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Serum Folate, Vitamin B-12, Vitamin A, γ-Tocopherol, α-Tocopherol, and Carotenoids Do Not Modify Associations between Cadmium Exposure and Leukocyte Telomere Length in the General US Adult Population[1–3]

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Abstract

Background: Leukocyte telomere length (LTL) is a biomarker of the aging process and is associated with the risk of chronic disease. Higher exposure to cadmium may be associated with shorter LTL, and adequate nutrient concentrations may be associated with longer LTL; however, the potential interaction between metals and nutrients on LTL has yet to be examined.

Objectives: The objective of this study was to evaluate whether serum concentrations of vitamins and carotenoids were associated with LTL, and whether they modified the association between blood cadmium and LTL in the US NHANES (1999–2002).

Methods: We evaluated cross-sectional associations between LTL and serum concentrations of vitamin A, γ-tocopherol, α-tocopherol, folate, and vitamin B-12 (1999–2002; $n = 7458$) and α-carotene, β-carotene, β-cryptoxanthin, lutein + zeaxanthin, and lycopene (2001–2002; $n = 4018$) in a nationally representative sample of US adults (≥20 y of age) with the use of multivariable linear regression. We further investigated whether vitamin and carotenoid concentrations modified associations between blood cadmium and LTL with models stratified by serum nutrient concentrations and the inclusion of an interaction term.

Results: Blood cadmium was inversely associated with LTL (percentage of LTL difference per 1 μg/L = −3.74; 95% CI: −5.35, −2.10). Serum vitamin A was positively associated (percentage of LTL difference per 1 μg/L = 4.01; 95% CI: 0.26, 7.90) and γ-tocopherol was inversely associated (percentage of LTL difference per 1 μg/dL = −2.49; 95% CI: −4.21, −0.73) with LTL. Serum folate (P-trend = 0.06) and α-tocopherol (P-trend = 0.10) were marginally positively associated with LTL, whereas vitamin B-12 (P-trend = 0.78) was not associated with LTL. Serum carotenoids were generally positively associated with LTL. Serum vitamin and carotenoid concentrations did not modify blood cadmium and LTL associations (P-interaction > 0.10).

Conclusions: Results from this cross-sectional study suggest that exposure to cadmium and certain nutrients may be associated with LTL in US adults, but the serum concentrations of the vitamins and carotenoids evaluated did not modify cross-sectional associations between cadmium exposure and LTL. *J Nutr* 2017;147:538–48.

Keywords: carotenoids, folate, vitamin B-12, vitamin A, α-tocopherol, β-tocopherol, telomere, vitamins, cadmium

Introduction

Biomarkers for monitoring the aging process and predicting health outcomes are a rapidly developing area of research. Among these biomarkers are telomeres, repetitive DNA (5′-TTAGGG$_n$-3′) sequences at the ends of chromosomes that serve to protect the ends of DNA strands and conserve the structural integrity of chromosomes (1). A high guanine content makes telomeres particularly sensitive to oxidative stress, which can lead to DNA strand breaks, thereby resulting in the shortening of telomeres (2, 3). Telomeric length decreases as humans age (4), and lifestyle exposures may contribute to telomere length regulation, potentially through mechanisms of oxidative stress and inflammation (5–7). There is suggestive evidence that higher physical activity levels (8–10), maintaining a normal body weight (11, 12) and consuming a healthy diet (13–17) may be associated with longer telomere lengths, whereas exposure to certain heavy metals (18),

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smoking (11, 19), and psychological stressors (8, 20) may lead to shorter telomere lengths. Telomere lengths are associated with chronic disease risk (6, 21–30) and may be associated with mortality (30–32).

In the general population, exposure to cadmium, a known human carcinogen, occurs mainly via the intake of contaminated foods and tobacco smoke exposure (33). Experimental and observational studies suggest an association between cadmium exposure and telomere shortening (18, 34–37). For example, higher blood cadmium (top quartile) concentrations were associated with 5.5% shorter leukocyte telomere length (LTL)[7] than were the lowest quartile concentrations in the NHANES, 1999–2002 (18). Cadmium is associated with several mechanisms that may result in LTL shortening, including oxidative stress, inflammation, and the inhibition of DNA repair (38–42). Research is limited, but current evidence suggests that the intake of antioxidant and DNA-repair vitamins and carotenoids (14, 43–54) may influence telomere regulation. For example, higher carotenoid concentrations and sufficient γ-tocopherol and α-tocopherol intake may contribute to the conservation of telomere length by reducing oxidative stress (55, 56), whereas folate or vitamin B-12 status could contribute to telomere conservation or shortening through DNA stability and repair capacity (57). Diet and nutritional status may modify the effects of cadmium exposure because of their antioxidant and anti-inflammatory properties or their role in oxidative- and inflammation-associated damage repair mechanisms (58–60). For example, a cross-sectional analysis in the NHANES found that diets high in antioxidant and anti-inflammatory nutrients modified associations between cadmium exposure and biomarkers of oxidative stress and inflammation, such as C-reactive protein and alkaline phosphatase (38).

To our knowledge, no previous studies have investigated whether circulating vitamin or carotenoid concentrations may modify the relation between cadmium exposure and telomere length. Given that cadmium exposure may shorten telomere length via oxidative stress, inflammation, and inhibition of DNA repair, and that nutrient intake may, conversely, conserve telomere lengths via similar pathways, we hypothesized that circulating concentrations of vitamins and carotenoids may modify associations between blood cadmium and LTL. The objective of this study was to evaluate whether measured serum concentrations of vitamins (folate, vitamin B-12, γ-tocopherol, α-tocopherol, and vitamin A) and carotenoids were associated with LTL, and whether the association between blood cadmium and LTL differed between those with higher or lower serum vitamin and carotenoid concentrations in the NHANES study population (1999–2002).

Methods

Study population. Data from the 1999–2000 and 2001–2002 cycles of the NHANES were used for this analysis. The NHANES is a cross-sectional study conducted by the National Center for Health Statistics in the CDC to assess the health and dietary status of a nationally representative sample of the noninstitutionalized US population. Participants are selected with the use of a multistage cluster design, and certain demographic groups, including older adults, Hispanic and non-Hispanic black individuals, and low income persons, are oversampled. The CDC Institutional Review Board approved the LTL measurements, and written informed consent was obtained from all participants.

[7] Abbreviations used: LOD, limit of detection; LTL, leukocyte telomere length; PIR, poverty-to-income ratio.

Between 1999 and 2002, DNA samples were collected from participants aged ≥20 y (n = 10,291 eligible subjects). Participants who provided DNA samples and consented to sample storage for future research, and whose samples contained sufficient DNA to measure LTL, were eligible for this analysis (n = 7826). Non-Hispanic black participants, women, and older participants (>60 y of age) were less likely to provide consent to store samples for future genetic research (61). Among participants with LTL data, participants missing data on blood cadmium (n = 5) or serum cotinine concentrations (n = 112), education level (n = 13), and BMI (in kg/m^2) (n = 249) were excluded in addition. In the analyses that evaluated nutrients measured in all 4 y, the analytic sample consisted of 7458 participants. In the 2001–2002 cycle, only 4018 participants had samples available for measuring vitamin and carotenoid concentrations. Participants with missing data for a given circulating vitamin concentration were excluded only from the analyses in which they had missing nutrient data. Missing data for serum vitamin concentrations among those who met inclusion criteria were as follows: folate (n = 9), vitamin B-12 (n = 7), γ-tocopherol (n = 496), α-tocopherol (n = 47), vitamin A (n = 1733), β-carotene (2001–2002 only) (n = 6), α-carotene (2001–2002 only) (n = 6), β-cryptoxanthin (2001–2002 only) (n = 25), lutein + zeaxanthin (2001–2002 only) (n = 9), lycopene (2001–2002 only) (n = 9), and combined carotenoids (2001–2002 only) (n = 55). Participants who were excluded in addition for missing data were more likely to be nonwhite, overweight or obese, have a lower poverty-to-income ratio (PIR), and have higher serum cotinine concentrations ($P > 0.05$). Age, sex, and education level were not statistically significantly different between included and excluded participants.

Data collection. NHANES data were collected at an in-home interview and during a physical examination at a mobile examination center. Demographic and lifestyle data for potential confounders, including age, educational attainment, race/ethnicity, and smoking history, were collected via interviewer-administered questionnaires. The PIR was calculated as the ratio of reported household income to poverty threshold and categorized as <1, 1–3, and >3 (where <1 is below poverty threshold). Anthropometric measurements and blood specimens were also collected at the mobile examination center visit. Blood specimens were processed, stored, and shipped to the Division of Laboratory Sciences at the CDC (Atlanta, Georgia) for analysis.

LTL measurements. LTL quantification methods have been previously reported in detail (62, 63). Briefly, purified DNA was shipped to the University of California, San Francisco, for LTL quantification. Purgene kits (D-50K; Gentra Systems) were used to isolate DNA from whole blood, which was then stored at −80°C. qPCR was used to measure LTL relative to a standard reference DNA (telomere-to–single-copy gene ratio). Laboratory personnel were blinded to all other study measurements. The CDC conducted a quality-control review before the public availability of the LTL data. Mean telomere length did not differ by study cycle (data not shown).

Vitamin and cadmium measurements. Detailed documentation of biomarker measurements and protocols is available online (64, 65). All vitamins and carotenoids measured in the years for which LTL measurements were available (1999–2000) were evaluated in this analysis. In the 1999–2000 and 2001–2002 cycles, serum concentrations of vitamin B-12, folate, vitamin A, α-tocopherol, and γ-tocopherol were measured. Serum folate and vitamin B-12 were measured with the use of a Quantaphase II folate and vitamin B-12 radioassay kit (Bio-Rad Laboratories). The limits of detection (LODs) for this method are 0.2 ng/mL for folate and 20 pg/mL for vitamin B-12. CV ranges were 3.1–7.2% for folate and 2.4–4.1% for vitamin B-12. Serum concentrations of vitamin A (retinol, 2 retinyl esters), α-tocopherol, and γ-tocopherol were measured with the use of HPLC with photodiode array detection. In the 2001–2002 cycle, serum β-carotene (sum of *cis* and *trans* β-carotene), α-carotene, β-cryptoxanthin, lutein + zeaxanthin, and lycopene were measured in addition with the use of HPLC. Combined carotenoid concentrations were estimated by summing β-carotene, α-carotene, β-cryptoxanthin, lutein + zeaxanthin, and lycopene. Serum β-carotene concentrations predominantly reflect *trans*

β-carotene, which was present in substantially higher concentrations than *cis* β-carotene. The CVs for these micronutrients were 1.9–5.7% for vitamin A, 1.8–3.9% for α-tocopherol, 1.9–6.2% for γ-tocopherol, 4.2–18.3% for α-carotene, 3.5–6.6% for *trans* β-carotene, 7.5–65% for *cis* β-carotene, 3.0–7.1% for β-cryptoxanthin, 5.5–13.4% for lutein + zeaxanthin, and 3.7–13.1% for lycopene.

Blood cadmium concentrations were measured with the use of a simultaneous multielement atomic absorption spectrometer (SIMAA 6000; PerkinElmer) with Zeeman background correction (64, 65). Assessments were conducted to verify the absence of contamination from collection, processing, and storage materials. The LOD for blood cadmium was 0.3 μg/L, and interassay coefficients were 6.1–7.3% for high cadmium and 4.1–4.4% for low cadmium (64, 65). The CDC replaces values below the LOD by the value equal to the LOD divided by the square root of 2.

Statistical analysis. All analyses were conducted in accordance with NHANES guidelines to account for study sampling design (66). Weighted analyses were modeled with the use of population weights from the subsample of the NHANES that provided DNA and blood samples. In the overall sample (combined 1999–2000 and 2001–2002 cycles), 4-y weights were used, whereas 2-y weights were used for vitamins evaluated only in the 2001–2002 cycle. Serum vitamin and carotenoid and blood cadmium means were calculated with the use of PROC SURVEYMEANS. Crude associations between population characteristics, serum nutrients, blood cadmium, and LTL were evaluated with the use of unadjusted linear regression models (PROC SURVEYREG). Correlations between age, serum nutrients, blood cadmium, and LTL were evaluated with the use of a Spearman correlation.

Associations between serum vitamins and carotenoids, blood cadmium, and LTL were evaluated with the use of multivariable linear regression (PROC SURVEYREG). Serum vitamin and carotenoid concentrations, blood cadmium, and LTL values were log-transformed to normalize distributions. Serum vitamin, serum carotenoids, and blood cadmium were assessed as both continuous and categorical (quartiles) variables. Quartile cutoffs were the 25th, 50th, and 75th percentiles of the weighted study sample. The percentage difference in LTL was calculated with the use of the formula % difference = $[\exp(\beta) - 1] \times 100$, and 95% CI = $[\exp(\beta) - \text{critical value} \times \text{standard error}] \times 100$, where β is the regression coefficient and the critical value used was based on df calculated in accordance with NHANES guidelines (67). Potential covariates were chosen a priori based on factors known to be associated with both LTL and blood cadmium or serum vitamin and carotenoid concentrations, with specific consideration for covariates included in previous cadmium and telomere analyses in the NHANES study population (18). Covariates in the full model were age (continuous), age squared (continuous), BMI (continuous), serum cotinine (log-transformed, continuous), education level (less than high school, high school graduate, some college, or college degree), sex (male or female), and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, other). Age squared was included to account for possible nonlinearity between age and LTL (18, 62). Serum cotinine concentrations were used to account for tobacco smoke exposure, because this biomarker captures recent primary and secondary smoke exposure and was more strongly associated with LTL than was self-reported smoking history (18). Physical activity has previously been shown to be associated with LTL, but was not associated with LTL in the NHANES 1999–2002 study populations (68), and not included in the final models. Plasma total homocysteine was evaluated as an additional confounder in serum folate and vitamin B-12 models. Additional adjustments for other vitamins or carotenoids did not change study conclusions. Individual carotenoids were not adjusted for other carotenoids because of concerns regarding overadjustment for the highly correlated carotenoids. However, all carotenoids were evaluated as a combined variable.

Blood cadmium and LTL associations were evaluated in addition in linear regression models stratified by circulating serum vitamin and carotenoid concentrations. Vitamins and carotenoids were categorized into a binary variable (low: <25th percentile, high: ≥25th percentile). This approach was chosen rather than using markers of nutritional deficiency because deficiency in measured nutrients was rare in this study population (69) and there are no established health cutoffs for carotenoids. Tests for multiplicative interaction were assessed by including an interaction term (nutrient-cadmium) in linear regression models, and were evaluated with nutrients and cadmium modeled as both categorical and continuous variables.

Because of the strong relation between telomere length and age, we repeated analyses evaluating associations between blood cadmium, serum vitamins and carotenoids, and LTL stratified by age categories (20 to <40, 40 to <60, and ≥60 y). Interactions between age and blood cadmium and serum vitamin or carotenoid concentrations were evaluated by including an interaction term in the models. All analyses were conducted in SAS 9.3. All P values are 2-sided, and $P < 0.05$ was considered to be statistically significant.

Results

Geometric means and 95% CIs for serum vitamin and carotenoid and blood cadmium concentrations by population characteristics in the NHANES 1999–2000 and 2001–2002 cycles are presented in **Table 1**. Age, race/ethnicity, and serum cotinine concentrations were significantly associated ($P < 0.01$) with serum vitamin, serum carotenoid, and blood cadmium concentrations. Sex was not associated ($P > 0.05$) with serum vitamin B-12 and serum γ-tocopherol concentrations, but was associated ($P < 0.01$) with all other vitamins and blood cadmium. Education, pack-years of smoking, and PIR were associated with all serum vitamin concentrations and blood cadmium ($P < 0.01$), except vitamin B-12 ($P > 0.05$). LTL and blood cadmium concentrations did not differ between study cycles ($P > 0.05$) (data not shown). Age was inversely correlated with LTL (Spearman r: −0.44, $P < 0.001$). For 1-y age differences, percentage of LTL declined by –0.60 (95% CI: −0.64, −0.55). Spearman correlations between LTL and blood cadmium and serum vitamin and carotenoid concentrations are outlined in **Supplemental Table 1** and **Supplemental Table 2**. Blood cadmium concentrations were generally not strongly correlated with serum nutrient concentrations, with the strongest correlation observed with serum β-cryptoxanthin ($r = -0.17$). Correlations between nutrients were generally modest, but were stronger for serum carotenoids.

Consistent with the previous NHANES cadmium analysis (18), blood cadmium concentrations were significantly inversely associated with shorter LTL when data were combined from both cycles (continuous percentage of LTL difference per 1 μg/L: −3.74; 95% CI: −5.35, −2.10) (**Table 2**). When stratified by NHANES study cycle, blood cadmium concentrations remained inversely associated with LTL in the 1999–2000 cycle (continuous percentage of LTL difference per 1 μg/L: −7.31; 95% CI: −10.3, −4.18), but not in the 2001–2002 cycle (continuous percentage of LTL difference per 1 μg/L: −0.67; 95% CI: −1.81, 0.48). Serum vitamin B-12 and α-tocopherol were not associated with LTL in all 4 y combined, and the lack of association was consistent in both study cycles. In continuous models, serum folate concentrations were marginally associated with longer LTL in the combined study cycle analysis (P-trend = 0.06) and in the 1999–2000 cycle (P-trend = 0.02). The direction of the association was similar in the 2001–2002 cycle continuous models, but the association was weaker (P-trend = 0.26). When serum folate was evaluated as quartiles, the association was weaker and there was not a clear pattern to the association across study cycles. Serum vitamin A concentrations were positively associated with LTL in models in all 4 y (continuous percentage of LTL difference per 1 μg/dL: 4.01; 95% CI: 0.26, 7.90). Evaluated separately by study cycle, serum

TABLE 1 Blood cadmium and serum folate, vitamin B-12, vitamin A, α-tocopherol, and γ-tocopherol concentrations in adults (NHANES 1999–2000 and 2001–2002)[1]

	n	Blood cadmium, μg/L	Serum folate, ng/dL	Serum vitamin B-12, ng/dL	Serum vitamin A, μg/dL	Serum α-tocopherol, mg/dL	Serum γ-tocopherol, μg/mL
Age, y							
20–39	2719	0.40 (0.36, 0.43)	11.3 (11.0, 11.9)	4.46 (4.39, 4.53)	56.9 (55.7, 58.1)	0.99 (0.98, 1.01)	2.06 (1.98, 2.15)
40–59	2269	0.47 (0.44, 0.49)	12.8 (12.3, 13.2)	4.61 (4.53, 4.69)	63.0 (61.8, 64.2)	1.30 (1.27, 1.33)	2.06 (1.94, 2.18)
60–84	2470	0.51 (0.48, 0.53)	16.8 (16.3, 17.3)	4.78 (4.66, 4.89)	67.3 (66.0, 68.6)	1.53 (1.50, 1.56)	1.74 (1.65, 1.84)
Sex							
Female	3865	0.40 (0.38, 0.42)	14.1 (13.7, 14.5)	4.88 (4.82, 4.95)	54.3 (58.2, 55.3)	1.12 (1.10, 1.14)	1.97 (1.89, 2.05)
Male	3593	0.38 (0.36, 0.40)	12.8 (12.4, 13.7)	4.88 (4.80, 4.97)	60.0 (58.6, 61.4)	1.07 (1.04, 1.16)	1.99 (1.91, 2.08)
Race/ethnicity							
Non-Hispanic white	3767	0.40 (0.37, 0.42)	14.1 (13.6, 14.6)	4.71 (4.65, 4.79)	59.8 (58.3, 61.3)	1.15 (1.13, 1.18)	1.94 (1.84, 2.05)
Non-Hispanic black	1264	0.37 (0.36, 0.39)	11.3 (10.9, 11.8)	5.68 (5.58, 5.79)	49.6 (48.7, 50.5)	0.92 (0.90, 0.94)	2.23 (2.15, 2.32)
Mexican American	1816	0.35 (0.33, 0.37)	12.4 (11.9, 12.9)	5.33 (5.13, 5.53)	49.7 (48.3, 51.0)	0.97 (0.94, 1.05)	2.06 (1.99, 2.14)
Other Hispanic	384	0.36 (0.33, 0.39)	12.6 (12.1, 13.2)	4.77 (4.65, 4.79)	53.2 (51.1, 55.4)	1.03 (0.99, 1.07)	1.87 (1.70, 2.06)
Other	227	0.46 (0.43, 0.49)	13.2 (12.4, 14.0)	4.98 (4.65, 5.34)	52.6 (49.7, 55.6)	1.06 (1.00, 1.12)	2.04 (1.86, 2.23)
Education level							
Less than high school	2497	0.55 (0.52, 0.58)	12.0 (11.5, 12.5)	4.64 (4.53, 4.75)	58.1 (57.6, 59.1)	1.14 (1.12, 1.16)	2.20 (2.09, 2.31)
High school graduate	1732	0.49 (0.47, 0.51)	12.3 (11.8, 12.7)	4.50 (4.41, 4.60)	61.9 (60.2, 63.7)	1.20 (1.16, 1.24)	2.20 (2.11, 2.29)
Some college	1838	0.42 (0.41, 0.45)	12.9 (12.3, 13.4)	4.54 (4.46, 4.61)	60.9 (59.7, 62.1)	1.20 (1.17, 1.22)	2.01 (1.92, 2.11)
College degree	1391	0.35 (0.33, 0.38)	15.0 (14.4, 15.6)	4.68 (4.56, 4.79)	64.7 (63.2, 66.2)	1.32 (1.28, 1.35)	1.60 (1.50, 1.70)
BMI, kg/m^2							
<25	2364	0.36 (0.34, 0.38)	14.5 (14.1, 14.9)	5.36 (5.28, 5.45)	52.6 (51.5, 53.7)	0.98 (0.96, 1.00)	1.74 (1.67, 1.81)
25 to <30	2714	0.42 (0.40, 0.45)	13.1 (12.7, 13.4)	4.62 (4.54, 4.70)	63.0 (61.8, 64.0)	1.22 (1.19, 1.07)	2.03 (1.97, 2.10)
≥30	2380	0.42 (0.39, 0.44)	12.2 (11.7, 12.6)	4.37 (4.29, 4.46)	58.7 (57.5, 60.0)	1.18 (1.16, 1.21)	2.45 (2.33, 2.58)
Pack-years of smoking							
0	3879	0.30 (0.29, 0.31)	14.1 (13.8, 14.5)	5.12 (5.07, 5.18)	53.8 (52.7, 54.9)	1.03 (1.01, 1.05)	1.94 (1.86, 2.02)
<30	2067	0.60 (0.57, 0.64)	12.0 (11.6, 12.4)	4.52 (4.39, 4.64)	61.9 (60.6, 63.3)	1.17 (1.14, 1.20)	2.03 (1.95, 2.12)
30–59	576	0.82 (0.76, 0.90)	12.9 (12.2, 13.7)	4.50 (4.35, 4.65)	65.4 (63.5, 67.4)	1.34 (1.28, 1.40)	2.08 (1.92, 2.25)
≥60	278	0.77 (0.69, 0.85)	13.0 (12.1, 14.0)	4.60 (4.38, 4.84)	67.5 (64.7, 70.5)	1.32 (1.27, 1.28)	2.22 (1.98, 2.50)
Serum cotinine, ng/mL							
0.015	2985	0.32 (0.31, 0.33)	15.7 (15.2, 16.3)	5.06 (4.98, 5.14)	58.5 (57.0, 60.1)	1.20 (1.17, 1.24)	1.75 (1.67, 1.82)
0.015 to <10	2608	0.31 (0.29, 0.32)	13.4 (13.0, 13.7)	5.00 (4.91, 5.10)	54.4 (53.0, 55.7)	1.02 (1.00, 1.05)	2.10 (2.02, 2.19)
≥10	1865	0.83 (0.80, 0.87)	10.8 (10.4, 11.2)	4.41 (4.31, 4.51)	59.5 (58.2, 60.9)	1.05 (1.03, 1.08)	2.18 (2.09, 2.28)
Poverty-to-income ratio							
<1	1195	0.41 (0.39, 0.44)	12.5 (12.0, 14.5)	4.96 (4.81, 5.12)	51.4 (50.1, 54.9)	0.94 (0.92, 0.96)	2.19 (2.09, 2.30)
1–3	2834	0.40 (0.38, 0.43)	13.0 (12.7, 13.4)	4.98 (4.89, 5.07)	55.4 (53.9, 61.6)	1.05 (1.02, 1.07)	2.12 (2.05, 2.22)
>3	2752	0.37 (0.35, 0.39)	14.1 (13.7, 14.6)	4.77 (4.71, 5.07)	60.6 (59.7, 61.6)	1.19 (1.16, 1.21)	1.82 (1.75, 2.10)

[1] Values are geometric means (95% CIs) calculated with the use of PROC SURVEYMEAN.

vitamin A was marginally associated with LTL (*P*-trend = 0.06) in the 1999–2000 population and was not associated in the 2001–2002 population (*P*-trend = 0.52). An inverse association between serum γ-tocopherol and LTL was observed, when evaluated both categorically (quartile 4 compared with quartile 1, all 4 y, percentage of LTL difference: −4.53; 95% CI: −7.23, −1.75) and continuously (continuous percentage of LTL differences per 1 μg/dL: −2.49; 95% CI: −4.21, −0.73), and the association was consistent across study cycles. The associations between serum folate and serum vitamin B-12 and LTL did not change when adjusted in addition for plasma homocysteine concentrations **Supplemental Table 3**.

Results for analyses evaluating nutrient concentrations measured in 2001–2002 only and LTL are presented in **Table 3**. Serum β-carotene (continuous percentage of LTL differences per 1 μg/dL: 2.66; 95% CI: 0.94, 4.42), serum β-cryptoxanthin (continuous percentage of LTL difference per 1 μg/dL: 2.76; 95% CI: 1.05, 4.49) and serum lycopene (continuous percentage of LTL difference per 1 μg/dL: 1.70; 95% CI: 0.13, 3.30) were positively associated with LTL. Serum lutein + zeaxanthin and serum α-carotene were positively associated with LTL, but did not reach statistical significance, whereas the combined serum carotenoid concentration was statistically significantly positively associated with LTL (continuous percentage of LTL difference LTL per 1 μg/dL: 4.23; 95% CI: 1.83, 6.69).

Associations between blood cadmium concentrations and LTL stratified by high or low vitamin serum concentrations measured in all 4 y are presented in **Table 4**. Serum folate and serum vitamin B-12 stratified models and tests for interaction with adjustment for homocysteine concentrations are provided in **Supplemental Table 4**. Tests for multiplicative interaction between blood cadmium and serum nutrient concentrations measured in both study cycles were not statistically significant. However, there were some qualitative differences in the association between LTL and blood cadmium when we stratified by nutrient serum concentrations. The LTL-cadmium association was more pronounced in the high–serum folate group (continuous percentage of LTL difference per 1 ng/dL: −4.33; 95% CI: −6.30, −2.32) than it was in the low–serum folate group (continuous percentage of LTL difference per 1 ng/dL: −2.58; 95% CI: −4.86, −0.23) (*P*-interaction = 0.19). Similar trends were observed for serum α-tocopherol. Conversely, the LTL–blood cadmium association was more pronounced in the low–serum γ-tocopherol group (continuous percentage of LTL difference per 1 μg/mL: −4.70; 95% CI: −7.38, −1.94) than it

TABLE 2 Percentage difference in telomere length (telomere-to–single-copy gene ratio) by circulating blood cadmium and serum vitamin B-12, folate, vitamin A, α-tocopherol, and γ-tocopherol concentrations (NHANES 1999–2000 and 2001–2002)[1]

	All 4 y			1999–2000			2001–2002		
	n	% Difference (95% CI)	*P*-trend[2]	*n*	% Difference (95% CI)	*P*-trend[2]	*n*	% Difference (95% CI)	*P*-trend[2]
Blood cadmium, μg/L			<0.001			<0.001			0.23
≤0.2 (quartile 1)	1687	Reference		551	Reference		1136	Reference	
>0.2 to ≤0.4 (quartile 2)	2271	−4.09 (−6.53, −1.59)		1081	−6.81 (−11.6, −1.72)		1190	−1.57 (−3.68, 0.59)	
>0.4 to ≤0.6 (quartile 3)	1633	−5.31 (−8.05, −2.48)		850	−8.70 (−13.7, −3.44)		783	−2.08 (−4.71, 0.61)	
>0.6 (quartile 4)	1862	−6.26 (−8.90, −3.43)		956	−11.9 (−16.7, −6.81)		906	−0.77 (−3.01, 1.52)	
Continuous (per 1 μg/L)	7453	−3.74 (−5.35, −2.10)	<0.001	3438	−7.31 (−10.3, −4.18)	<0.001	4015	−0.67 (−1.81, 0.48)	0.23
Serum folate, ng/dL			0.07			0.10			0.13
≤9.7 (quartile 1)	2191	Reference		971	Reference		1220	Reference	
>9.07 to ≤13.6 (quartile 2)	1851	0.74 (−1.24, 2.76)		768	1.81 (−1.88, 5.65)		1083	−0.31 (−2.75, 2.19)	
>13.6 to ≤18.7 (quartile 3)	1708	1.86 (0.01, 3.74)		777	2.60 (0.08, 5.19)		931	1.37 (−1.45, 4.28)	
>18.7 (quartile 4)	1699	1.77 (−0.66, 4.27)		924	1.82 (−0.69, 4.39)		775	2.84 (−1.76, 7.66)	
Continuous (per 1 ng/dL)	7449	1.58 (−0.05, 3.24)	0.06	3440	2.29 (0.46, 4.15)	0.02	4009	1.58 (−1.30, 4.54)	0.26
Serum vitamin B-12, ng/dL			0.80			0.30			0.15
≤3.65 (quartile 1)	2152	Reference		1003	Reference		1149	Reference	
>3.65 to ≤4.85 (quartile 2)	1977	0.01 (−1.68, 1.72)		885	−1.00 (−3.54, 1.61)		1092	1.70 (−0.59, 4.05)	
>4.85 to ≤6.47 (quartile 3)	2236	0.13 (−1.97, 2.28)		831	−1.34 (−4.49, 1.93)		973	2.78 (−0.37, 6.03)	
>6.47 (quartile 4)	1518	0.20 (−1.49, 1.92)		720	−1.54 (−4.47, 1.47)		798	0.69 (−2.21, 3.69)	
Continuous (per 1 ng/dL)	7451	0.17 (−1.07, 1.43)	0.78	3439	−1.12 (−3.27, 1.09)	0.30	4012	1.18 (−0.68, 3.07)	0.20
Serum vitamin A, μg/dL			0.04			0.05			0.64
≤46.3 (quartile 1)	1114	Reference		428	Reference		686	Reference	
>46.3 to ≤57.8 (quartile 2)	1413	2.07 (−0.57, 4.78)		513	3.92 (−0.03, 8.03)		900	0.44 (−2.90, 3.89)	
>57.8 to ≤71.1 (quartile 3)	1553	2.91(0.61, 5.25)		507	5.09 (1.12, 9.20)		1046	0.81 (−2.24, 3.95)	
>71.1 (quartile 4)	1645	3.46 (0.55, 6.45)		529	6.50 (0.77, 12.6)		1116	0.69 (−2.22, 3.69)	
Continuous (per 1 μg/dL)	5725	4.01 (0.26, 7.90)	0.04	1977	7.16 (−0.38, 15.3)	0.06	3748	0.99 (−2.17, 4.26)	0.52
Serum α-tocopherol, mg/dL			0.41			0.98			0.39
≤8.14 (quartile 1)	1023	Reference		516	Reference		507	Reference	
>8.14 to ≤1.03 (quartile 2)	1677	0.92 (−0.87, 2.74)		768	0.58 (−2.36, 3.61)		909	1.21 (−1.04, 3.51)	
>1.03 to ≤1.38 (quartile 3)	2271	0.68 (−1.55, 3.00)		1040	−0.91 (−5.62, 4.03)		1231	1.36 (−0.38, 3.13)	
>1.38 (quartile 4)	2440	1.37 (−1.42, 4.25)		1070	0.39 (−4.20, 5.19)		1370	1.66 (−2.02, 5.68)	
Continuous (per 1 mg/dL)	7411	1.70 (−0.32, 3.76)	0.10	3394	0.87 (−2.32, 4.17)	0.58	4017	1.79 (−1.15, 4.81)	0.22
Serum γ-tocopherol, μg/mL			0.001			0.04			0.02
≤1.43 (quartile 1)	1758	Reference		727	Reference		1031	Reference	
>1.43 to ≤2.12 (quartile 2)	1600	−0.84 (−3.02, 1.39)		680	−1.00 (−4.20, 2.31)		920	−0.91 (−3.86, 2.13)	
>2.12 to ≤2.94 (quartile 3)	3939	−1.76 (−3.85, 0.38)		697	−1.80 (−5.39, 1.93)		986	−1.65 (−4.06, 0.83)	
>2.94 (quartile 4)	1921	−4.53 (−7.23, −1.75)		869	−3.44 (−6.75, 0.00)		1052	−5.12 (−9.28, −0.76)	
Continuous (per 1 μg/mL)	6962	−2.49 (−4.21, −0.73)	0.007	2973	−2.16 (−4.45, 0.19)	0.07	3989	−2.65 (−5.21, −0.02)	0.05

[1] Quartile cutoffs are based on 25th, 50th and 75th percentiles (weighted) in the 1999–2000 and 2001–2002 combined population. Linear regression models were adjusted for age, age squared, BMI, serum cotinine, education level, sex, and race/ethnicity.
[2] Cadmium or nutrient quartiles were evaluated as a continuous variable.

was in the high–serum γ-tocopherol group (continuous percentage of LTL difference per 1 μg/mL: −2.61; 95% CI: −4.17, −1.02) (*P*-interaction = 0.08). When evaluated separately by study cycle, tests for interaction were generally not statistically significant (**Supplemental Table 5**). The 1999–2000 results were similar to those observed in the combined analyses, but LTL–blood cadmium associations by folate, vitamin A, and γ-tocopherol high compared with low serum concentrations tended to be stronger than in all 4 y combined. In 2001–2002, there were no associations between LTL and blood cadmium across nutrient groups, and associations generally did not differ by circulating serum vitamin or carotenoid concentrations. Tests for interaction between serum carotenoids, LTL, and blood cadmium were not statistically significant (**Table 5**). However, inverse associations between blood cadmium and LTL were stronger in participants with lower serum lycopene concentrations (continuous percentage of LTL difference per 1 μg/mL: −2.30; 95% CI: −4.59, 0.04) than in those with higher serum lycopene concentrations (continuous percentage of LTL difference per 1 μg/mL: −0.01; 95% CI: −1.35, 1.36) (*P*-interaction = 0.23).

Associations between blood cadmium and serum vitamin or carotenoid concentrations evaluated by age category (20 to <40, 40 to <60, and ≥60 y) were generally consistent with overall study results (**Supplemental Table 6** and **Supplemental Table 7**).

Discussion

In this cross-sectional study, blood cadmium concentration and serum concentrations of several vitamins and carotenoids were associated with LTL. In the combined study population, blood cadmium concentrations were inversely associated with LTL. Among vitamins measured in all 4 y, serum vitamin A was positively associated and serum γ-tocopherol inversely associated with LTL. Serum carotenoids (measured in 2001–2002 only) tended to be positively associated with LTL. In general,

TABLE 3 Percentage difference in telomere length (telomere-to–single-copy gene ratio) by circulating serum carotenoid concentrations (NHANES 2001–2002 only)[1]

	n	% Difference (95% CI)	*P*-trend[2]
Serum α-carotene, μg/dL			0.08
≤1.3 (quartile 1)	950	Reference	
>1.3 to ≤2.4 (quartile 2)	865	0.51 (−2.32, 3.42)	
>2.4 to ≤4.7 (quartile 3)	1091	3.11 (−2.72, 9.29)	
>4.7 (quartile 4)	1106	4.47 (−0.75, 9.96)	
Continuous (per 1 μg/dL)	4012	2.14 (−0.07, 4.39)	0.06
Serum β-carotene, μg/dL			0.003
≤7.69 (quartile 1)	949	Reference	
>7.69 to ≤12.7 (quartile 2)	899	1.70 (−0.49, 4.05)	
>12.7 to ≤21.8 (quartile 3)	998	3.11 (−0.38, 6.04)	
>21.8 (quartile 4)	1166	4.47 (2.36, 9.60)	
Continuous (per 1 μg/dL)	4012	2.66 (0.94, 4.42)	0.005
Serum β-cryptoxanthin, μg/dL			0.006
≤4.8 (quartile 1)	939	Reference	
>4.8 to ≤7.5 (quartile 2)	897	2.79 (0.21, 5.44)	
>7.5 to ≤11.7 (quartile 3)	933	4.13 (0.87, 7.48)	
>11.3 (quartile 4)	1224	4.86 (1.76, 8.05)	
Continuous (per 1 μg/dL)	3993	2.76 (1.05 4.49)	0.004
Serum lutein + zeaxanthin, μg/dL			0.12
≤9.4 (quartile 1)	781	Reference	
>9.4 to ≤12.9 (quartile 2)	881	1.78 (−2.00, 5.71)	
>12.9 to ≤18.0 (quartile 3)	1019	1.15 (−2.10, 4.50)	
>18.0 (quartile 4)	1328	2.85 (−0.47, 6.30)	
Continuous (per 1 μg/dL)	4009	1.54 (−0.68, 3.82)	0.16
Serum lycopene, μg/dL			0.01
≤15.5 (quartile 1)	1183	Reference	
>15.5–22.1 (quartile 2)	995	0.27 (−1.80, 2.39)	
>22.1 to ≤29.7 (quartile 3)	919	0.32 (−1.59, 2.28)	
>29.7 (quartile 4)	912	3.21 (0.61, 5.88)	
Continuous (per 1 μg/dL)	4009	1.70 (0.13, 3.30)	0.04
Combined serum carotenoids, μg/dL			0.002
≤84.4 (quartile 1)	924	Reference	
>62.8 to ≤84.4 (quartile 2)	912	1.53 (−0.60, 3.71)	
>46.6 to ≤62.8 (quartile 3)	940	3.15 (0.09, 6.31)	
>46.6 (quartile 4)	1215	5.28 (2.29, 8.35)	
Continuous (per 1 μg/dL)	3991	4.23 (1.83, 6.69)	0.002

[1] Quartile cutoffs were based on 25th, 50th and 75th percentiles (weighted for population) in the 1999–2000 and 2001–2002 combined dataset. Linear regression models were adjusted for age, age-squared, BMI, serum cotinine, education level, sex, and race/ethnicity.

[2] Cadmium or nutrient quartiles were evaluated as a continuous variable.

serum vitamin and carotenoid concentrations did not appear to modify associations between blood cadmium and LTL.

Oxidative stress is considered to be an important contributing factor for telomere shortening because of the high guanine content in telomeres. Antioxidant vitamins, including α-tocopherol, γ-tocopherol, and carotenoids, may limit the effects of oxidative stress and possibly slow telomeric attrition. Few studies have evaluated antioxidant vitamins, and results have been inconsistent. We observed no association between α-tocopherol and LTL and an inverse association between γ-tocopherol and LTL. Our results for α-tocopherol differ from 2 previous studies that reported a positive association with dietary and supplemental α-tocopherol intake (14, 43), but are in agreement with a previous study that, to our knowledge, is the only one to evaluate circulating α-tocopherol concentrations (45). To our knowledge, the only previous study to evaluate γ-tocopherol found no association between circulating concentrations and LTL (45). Results from the present analysis suggest that higher serum carotenoid concentrations may be associated with longer LTL. Two previous studies reported on associations between circulating carotenoids and LTL, including one previous analysis that used NHANES 2001–2002 data (44, 45). Our results are largely in agreement with the previously published NHANES analysis (44). Effect estimates and statistical significance were consistent for associations between circulating serum concentrations of β-carotene (positive, $P < 0.05$), β-cryptoxanthin (positive, $P < 0.05$), and lutein + zeaxanthin (positive, $P > 0.05$) and LTL. Both serum α-carotene and lycopene were also positively associated with LTL length in both studies, but the level of statistical significance differed. The association was weaker between α-carotene and LTL in our analysis, whereas the association between lycopene and LTL was stronger. Differences in associations for some nutrients likely are due to differences in included study population size (present analysis, $n = 4018$; previous analysis, $n = 3660$), quartile cutoffs (higher cutoffs in the previous study) and covariate selection. A study of 786 Austrian adults observed an association between higher circulating lutein + zeaxanthin and longer LTL, but no associations with other carotenoids (45). Consistent with the NHANES data, 2 previous studies observed longer LTL in participants with higher reported dietary β-carotene intake (70, 71).

In addition to evaluating vitamins with antioxidant properties, we evaluated whether serum vitamin A, folate, and vitamin B-12 concentrations were associated LTL. Although provitamin A (e.g., β-carotene) has been previously evaluated, preformed vitamin A has rarely been evaluated in relation to telomere length. Vitamin A has widespread physiologic roles, including in immune function, vision, reproduction, and cell communication. Among the plausible mechanisms by which vitamin A could influence LTL are its roles in immune function, inflammation, and the regulation of gene expression and epigenetic modifications (72–77). Two previous studies assessed associations between serum vitamin A and LTL (43, 45). We observed a modestly statistically significant positive association between LTL and serum vitamin A. This is consistent with the previously reported positive association between dietary intake of vitamin A and LTL in a study of 2284 women (43). Conversely, plasma vitamin A concentrations were not associated with LTL in a study of 786 adults (45).

Folate and vitamin B-12 may influence telomere length through several mechanisms, including mitigation of homocysteine-related oxidative stress (48, 51), sufficient availability of thymine for DNA repair and synthesis, and adequate synthesis of *S*-adenosylmethionine (57). Based on these hypothesized mechanisms, higher availability of folate and vitamin B-12 might be expected to promote conservation of telomeric DNA. In the present analysis, higher serum folate concentrations were associated with marginally longer LTL, which is consistent with the hypothesized relation, but results were only statistically significant in the 1999–2000 study cycle. A larger number of studies have investigated folate (43, 46–54). Two of these studies evaluated dietary intake; one observed a positive association between folate intake and LTL in nonmultivitamin users only (43), whereas the other observed no association (46). Circulating plasma or serum folate concentrations have been previously reported to be statistically significantly associated with longer LTL (48, 51, 53, 54). In one of the studies, the association was only present in participants with folate concentrations above the median (48), whereas in 2 others, the association was only statistically significant in participants with either atherosclerosis (53) or hyperhomocysteinemia (54). Three other studies observed no statistically significant associations, but there tended to be a positive association between higher folate concentrations and

TABLE 4 Interactions between circulating blood cadmium concentrations and circulating serum concentrations of folate, vitamin B-12, vitamin A, α-tocopherol, and γ-tocopherol and percentage difference in telomere length (telomere-to–single-copy gene ratio) (NHANES 1999–2000 and 2001–2002)[1]

	Low			High			
	n	% Difference (95% CI)	*P*-trend[3]	*n*	% Difference (95% CI)	*P*-trend[3]	*P*-interaction[2]
Serum folate							
Blood cadmium, μg/L			0.02			<0.001	0.96
≤0.2 (quartile 1)	467	Reference		1219	Reference		
>0.2 to ≤0.4 (quartile 2)	598	−4.81 (−8.91, −0.53)		1670	−3.89 (−6.88, −0.80)		
>0.4 to ≤0.6 (quartile 3)	423	−5.80 (−10.6, −0.73)		1207	−5.19 (−8.53, −1.72)		
>0.6 (quartile 4)	737	−5.72 (−10.1, −1.09)		1160	−6.56 (−9.84, −3.17)		
Continuous (per 1 μg/L)	2188	−2.58 (−4.86, −0.23)	0.03	5256	−4.33 (−6.30, −2.32)	<0.001	0.19
Serum vitamin B-12							
Blood cadmium, μg/L			0.01			<0.001	0.93
≤0.2 (quartile 1)	489	Reference		1197	Reference		
>0.2 to ≤0.4 (quartile 2)	659	−4.46 (−7.62, −1.18)		1608	−4.03 (−6.96, −1.01)		
>0.4 to ≤0.6 (quartile 3)	472	−5.29 (−9.55, −0.83)		1160	−5.52 (−8.52, −1.72)		
>0.6 (quartile 4)	531	−6.80 (11.8, −1.51)		1330	−6.00 (−9.84, −3.17)		
Continuous (per 1 μg/L)	2151	−3.76 (−6.52, −0.92)	0.009	5295	−3.73 (−5.62, −1.89)	<0.001	0.92
Serum vitamin A							
Blood cadmium, μg/L			0.13			0.06	0.11
≤0.2 (quartile 1)	262	Reference		1020	Reference		
>0.2 to ≤0.4 (quartile 2)	319	−1.17 (−5.73, 3.60)		1431	−3.14 (−6.18, −0.00)		
>0.4 to ≤0.6 (quartile 3)	265	−5.72 (−10.0, −1.20)		981	−2.17 (−5.36, 1.14)		
>0.6 (quartile 4)	265	−3.09 (−9.12, 3.32)		1177	−3.02 (−6.01, 0.07)		
Continuous (per 1 μg/L)	1111	−0.43 (−3.28, 2.50)	0.75	4609	−2.03 (−3.90, −0.13)	0.03	0.95
Serum α-tocopherol							
Blood cadmium, μg/L							
≤0.2 (quartile 1)	268	Reference	0.18	1397	Reference	<0.001	0.15
>0.2 to ≤0.4 (quartile 2)	254	−4.75 (−5.73, 3.48)		2003	−3.94 (−6.89, −0.91)		
>0.4 to ≤0.6 (quartile 3)	189	−0.94 (−4.84, 3.12)		1437	−5.65 (−8.82, −2.37)		
>0.6 (quartile 4)	312	−3.97 (−9.08, 1.43)		1546	−6.38 (−9.30, −3.40)		
Continuous (per 1 μg/L)	1023	−1.82 (−4.77, 1.23)	0.21	6383	−3.98 (−5.84, −2.10)	<0.001	0.39
Serum γ-tocopherol							
Blood cadmium, μg/L			<0.001			0.002	0.10
≤0.2 (quartile 1)	430	Reference		1161	Reference		
>0.2 to ≤0.4 (quartile 2)	577	−2.49 (−5.74, 0.87)		1548	−4.53 (−7.14, −1.86)		
>0.4 to ≤0.6 (quartile 3)	402	−4.99 (−9.07, −0.74)		1088	−4.04 (−6.93, −1.06)		
>0.6 (quartile 4)	348	−7.99 (−13.0, −2.67)		1403	−4.56 (−7.41, −1.62)		
Continuous (per 1 μg/L)	1757	−4.70 (−7.38, −1.94)	0.001	5200	−2.61 (−4.17, −1.02)	0.002	0.08

[1] Low: ≤25th percentile; high: >25th percentile. Serum folate—low: ≤9.7 ng/dL, high: >9.7 ng/dL; serum vitamin B-12—low: ≤3.65 ng/dL, high: >3.65 ng/dL; serum vitamin A—low: ≤46.3 μg/dL, high: >46.3 μg/dL; serum α-tocopherol—low: ≤8.14 mg/dL, high: >8.14 mg/dL; serum γ-tocopherol—low: ≤1.43 μg/mL, high: >1.43 μg/mL.
[2] Model also included nutrient and nutrient-cadmium interaction terms.
[3] Linear regression models were adjusted for age, age squared, BMI, serum cotinine, education level, sex, and race/ethnicity and evaluated by circulating nutrient category (low or high). Nutrient categories were evaluated as a population domain.

longer LTL (46, 47, 50, 52). Conversely, 1 study observed a statistically significant inverse association between plasma folate and LTL in 1044 older adults (49). Vitamin B-12 was evaluated in 6 studies, and previous results are generally in agreement with associations in the present study (46, 47, 50, 52–54). In 4 of these studies, circulating vitamin B-12 concentration was not associated with LTL (46, 47, 50, 52), whereas in 2 other studies, vitamin B-12 concentration was positively associated with LTL only in patients with atherosclerosis (53) or hypertension (54).

Acute high cadmium exposure in the United States is rare, but chronic low-dose cadmium exposure via food and smoking has been shown to be associated with chronic health issues (78). A previous study that used data from the NHANES 1999–2002 reported statistically significant inverse associations between LTL and 2 separate biomarkers of cadmium exposure (blood and urine) (18). A growing body of experimental and epidemiologic evidence suggests that cadmium exposure may induce telomere shortening. For example, in pregnant Chinese women, placental cadmium concentration was inversely associated with placental telomere length (34), and urinary cadmium was inversely associated with salivary telomere length in Nepalese adolescents (35). Although the analysis that includes both cycles provides the most statistical power, our analysis stratified by cycle indicates that the results are stronger in 1999–2000 than in the 2001–2002 cycle. A possible explanation for the difference may include the fact that either the finding for 1999–2000 or the lack of association in 2001–2002 may be a spurious result. Another potential reason for differing results is residual confounding. Although the population characteristics evaluated were generally similar between 1999–2000 and 2001–2002, there may be an unknown confounder. For example, in 1999–2000, there could have been higher exposure to another chemical correlated with cadmium exposure and associated

TABLE 5 Interactions between circulating blood cadmium concentrations and circulating serum concentrations of carotenoids and percentage difference in telomere length (telomere-to–single-copy gene ratio) (NHANES 2001–2002 only)[1]

	Low			High			
	n	% Difference (95% CI)	*P*-trend[3]	*n*	% Difference (95% CI)	*P*-trend[3]	*P*-interaction[2]
Serum α-carotene							
Blood cadmium, μg/L			0.27			0.59	0.09
≤0.2 (quartile 1)	220	Reference		916	Reference		
>0.2 to ≤0.4 (quartile 2)	200	−5.79 (−10.5, −0.79)		989	−0.56 (−3.16, 2.10)		
>0.4 to ≤0.6 (quartile 3)	168	−7.60 (−13.0, −1.83)		613	−0.46 (−2.88, 2.02)		
>0.6 (quartile 4)	361	−2.80 (−8.16, 2.48)		542	0.16 (−3.18, 2.11)		
Continuous (per 1 μg/L)	949	−1.66 (−4.16, 0.90)	0.23	3060	−0.17 (−1.27, 0.80)	0.63	0.62
Serum β-carotene							
Blood cadmium, μg/L			0.50			0.59	0.25
≤0.2 (quartile 1)	239	Reference		897	Reference		
>0.2 to ≤0.4 (quartile 2)	231	−4.33 (−9.05, 0.64)		958	−0.44 (−3.30, 2.52)		
>0.4 to ≤0.6 (quartile 3)	157	−5.93 (−11.7, 0.23)		624	−0.88 (−3.55, 1.86)		
>0.6 (quartile 4)	320	−2.17 (−9.05, 5.23)		583	−0.62 (−2.97, 1.79)		
Continuous (per 1 μg/L)	947	−1.25 (−4.78, 2.40)	0.47	3062	−0.33 (−1.64, 0.97)	0.59	0.52
Serum β-cryptoxanthin							
Blood cadmium, μg/L			0.21			0.54	0.99
≤0.2 (quartile 1)	203	Reference		926	Reference		
>0.2 to ≤0.4 (quartile 2)	229	−1.97 (−5.33, 1.52)		955	−1.40 (−3.83, 1.08)		
>0.4 to ≤0.6 (quartile 3)	171	−3.41 (−7.59, 0.96)		604	−2.03 (−5.31, 1.36)		
>0.6 (quartile 4)	334	−2.25 (−6.40, 2.08)		568	−0.08 (−2.75, 2.26)		
Continuous (per 1 μg/L)	937	−0.90 (−3.49, 1.76)	0.47	3053	−0.58 (−2.10, 0.83)	0.39	0.46
Serum lutein + zeaxanthin							
Blood cadmium, μg/L			0.56			0.38	0.55
≤0.2 (quartile 1)	202	Reference		932	Reference		
>0.2 to ≤0.4 (quartile 2)	200	−5.43 (−9.87, −0.78)		986	−0.44 (−3.46, 2.69)		
>0.4 to ≤0.6 (quartile 3)	129	−2.62 (−12.6, −0.28)		652	−1.58 (−4.10, 1.01)		
>0.6 (quartile 4)	249	−1.71 (−6.50, 3.32)		656	−0.45 (−3.09, 2.26)		
Continuous (per 1 μg/L)	780	−0.82 (−3.35, 1.78)	0.51	3226	−0.65 (−2.10, 0.83)	0.36	0.88
Serum lycopene							
Blood cadmium, μg/L			0.19			0.70	0.30
≤0.2 (quartile 1)	269	Reference		865	Reference		
>0.2 to ≤0.4 (quartile 2)	317	1.83 (−6,10, 2.63)		869	−1.39 (−4.20, 1.50)		
>0.4 to ≤0.6 (quartile 3)	270	−2.12 (−7.01, 3.03)		511	−2.23 (−4.86, 0.47)		
>0.6 (quartile 4)	326	−3.55 (−8.37, 1.53)		579	−0.45 (−3.53, 2.72)		
Continuous (per 1 μg/L)	1182	−2.30 (−4.75, 0.21)	0.07	2824	−0.01 (−1.45, 1.45)	0.99	0.23
Combined serum carotenoids							
Blood cadmium, μg/L			0.55			0.36	0.94
≤0.2 (quartile 1)	214	Reference		915	Reference		
>0.2 to ≤0.4 (quartile 2)	217	−3.03 (−7.20, 1.32)		967	−1.19 (−3.89, 1.59)		
>0.4 to ≤0.6 (quartile 3)	170	−2.77 (−7.67, 2.38)		605	−2.30 (−3.63, 1.06)		
>0.6 (quartile 4)	322	−1.58 (−6.91, 4.06)		578	−0.51 (−3.60, 1.93)		
Continuous (per 1 μg/L)	923	−1.52 (−4.00, 1.03)	0.22	3065	−0.37 (−1.85, 1.13)	0.66	0.84

[1] Low: ≤25th percentile; high: >25th percentile. Serum α-carotene—low: ≤1.3 μg/dL, high: >1.3 μg/dL; serum β-carotene—low: ≤7.69 μg/dL, high: >7.69 μg/dL; serum β-cryptoxanthin—low: ≤4.8 μg/dL, high: >4.8 μg/dL; serum lutein + zeaxanthin—low: ≤9.4 μg/dL, high: >9.4 μg/dL; serum lycopene—low: ≤15.5 μg/dL, high: >15.5 μg/dL; combined serum carotenoids—low: ≤46.6 μg/dL, high: >46.6 μg/dL.

[2] Model also included nutrient and nutrient-cadmium interaction terms.

[3] Linear regression models were adjusted for age, age squared, BMI, serum cotinine, education level, sex, and race/ethnicity and evaluated by circulating nutrient category (low or high). Nutrient categories were evaluated as a population domain.

with telomere length driving the stronger association. Study authors in a previous study did examine associations between blood lead and LTL and did not find an association (18).

Humans are exposed to a diverse combination of chemicals, heavy metals, nutrients, and bioactive food components, among others, that have the potential to interact and influence health outcomes. Investigating the joint effects of multiple environmental exposures is of growing scientific interest. Assessing whether circulating vitamin or carotenoid concentrations modified associations between blood cadmium concentrations and LTL was the primary aim of this analysis (79). To our knowledge, no previous studies have investigated whether cadmium exposure and LTL associations differ by vitamin or carotenoid intake or circulating serum or plasma concentrations. Oxidative stress is considered to be an important contributing factor for telomere shortening because of the high guanine content in telomeres. Guanine is highly sensitive to reactive oxygen species, resulting in the production of 8-oxo-7,8-dihydrodeoxyguanosine, which can

lead to DNA strand breaks, resulting in telomeric attrition (2, 3). Current data also indicate that single-strand breaks in telomeric DNA may be less efficiently repaired, leading to an accumulation of strand breaks (2, 5). As antioxidants, α-tocopherol, γ-tocopherol, and carotenoids could counter oxidative stress and reactive oxygen species from cadmium exposure. The widespread physiologic importance of vitamin A provides several potential routes for modifying the effects of cadmium exposure, including its role in inflammatory processes and immune function (74–77). Adequate folate and vitamin B-12 concentrations may contribute to the repair of DNA damage or counter the cadmium-associated inhibition of DNA repair.

We hypothesized that higher serum concentrations of vitamins and carotenoids would attenuate the association between blood cadmium concentrations and LTL. Among vitamins measured all 4 y, associations between blood cadmium concentrations generally did not differ when stratified by high (>25th percentile) and low (≤25th percentile) categories. Because carotenoids were only measured in 2001–2002, interactions between circulating serum carotenoid and blood cadmium concentrations could only be evaluated in a subset. However, further exploration of modification by carotenoids on factors associated with telomere length may be warranted because of the lack of blood cadmium and LTL associations observed in the 2001–2002 subset. Although not statistically significant, the inverse association between blood cadmium and LTL was more evident in the low concentration stratum for α-carotene, β-carotene, lycopene, and combined carotenoids than it was in the high concentration stratum.

A strength of this analysis is the study population. The NHANES is a large nationally representative sample of noninstitutionalized adults with comprehensive biomarkers and health information. An additional strength is the use of objectively measured biomarkers in the analysis rather than relying on self-reported dietary intake. A limitation of the NHANES data is the cross-sectional study design, which does not allow for causal inference. Another limitation is the inability to evaluate potential interactions between blood cadmium and serum carotenoids in both study cycles, particularly given that serum carotenoid concentrations tended to be positively associated with LTL and that blood cadmium was not associated with LTL in the 2001–2002 cycle. A related limitation is that only a limited number of nutrients were measured in the 1999–2000 and 2001–2002 NHANES study cycles, preventing a more comprehensive evaluation of associations between more nutrients and LTL. There is also the possibility of residual confounding. Circulating concentrations of nutrients may be a marker for an overall healthier lifestyle. Although we accounted for several lifestyle factors, such as BMI, smoking, and physical activity level, it is possible that the inclusion of these covariates did not completely account for factors that may confound the associations between micronutrient and LTL. In addition, dietary data were collected with the use of a single 24-h recall, which is considered to be insufficient to evaluate typical diet and diet patterns in relation to an outcome at an individual level (compared with the population-level status), which limited assessments of nutrient status as a surrogate for an overall healthier diet (80). A final limitation is that major nutrient deficiencies are rare in the US NHANES study population (69). Carotenoids are nonessential nutrients, so a population with relatively lower compared with higher intake subpopulations may be sufficient to detect associations between carotenoids and LTL. However, it is possible that for essential nutrients, the concentrations in this study population were not sufficiently low to affect LTL and may have limited our ability to observe associations between these nutrients and LTL.

In conclusion, results from this study suggest that concentrations of some micronutrients may be associated with LTL length. In particular, higher concentrations of antioxidants such as vitamin A and carotenoids may limit telomeric attrition. Current study results suggest that vitamin and carotenoid concentrations do not modify associations between cadmium exposure and LTL. Given that, to our knowledge, this is the first study to evaluate an interaction between cadmium and these nutrients and the inability to fully evaluate interactions with carotenoids, further research is needed. Future projects evaluating vitamin or carotenoid concentrations before measuring LTL and studies with repeated measures of nutrients and LTL overtime could help clarify the inconsistencies in existing research.

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SJON and ARZ analyzed the data; and SJON, KR, and ARZ designed the research and wrote the paper. All authors read and approved the final manuscript.

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