.73	*0.75*	16.85	*0.66*
Hispanics	Continuous	−11.25	*0.56*	−6.16	*0.75*	−12.31	*0.55*
	First quartile	Reference group					
	Second quartile	−93.94	*0.30*	−53.5	*0.56*	−89.54	*0.35*
	Third quartile	34.8	*0.69*	79.47	*0.37*	31.66	*0.73*
	Fourth quartile	−60.94	*0.46*	−38.38	*0.65*	−63.27	*0.47*
	p Trend	−8.64	*0.74*	−1.13	*0.97*	−10.30	*0.71*

Model 1: Adjusted for age (at time of blood sample collection for telomere), sex, education, ethnicity, caloric intake; no ethnicity in the ethnic-stratified analysis; a total of 1743 subjects included in the analysis. Model 2: Adjusted for age (at time of blood sample collection for telomere), sex, education, ethnicity, caloric intake, smoking status, and leisure/physical activities; no ethnicity in the ethnic-stratified analysis; a total of 1711 subjects included in the analysis due to missing values. Model 3: Adjusted for age (at time of blood sample collection for telomere), sex, education, ethnicity, caloric intake, smoking status, leisure/physical activities, VHS, cognitive z-score, and functional ADL score; no ethnicity in the ethnic-stratified analysis; a total of 1552 subjects included in the analysis due to missing values

The italic font was used for all *p*-values. The bold font was used for those beta coefficients along with their *p*-values for any $p \leq 0.05$. The bold-italic font was for *p*-values that were ≤ 0.05

Supplementary analyses

When 228 demented subjects were excluded from the analysis, we found similar results: MeDi was not associated with LTL ($\beta=28.0$, $p=0.25$) in the whole population but was significantly associated with LTL in whites ($\beta=60.1$, $p=0.02$) in the adjusted model. In the adjusted model, higher-than-median intake of cereals was negatively associated with LTL ($\beta=-115.3$, $p=0.01$) in overall population and in whites ($\beta=-163.3$, $p=0.05$); lower-than-median intake of dairy and meat

was also each associated with longer LTL among whites ($\beta=176.4$, $p=0.03$ and 252.5, $p=0.003$, respectively).

When we used alternative MeDi score by adding nuts as a separate food component and by replacing cereals with whole grain cereals, we found similar results. We found that one-unit increase in alternative MeDi score was associated with 19.9 bp longer LTL ($\beta=19.9$, $p=0.09$). Among whites, one-unit increase in alternative MeDi score was associated with 57.7 bp longer LTL ($\beta=57.7$, $p=0.01$), and the second, third, and fourth quartiles of MeDi

Table 3 Association between the nine food components of Mediterranean diet and telomere length

		Model 1		Model 2		Model 3	
		β	p	β	p	β	p
All subjects	Fruit and nuts[a]	−26.19	0.54	−37.45	0.38	−41.33	0.35
	Vegetables[a]	**80.84**	**0.06**	**89.13**	**0.04**	70.77	0.12
	Fish[a]	−0.03	1.00	3.13	0.94	12.33	0.78
	Legume[a]	0.94	0.98	−11.45	0.80	−6.26	0.89
	Cereal[a]	**−92.50**	**0.03**	**−93.51**	**0.03**	**−96.92**	**0.03**
	MUFA/SFA[a]	56.44	0.17	52.93	0.20	38.32	0.37
	Dairy[a]	54.42	0.19	56.34	0.18	59.16	0.18
	Meat[a]	36.03	0.40	27.72	0.52	47.83	0.29
	Alcohol[a]	5.73	0.91	3.90	0.94	−20.37	0.70
	Nuts	52.06	0.24	55.11	0.22	31.17	0.51
	Whole grain cereals	34.00	0.41	26.52	0.53	−8.20	0.85
Whites	Fruit and nuts[a]	−4.83	0.95	−23.73	0.78	−31.89	0.71
	Vegetables[a]	153.28	0.07	152.52	0.07	122.07	0.16
	Fish[a]	−16.36	0.84	−37.94	0.65	−39.83	0.63
	Legume[a]	−90.23	0.30	−97.12	0.27	−87.67	0.33
	Cereal[a]	−142.08	0.08	−143.62	0.08	−141.12	0.09
	MUFA/SFA[a]	68.33	0.39	66.49	0.41	42.13	0.61
	Dairy[a]	**160.67**	**0.04**	**154.68**	**0.05**	**175.73**	**0.03**
	Meat[a]	**252.33**	**0.002**	**240.54**	**0.004**	**261.08**	**0.002**
	Alcohol[a]	107.24	0.21	107.36	0.22	66.63	0.45
	Nuts	59.58	0.49	30.03	0.65	9.98	0.91
	Whole grain cereals	70.62	0.40	68.13	0.48	74.08	0.39
African Americans	Fruit and nuts[a]	−78.16	0.31	−95.38	0.22	−101.36	0.21
	Vegetables[a]	59.22	0.44	53.99	0.49	51.60	0.53
	Fish[a]	−3.93	0.96	−10.18	0.89	23.99	0.76
	Legume[a]	19.94	0.79	22.44	0.77	37.39	0.65
	Cereal[a]	−79.95	0.30	−83.12	0.29	−64.08	0.44
	MUFA/SFA[a]	60.61	0.40	53.89	0.46	55.96	0.47
	Dairy[a]	64.19	0.39	69.37	0.36	46.59	0.56
	Meat[a]	8.15	0.92	−2.22	0.98	−13.37	0.88
	Alcohol[a]	3.11	0.97	16.81	0.85	−0.97	0.99
	Nuts	153.65	0.05	147.40	0.07	124.86	0.14
	Whole grain cereals	30.37	0.68	32.54	0.66	20.50	0.79
Hispanics	Fruit and nuts[a]	−26.30	0.68	−27.15	0.67	−15.32	0.82
	Vegetables[a]	45.95	0.47	77.24	0.24	46.11	0.50
	Fish[a]	28.14	0.66	65.87	0.31	62.20	0.36
	Legume[a]	36.56	0.59	19.99	0.77	13.02	0.86
	Cereal[a]	−61.13	0.35	−54.53	0.42	−73.06	0.29
	MUFA/SFA[a]	58.30	0.35	45.30	0.47	12.32	0.85
	Dairy[a]	−37.78	0.55	−34.18	0.59	−30.36	0.65
	Meat[a]	−92.34	0.15	−97.28	0.13	−67.62	0.32
	Alcohol[a]	−140.78	0.12	−143.47	0.12	−168.97	0.08

Table 3 (continued)

	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
Nuts	−71.65	0.30	−77.09	0.28	−65.21	0.37
Whole grain cereals	−85.83	0.19	−81.03	0.23	−73.76	0.29

Model 1: Adjusted for age (at time of blood sample collection for telomere), sex, education, ethnicity, and caloric intake. Model2: Adjusted for age (at time of blood sample collection for telomere), sex, education, ethnicity, caloric intake, smoking status, and leisure/physical activities. Model 3: Adjusted for age (at time of blood sample collection for telomere), sex, education, ethnicity, caloric intake, smoking status, leisure/physical activities, VHS, cognitive status, and functional status. All food components of MeDi were included in the model simultaneously; no ethnicity in the ethnic-stratified analysis. Comparisons for the estimated β (p) were above median vs. below median for fruits and nuts, vegetables, fish, legume, cereal, MUFA/SFA, nuts, and whole grain cereals, were below median vs. above median for dairy and meat intakes, and were moderate vs. others for alcohol intake

[a] Food components of MeDi were entered into models simultaneously

The bold entries are those with p-value <=0.05

were all associated with 187 bp ($p=0.13$), 263 bp ($p=0.01$), 221 bp ($p=0.08$), respectively, longer LTL (p trend=0.03) compared to the lowest quartile, in adjusted models (model 2).

Discussion

In this cross-sectional analysis of elderly subjects, we found that higher MeDi adherence was not associated with LTL in the overall study population. Among all the nine food components of MeDi, higher intake of vegetables was associated with longer LTL and higher intake of cereal was associated with shorter LTL. Among whites, we found that greater adherence to the MeDi was significantly associated with longer LTL, and lower intake of meat or dairy was each associated with longer LTL. There was no significant association between MeDi or any component of MeDi and LTL among African Americans or Hispanics.

Our finding in whites is consistent with the two reports studying the cross-sectional relationship between MeDi and LTL, both of which included white individuals only and found that high adherence to a MeDi was related to longer LTL (Boccardi et al. 2013; Crous-Bou et al. 2014). Furthermore, these findings of a beneficial role of MeDi on LTL echo with the findings from a recent intervention study promoting MeDi, which found a higher adherence to the MeDi strengthened the prevention of telomere shortening among carriers of the Ala allele of the peroxisome proliferator-activated receptor-γ2 (PPARγ2) gene (Garcia-Calzon

et al. 2014). In line with our observation of an association between vegetable consumption and LTL length, a study of 1942 participants aged 57–70 years from the Helsinki Birth Cohort Study (HBCS) also found that women consuming more vegetables had longer LTL (Tiainen et al. 2012). In a case-control study of more than 1600 participants from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (Mirabello et al. 2009), vegetable intake was not associated with LTL, but a healthy lifestyle characterized by higher fruit and vegetable intake, low or no cigarette use, lower BMI, and more physical activity was positively correlated with longer LTL. Finally, data from 840 subjects of the Multi-Ethnic Study of Atherosclerosis (MESA) study suggested that intake of processed meat was associated with shorter LTL (Nettleton et al. 2008). Our finding of negative association between meat intake and LTL thus echoed the above study.

Despite some similarities between our study and some previous ones, the current evidence regarding dietary intake and LTL is still scarce and there are also inconsistencies. While our study and a couple of other studies suggest a positive role of vegetables on LTL, other studies did not find a significant association between vegetables and LTL (MESA (Nettleton et al. 2008); PLCO study (Mirabello et al. 2009); Nurses' Health Study (Cassidy et al. 2010), and men in HBCS (Tiainen et al. 2012)). A cross-sectional study of 2284 female participants from the Nurses' Health Study (NHS) (Cassidy et al. 2010) found that dietary fiber, especially cereal fiber, was positively associated with LTL. However, in the MESA study (Nettleton et al.

2008), none of the foods that are usually the main sources of fiber (whole grain, refined grain, fruit, and vegetables) was associated with LTL. In the present study, cereal intake tended to be associated with shorter LTL. Similar inconsistencies exist regarding the association between fat intake and LTL. A few studies pointed to a negative role of fat or butter intake in the LTL. For example, The women-only NHS (Cassidy et al. 2010) found that total fat, especially PUFA, was inversely associated with LTL. The HBCS study found that men consuming total fat, SFA, as well as butter, had significantly shorter telomeres (Tiainen et al. 2012). The MESA (Nettleton et al. 2008) study also found that a PCA-derived dietary pattern "fats and processed meat" was inversely associated with LTL. Nevertheless, such association was not found in the PLCO study (Mirabello et al. 2009). More studies are needed to better understand the relationship between diet and LTL.

We did not observe a significant association between MeDi and LTL in the overall population, possibly because (1) the MeDi dietary score may include food groups not associated with telomere length but included in dietary pattern score computation, and (2) the study population included multiple ethnic groups, and among some, there may not be an association between MeDi and LTL.

Among the food components of MeDi, higher vegetables, lower meat, and lower dairy intakes are in the expected direction of being "healthier foods" and associated with increased LTL. While cereal was traditionally considered as a beneficial component in MeDi, our study found it might be related with shorter LTL. Thus, including cereal as a beneficial component for MeDi construction might potentially cancel out the effects of vegetables, dairy, and meats in the whole population. The mechanism underlying a biological association between dietary factors (vegetables, meat, dairy, and cereal) and LTL is not evident. It is possible that inflammatory and oxidative pathways (de Vos-Houben et al. 2012; O'Donovan et al. 2011; von Zglinicki 2002) could be involved. Vegetables are the main dietary sources of flavonoids which are shown to have antioxidative activity (Yao et al. 2004). Dairy and meat products probably represent the largest sources of saturated fatty acids (Givens 2009). Furthermore, data from NHS found that a Western pattern, which was characterized by higher intakes of red and processed meats, sweets, desserts, French fries, and refined grains, was associated with markers of inflammation (Lopez-Garcia et al. 2004). Therefore, the associations between these four

food groups and LTL in our study population could be due to inflammatory and oxidative properties of these food groups.

It is unclear why the association between MeDi and some food components with LTL was found in whites only. There are several possible explanations. In the MESA population (Diez Roux et al. 2009), it was found that cross-sectional associations of age with shorter telomeres were stronger in African Americans and Hispanics than in whites, after adjustment for many environmental factors such as BMI, diet, SES, smoking, and physical activity. Therefore, the effect of diet on LTL, beyond and above the effect of chronological age, might not be substantial among African Americans and Hispanics. While in whites, in addition to the age, diet may still be able to exert significant modification on LTL. In addition, MESA and another study including subsamples of the Family Heart Study (FHS) ($n=1968$) and the Bogalusa Heart Study (BHS) ($n=573$) (Hunt et al. 2008) both found a steeper decline in LTL with age in African Americans (in MESA (Diez Roux et al. 2009) and FHS/BHS (Hunt et al. 2008)) or Hispanics (in MESA (Diez Roux et al. 2009)) than in whites. These findings again suggested a larger effect of aging (chronological age) on LTL attrition among African Americans or Hispanics than among whites, probably leaving less space for lifestyle or other environmental factors to modulate the LTL. Secondly, as discussed above, the diet may exert an effect on LTL through inflammation or oxidative pathways. It has been shown that the underlying inflammation or oxidative status might differ among different ethnic groups. A previous study found heightened oxidative stress and inflammation in African Americans both in vitro and in vivo (Feairheller et al. 2011). Population-based studies also found that compared to whites, African Americans or Hispanics had higher levels of markers of oxidative stress (Morris et al. 2012), lower concentrations of antioxidant alpha-tocopherol (Ford et al. 2006), or higher levels of inflammatory markers such as CRP and IL-6 (Kelley-Hedgepeth et al. 2008; Paalani et al. 2011). Given higher underlying levels of inflammation and oxidative stress status among African Americans or Hispanics, it is conceivable that that dietary intake may not be sufficient to modulate LTL via these pathways as in whites. Finally, it is also possible that nonbiological mechanisms have led to the observation. For example, although we have controlled for many important potential confounders, we could not rule out the

possibility that an unknown confounder, if having similar confounding effect but just unevenly distributed in whites or African Americans, might have led to the findings in one ethnic but not the other ethnic group.

Our study has limitations. The present study analyzed the cross-sectional association between dietary factors and LTL; therefore, no temporal relationship between these two can be established from our study. Our study showed a statistical association between MeDi and LTL in one ethnic group, but this may not necessarily be a biological association. It is unknown whether among the elderly, dietary factors could affect the telomere attrition rate over time. Further studies such as longitudinal studies might be helpful. Thus, examining the longitudinal relationship between dietary factors and dynamics of LTL might give additional information, as might measurements of telomerase activity. Another limitation of the study is that we did not specifically collect information on olive oil, which is a key beneficial food in the Mediterranean (Estruch et al. 2013). Finally, our dietary information was collected using a SFFQ, a *subjective measure of food consumptions*. While good validity and reliability have been found for some dietary elements in our study population, we cannot rule out the possibility of measurement errors, although these should not be systemically different by LTL. In addition, it has been argued that, using FFQ, study participants remain reasonably well ranked with respect to dietary consumption, especially after energy adjustment (Kipnis et al. 2003), such that meaningful comparisons across intake quantiles can still be made (Schatzkin et al. 2009). Future studies may also consider using more objective measures, such as biological markers of nutrients consumption, to estimate food intake.

Our study also has strengths. The relatively large sample size allows us to have statistical power to identify significant associations between dietary factors and LTL. Sensitivity analysis excluding dementia subjects yielded similar results as the main findings, suggesting that the results were unlikely to be subject to recall bias. Several important lifestyle factors were considered and controlled for in the analysis.

In summary, we found that greater adherence to a MeDi was significantly associated with longer LTL among whites. In addition, consuming high vegetable and low meat, dairy, or cereal might be beneficial in terms of LTL. More studies, with longitudinal and possibly interventional components, could enhance or confirm our findings.

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