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Original Contribution

Associations of Cadmium and Lead Exposure With Leukocyte Telomere Length: Findings From National Health and Nutrition Examination Survey, 1999–2002

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Cadmium and lead are ubiquitous environmental contaminants that might increase risks of cardiovascular disease and other aging-related diseases, but their relationships with leukocyte telomere length (LTL), a marker of cellular aging, are poorly understood. In experimental studies, they have been shown to induce telomere shortening, but no epidemiologic study to date has examined their associations with LTL in the general population. We examined associations of blood lead and cadmium ($n = 6{,}796$) and urine cadmium ($n = 2{,}093$) levels with LTL among a nationally representative sample of US adults from the National Health and Nutrition Examination Survey (1999–2002). The study population geometric mean concentrations were 1.67 μg/dL (95% confidence interval (CI): 1.63, 1.70) for blood lead, 0.44 μg/L (95% CI: 0.42, 0.47) for blood cadmium, and 0.28 μg/L (95% CI: 0.27, 0.30) for urine cadmium. After adjustment for potential confounders, the highest (versus lowest) quartiles of blood and urine cadmium were associated with −5.54% (95% CI: −8.70, −2.37) and −4.50% (95% CI: −8.79, −0.20) shorter LTLs, respectively, with evidence of dose-response relationship (P for trend < 0.05). There was no association between blood lead concentration and LTL. These findings provide further evidence of physiological impacts of cadmium at environmental levels and might provide insight into biological pathways underlying cadmium toxicity and chronic disease risks.

chronic disease; environmental exposures; metals; NHANES; telomeres; United States

Abbreviations: CDC, US Centers for Disease Control and Prevention; CI, confidence interval; LOD, limit of detection; LTL, leukocyte telomere length; NHANES, National Health and Nutrition Examination Survey; SES, socioeconomic status.

Cadmium and lead pose a major public health challenge because of their ubiquitous presence in the environment and their established toxicity even at low levels. Although these metals are naturally occurring elements found in the Earth's crust, their widespread occurrence in the environment is largely the result of anthropogenic activity. Lead and cadmium are global contaminants (1–3) and they accumulate in the body (4, 5), resulting in widespread exposure. The major exposure sources in the general population are diet and tobacco smoke (1–3). Contaminated dust and air can be important sources of these metals in communities near industrial sites and in certain occupational settings (2, 3).

An increasing body of epidemiologic evidence suggests that environmental exposures to lead and cadmium might contribute to the etiology of chronic diseases, such as cardiovascular disease (6–8) and chronic kidney disease (9–11). Although the mechanisms of these associations are poorly understood, they may be mediated in part through oxidative stress and inflammatory intermediaries. In experimental studies, both metals were found to contribute to oxidative stress (12) and stimulate cytokine production (13, 14). In epidemiologic studies, cadmium and lead exposure have been positively associated with biological markers of oxidative stress and inflammation, such as γ-glutamyl transferase and C-reactive protein (15–18).

Telomeric attrition may also be an important mechanism for metal-induced toxicity. Telomeres are DNA protein structures that function to protect the ends of eukaryotic chromosomes.

Telomeres can shorten every time a cell divides, in part because the terminal portion of the telomeric DNA repeated sequence fails to replicate because of the end replication problem (19). In addition, it has been shown that oxidative stress more generally contributes to telomere shortening (20). The enzyme telomerase can lengthen telomeres (21), but this enzyme is expressed at low levels in most normal somatic human cells, leaving telomeres vulnerable to intracellular biochemical stressors. When telomeres become critically shortened, cellular senescence is triggered, and cells lose their ability to divide. Such senescent cells can cause functional deficits and greater secretion of inflammatory factors and are found in aged and degenerative tissue (22, 23). In addition to being a key mechanism of cellular aging, telomere shortening has been hypothesized to contribute to organismal aging (24). In epidemiologic studies, investigators have reported that shorter peripheral blood leukocyte telomere length (LTL) is associated with diseases of aging, including cardiovascular disease (25–28), type 2 diabetes mellitus (29, 30), dementia (31–33), and cancer (34, 35), independent of chronological age. There is also growing evidence that shorter LTL is associated with an increased odds of death (34, 36–38), although this relationship has been less consistent across studies (39, 40).

The most consistent correlate of LTL is age, with older individuals having on average shorter LTLs (41). Although data from twin studies suggested that LTL is in part heritable (42, 43), the evidence of heritability in twins decreases with age, which suggests that there are environmental influences (44). LTL is also associated with behavioral risk factors, such as smoking (45) and physical exercise (46), and psychosocial factors, including measures of socioeconomic status (SES) (47) and perceived stress (48).

There is a growing interest in identifying environmental and occupational determinants of LTL. Experimental studies have suggested that exposure to lead (49) and cadmium (50, 51) can induce telomere shortening; however, to our knowledge, only 2 prior epidemiologic studies (52, 53) have attempted to examine associations between lead or cadmium exposure and telomere length, and both of these occurred in study populations with known or suspected sources of metal pollution. In a study of 320 pregnant Chinese women conducted near electronic equipment waste industries, Lin et al. (52) found that placental telomere length was inversely correlated to placental cadmium but not lead. In a study of Chinese workers in a battery factory, investigators reported that the 84 workers with high levels of lead in their blood (mean = 60.3 μg/dL) had shorter LTLs than did the 60 workers with normal levels (mean = 30.9 μg/dL), but the association did not persist in multivariate models (53).

Although exposure to environmental metals may influence LTL, no study to date has characterized this relationship in a population-based sample. We conducted a cross-sectional study to examine the associations of blood lead and cadmium, markers of recent exposure, and urine cadmium, a marker of cumulative exposure, with LTL in a representative sample of US adults who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2002.

METHODS

Study population

We used data from the 1999–2000 and 2001–2002 cycles of NHANES, a nationally representative survey of the civilian, noninstitutionalized US population conducted by the Centers for Disease Control and Prevention (CDC). Between 1999 and 2002, DNA specimens were collected from participants who were 20 years of age or older for future genetic research. Of the 10,291 eligible participants, 7,826 (76%) provided DNA, consented to its use in future research, and had a sufficient quantity of DNA to estimate LTL. Non-Hispanic blacks, women, and subjects older than 60 years of age were less likely to give consent for future genetic research (54).

Of the 7,826 participants with LTL data, we excluded participants with missing information on blood cadmium or lead levels ($n = 5$) or critical covariates, including cumulative smoking history ($n = 685$), serum cotinine levels ($n = 114$), educational level ($n = 12$), and/or body mass index (weight (kg)/height $(m)^2$) ($n = 249$) (numbers in parentheses are not mutually exclusive), leaving a total of 6,796 participants. Compared with the study sample, persons who were excluded had higher levels of blood cadmium and cotinine and were more likely to be male, nonwhite, and not obese ($P < 0.05$) (data not shown).

LTL measurements

Analytical methods for LTL quantification have been described in detail previously (47). Briefly, aliquots of purified DNA were provided by the National Center for Health Statistics. DNA was isolated from whole blood using the Puregene (D-50K) kit protocol (Gentra Systems, Inc., Minneapolis, Minnesota) and stored at −80°C. The LTL assay was performed in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco, using the quantitative polymerase chain reaction method to measure LTL relative to standard reference DNA (also known as the T/S ratio) (55, 56). The conversion from T/S ratio to base pairs was calculated based on comparison of telomeric restriction fragment length from Southern blot analysis and T/S ratios using DNA samples from the human diploid fibroblast cell line IMR90 at different population doublings. The formula to convert T/S ratio to base pairs was $3{,}274 + 2{,}413 \times (T/S)$. DNA samples were coded and the laboratory personnel were blinded to all other measurements in the study. The CDC conducted a quality control review before linking the LTL data to the NHANES public-use data files. The CDC Institutional Review Board provided human subject approval for this study.

Cadmium and lead measurements

Blood cadmium and lead levels were measured at the CDC's National Center for Environmental Health (Atlanta, Georgia) after confirming the absence of background contamination in collection and storage materials (57, 58). Cadmium and lead concentrations were measured using a simultaneous multielement atomic absorption spectrometer (SIMAA 6000; PerkinElmer, Norwalk, Connecticut) with

Zeeman background correction (57, 58). Cadmium was also measured in urine samples in a subset of participants (n = 2,093) using inductively coupled plasma-mass spectrometry (PerkinElmer/SCIEX model 500, Norwalk, Connecticut) corrected for molybdenum oxide interference (59, 60). The interassay coefficients of variation for quality-control samples ranged from 4.0%–7.0% and 3.1%–3.2% for low and high blood lead concentrations; 6.1%–7.3% and 4.1%–4.4% for low and high blood cadmium concentrations; and 3.6%–6.7% and 1.3%–1.9% for low and high urine cadmium concentrations, respectively (57–60).

The limits of detection (LOD) were 0.3 μg/dL for blood lead, 0.3 μg/L for blood cadmium, and 0.06 μg/L for urine cadmium. Among the study population, 0.5% had blood lead concentrations below the LOD, 25% had blood cadmium concentrations below the LOD, and 6% had urinary cadmium concentrations below the LOD. Values below the LOD were replaced with the LOD divided by the square root of 2 because this method is used by the CDC (1) and produces reasonably nonbiased estimates (61).

Statistical analysis

Analyses were conducted using SUDAAN, version 10.0 (RTI International, Research Triangle Park, North Carolina). The degrees of freedom for the study population were estimated according to NHANES analytical guidelines (62) and corresponded to a critical value of 2.05 for the calculation of confidence intervals. All analyses were adjusted for the clustered sampling design. Blood lead and cadmium models were analyzed using population weights from the subsample of NHANES who provided DNA and urine cadmium models were analyzed with weights from the urine metals subsample.

We used multivariable regression models to assess the relationship between LTL and each metal exposure biomarker. We natural log–transformed LTL to improve normality and stabilize the variance. Because the dose-response relationships between metal concentrations and LTL appeared log-linear, we log-transformed metal biomarkers to capture potential log-linear relationships. We estimated the percent difference in LTL for a doubling of metal concentration as $(\exp(\ln 2 \times \beta) - 1) \times 100\%$, with the 95% confidence intervals estimated as $(\exp[\ln 2 \times (\beta \pm 2.05 \times \mathrm{SE})] - 1) \times 100\%$, where β and SE are the regression coefficient and standard error, respectively (63, 64). We also modeled lead and cadmium data as quartiles to allow for potential nonlinear associations. For quartiles, percent differences were estimated by comparing each of the upper 3 quartiles to the lowest quartile, and statistical tests for linear trends were conducted by modeling quartiles as an ordinal variable using integer values.

We used sequential models to control for potential confounders. Model 1 was adjusted for age (continuous and age squared). In Model 2, we included the following covariates that were significant predictors of LTL in the analysis of the NHANES sample by Needham et al. (47): sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, or other), educational level (<high school graduate, high school graduate, some college, or college degree), body mass index (continuous), and cumulative smoking history (0 pack-years, <30 pack-years, 30–59 pack-years, and ≥ 60 pack-years). We also adjusted for serum cotinine, a biological marker of environmental tobacco smoke

Table 1. Characteristics of Study Participants With Measurements of Leukocyte Telomere Length and Metal Biomarkers, National Health and Nutrition Examination Survey, 1999–2002

Characteristic	Study Participants (n = 6,796)		Urine Cadmium Subsample (n = 2,093)	
	GM (GSE)	% (SE)	GM (GSE)	% (SE)
T/S ratio	1.03 (0.01)		1.02 (0.01)	
Serum cotinine, ng/mL	0.52 (0.07)		0.49 (0.08)	
Age, years				
20–39		39 (1.1)		39 (1.7)
40–59		38 (0.9)		39 (1.6)
60–84		23 (0.7)		22 (1.5)
Male sex		47 (0.5)		47 (1.6)
Race/ethnicity				
Non-Hispanic white		71 (1.8)		73 (1.8)
Non-Hispanic black		11 (1.3)		10 (1.2)
Mexican American		7 (0.8)		7 (0.8)
Other Hispanic		6 (1.5)		6 (1.4)
Other		4 (0.7)		4 (0.8)
Educational level				
Less than high school		22 (0.9)		22 (1.0)
High school graduate		26 (1.1)		28 (1.4)
Some college		28 (0.9)		26 (1.0)
College degree		24 (1.6)		25 (1.9)
Body mass index[a]				
<25		35 (0.9)		34 (1.6)
25–29.9		35 (1.0)		37 (1.5)
≥30		31 (1.1)		30 (1.7)
Pack-years of smoking				
0		56 (1.3)		55 (1.9)
<30		32 (0.9)		35 (1.6)
30–59		8 (0.5)		8 (0.7)
≥60		4 (0.3)		3 (0.4)
Poverty-income ratio[b]				
<1		14 (0.9)		14 (1.3)
1–3		36 (1.4)		35 (2.0)
>3		50 (2.0)		51 (2.3)

Abbreviations: GM, geometric mean; GSE, geometric standard error; T/S ratio, leukocyte telomere length relative to standard reference DNA; SE, standard error.

[a] Weight (kg)/height $(m)^2$.

[b] Poverty-income ratio data were missing for 634 participants in the overall cohort and 207 participants in subsample in which urine cadmium was measured.

Table 2. Geometric Means of Blood Lead, Blood Cadmium, and Urine Cadmium by Participant Characteristic, National Health and Nutrition Examination Survey, 1999–2002

Characteristic	Blood Lead, μg/dL (*n* = 6,796)		Blood Cadmium, μg/L (*n* = 6,796)		Urine Cadmium, μg/L (*n* = 2,093)	
	GM	95% CI	GM	95% CI	GM	95% CI
Total population	1.67	1.63, 1.70	0.44	0.42, 0.47	0.28	0.27, 0.30
Age, years						
20–39	1.31[a]	1.25, 1.36	0.39[a]	0.37, 0.43	0.21[a]	0.19, 0.23
40–59	1.80	1.72, 1.88	0.46	0.44, 0.50	0.32	0.29, 0.35
60–84	2.20	2.12, 2.27	0.50	0.47, 0.52	0.38	0.35, 0.41
Sex						
Male	2.10[a]	2.03, 2.16	0.42[a]	0.39, 0.45	0.28	0.26, 0.31
Female	1.35	1.31, 1.39	0.46	0.44, 0.49	0.28	0.26, 0.30
Race/ethnicity						
Non-Hispanic white	1.65[a]	1.60, 1.70	0.44[a]	0.41, 0.48	0.27[a]	0.25, 0.29
Non-Hispanic black	1.77	1.67, 1.90	0.45	0.42, 0.48	0.41	0.35, 0.48
Mexican American	1.72	1.60, 1.86	0.40	0.37, 0.44	0.25	0.23, 0.28
Other Hispanic	1.67	1.57, 1.79	0.40	0.36, 0.45	0.32	0.28, 0.38
Other	1.51	1.36, 1.67	0.54	0.49, 0.60	0.29	0.23, 0.36
Educational level						
Less than high school	2.08[a]	1.99, 2.14	0.54[a]	0.51, 0.57	0.36[a]	0.32, 0.39
High school	1.72	1.65, 1.80	0.49	0.46, 0.51	0.30	0.27, 0.34
Some college	1.48	1.43, 1.50	0.43	0.40, 0.45	0.27	0.24, 0.30
College degree	1.48	1.42, 1.55	0.35	0.33, 0.38	0.22	0.20, 0.25
Body mass index[b]						
<25	1.68[a]	1.62, 1.75	0.47[a]	0.44, 0.51	0.27	0.24, 0.30
25–29.9	1.77	1.68, 1.86	0.43	0.41, 0.46	0.29	0.27, 0.31
≥30	1.51	1.45, 1.58	0.42	0.40, 0.44	0.29	0.26, 0.32
Pack-years of smoking						
0	1.39[a]	1.35, 1.45	0.33[a]	0.31, 0.34	0.22[a]	0.21, 0.23
<30	1.90	1.84, 1.95	0.60	0.57, 0.64	0.33	0.30, 0.36
30–59	2.46	2.29, 2.61	0.83	0.76, 0.90	0.59	0.49, 0.71
≥60	2.89	2.64, 3.16	0.76	0.68, 0.85	0.68	0.54, 0.86
Serum cotinine, ng/mL						
<0.015	1.26[a]	1.17, 1.35	0.32[a]	0.30, 0.34	0.21[a]	0.19, 0.24
0.015–9.9	1.55	1.51, 1.62	0.35	0.33, 0.36	0.25	0.23, 0.26
≥10	2.16	2.10, 2.25	0.89	0.86, 0.92	0.44	0.39, 0.48
Poverty-income ratio[c]						
<1	1.73[a]	1.63, 1.84	0.52[a]	0.47, 0.58	0.31	0.25, 0.38
1–3	1.72	1.65, 1.79	0.48	0.45, 0.51	0.30	0.28, 0.34
>3	1.55	1.49, 1.60	0.40	0.38, 0.42	0.26	0.23, 0.28

Abbreviations: CI, confidence interval; GM, geometric mean.

[a] $P < 0.05$. Statistical significance evaluated by the Wald F test.

[b] Weight (kg)/height $(m)^2$.

[c] Poverty-income ratio data were missing for 634 participants in the overall cohort and 207 participants in subsample in which urine cadmium was measured.

exposure, and urine creatinine (in urine cadmium models only), a marker of urine dilution (65).

Because smoking has previously been identified as a predictor of LTL (47) and cadmium is a component of cigarette smoke (66), we tested whether cadmium exposure in part mediated the association between pack-years of smoking and LTL by examining the difference in coefficients in models with and without blood cadmium. We further tested this mediation

Table 3. Percent Difference in Leukocyte Telomere Length by Lead and Cadmium Exposure, National Health and Nutrition Examination Survey, 1999–2002

Exposure	No. of Subjects	Model 1[a]			Model 2[b,c]		
		Percent Difference	95% CI	*P* for Trend	Percent Difference	95% CI	*P* for Trend
Per doubling of blood lead	6,796	−0.83	−1.79, 0.07		−0.07	−1.38, 1.26	
Blood lead concentration, μg/dL				0.01			0.90
<1.10 (Quartile 1)	1,434	Referent			Referent		
1.10–1.69 (Quartile 2)	1,668	0.80	−1.09, 2.63		1.41	−0.40, 3.25	
1.70–2.49 (Quartile 3)	1,615	−0.70	−2.37, 1.01		0.70	−1.09, 2.53	
≥2.50 (Quartile 4)	2,079	−1.88[d]	−3.54, −0.20		0.20	−2.37, 2.74	
Per doubling of blood cadmium	6,796	−2.13[d]	−3.00, −1.31		−2.46[d]	−3.74, −1.17	
Blood cadmium concentration, μg/L				<0.0001			0.001
<0.21 (Quartile 1)	1,579	Referent			Referent		
0.21–0.40 (Quartile 2)	2,073	−4.40[d]	−6.95, −1.88		−4.59[d]	−7.13, −1.98	
0.41–0.69 (Quartile 3)	1,465	−5.16[d]	−7.96, −2.27		−5.35[d]	−8.33, −2.37	
≥0.70 (Quartile 4)	1,679	−5.73[d]	−8.15, −3.25		−5.54[d]	−8.70, −2.37	
Per doubling of urine cadmium	2,093	−1.47[d]	−2.52, −0.40		−1.10	−2.26, 0.07	
Urine cadmium concentration, μg/L				0.001			0.02
<0.16 (Quartile 1)	471	Referent			Referent		
0.16–0.29 (Quartile 2)	507	−1.26	−5.11, 2.74		−1.09	−4.97, 2.94	
0.30–0.56 (Quartile 3)	541	−5.15[d]	−9.02, −1.13		−4.59	−8.97, 0.20	
≥0.57 (Quartile 4)	574	−5.68[d]	−9.36, −1.84		−4.50[d]	−8.79, −0.20	

Abbreviation: CI, confidence interval.

[a] Adjusted for age and age squared.

[b] Adjusted for age, age squared, sex, race/ethnicity, educational level, body mass index, pack-years of smoking, and cotinine level. All models that included urine cadmium were further adjusted for creatinine (a marker of urine dilution).

[c] Results of multivariate models are presented in Web Tables 1 and 2.

[d] $P < 0.05$.

by estimating the significance of the natural indirect association (smoking → cadmium → LTL) using an approach adapted from Valeri and VanderWeele (67); because these methods have not been adapted for complex survey data, our results are only approximate. Smoking was modeled as a dichotomous variable (<30 pack-years versus ≥30 pack-years of smoking). Models included all potential confounders listed above except for cotinine because we wanted to isolate the relationship among cumulative smoking history, blood cadmium, and LTL.

Poverty-income ratio, the ratio of household income to poverty threshold, was not included in our primary analysis because it was not associated with LTL in the analysis by Needham et al. (47), and 9% of our sample were missing data on poverty-income ratio. In a sensitivity analysis, we adjusted for poverty-income ratio (<1 (i.e., beneath the poverty threshold), 1–3, and >3) to account for residual confounding by SES. All *P* values are 2-sided.

RESULTS

The weighted distributions of study population characteristics between the entire sample and the subsample in which urine cadmium concentrations were measured were similar, as were the geometric means of LTL (T/S ratio of 1.03 vs. 1.02). The majority of participants were younger than 60 years of age, were non-Hispanic white, and had at least a high school diploma (Table 1).

Geometric means were 1.67 μg/dL (95% CI: 1.63, 1.70) for blood lead, 0.44 μg/L (95% CI: 0.42, 0.47) for blood cadmium, and 0.28 μg/L (95% CI: 0.27, 0.30) for urine cadmium (Table 2). Blood cadmium was moderately correlated with blood lead (Spearman's $\rho = 0.36$, $P < 0.0001$) and urine cadmium (Spearman's $\rho = 0.46$, $P < 0.0001$). Blood lead and cadmium concentrations were higher in participants who were older, were less educated, had lower income, had a body mass index <30, and were ever smokers. Blood lead and cadmium concentrations also differed by race/ethnicity; blood lead was highest in non-Hispanic blacks, and blood cadmium was highest among those of other races/ethnicities. Urine cadmium generally showed trends similar to those of blood cadmium, except that urine cadmium concentrations did not differ by sex or body mass index and differences by income were less pronounced.

In age-adjusted models, blood lead was inversely associated with LTL (percent change = −0.83%, 95% CI: −1.79, 0.07), but the association moved substantially towards the null after adjustment for other covariates (percent change = −0.07%,

Table 4. Percent Difference in Leukocyte Telomere Length by Cumulative Smoking History With and Without Adjustment for Blood Cadmium Levels, National Health and Nutrition Examination Survey, 1999–2002

	Model 1[a] (Without Blood Cadmium) ($n = 6,796$)			Model 2[a] (With Blood Cadmium) ($n = 6,796$)		
	Percent Difference	95% CI	*P* for Trend	Percent Difference	95% CI	*P* for Trend
Pack-years of smoking[b]						0.92
<30	−0.60	−1.88, 0.60		1.41	−0.20, 3.05	
30–59	−3.44[c]	−6.20, −0.60		−0.50	−3.73, 2.94	
≥60	−3.82	−7.69, 0.20	0.009	−0.05	−0.38, 0.29	

Abbreviation: CI, confidence interval.
[a] Adjusted for age, age squared, sex, race/ethnicity, educational level, and BMI.
[b] The reference category is no smoking.
[c] $P < 0.05$.

95% CI: −1.38, 1.26) (Table 3 and Web Table 1, available at http://aje.oxfordjournals.org/). Similar results were observed when blood lead concentrations were examined by quartile. Blood cadmium was inversely associated with LTL in both crude and adjusted models. When modeled continuously with covariate adjustment, a doubling of blood cadmium was associated with −2.46% (95% CI: −3.74, −1.17) shorter LTLs. Blood cadmium concentrations in the highest quartile compared with the lowest quartile were associated with −5.54% (95% CI: −8.70, −2.37) shorter LTLs, with evidence of a dose-response relationship (*P* for trend = 0.001). Associations between urine cadmium and LTL were similar to those of blood cadmium, although coefficients were weaker and less precise. In the fully adjusted model, a doubling in urine cadmium was associated with −1.10% (95% CI: −2.26, 0.07) shorter LTLs. The highest quartile of urine cadmium compared with the lowest quartile was associated with −4.50% (95% CI: −8.79, −0.20) shorter LTLs, with evidence of dose-response relationship (*P* for trend = 0.02) (Table 3 and Web Table 2). Results did not meaningfully differ after adjustment for poverty-income ratio.

We then examined whether cadmium exposure mediated the association between cumulative smoking history and LTL. Table 4 shows the covariate-adjusted association between smoking and LTL in models with and without blood cadmium. In the former (model 1), there was evidence of a dose-response relationship (*P* for trend = 0.009) between cumulative smoking history and LTL. Compared with never smokers, those who smoked for 30–59 pack-years and 60 or more pack-years had −3.44% (95% CI: −6.20, −0.60) and −3.82% (95% CI: −7.69, 0.20) shorter LTLs, respectively. In the latter (model 2), there was no evidence of a dose-response relationship, and the estimates for smokers (vs. never smokers) decreased substantially (for 30–59 pack-years, percent difference = −0.50%, 95% CI: −3.73, 2.94; for ≥60 pack-years, percent difference = −0.05%, 95% CI: −0.38, 0.29). Further mediation analyses revealed a significant indirect pathway between smoking and LTL via blood cadmium (natural indirect association = −0.015, 95% CI: −0.021, −0.010; $P < 0.0001$), which explained approximately 47% of the total association of smoking on LTL (Web Table 3).

DISCUSSION

It is critical to identify malleable factors that lead to accelerated telomere attrition. There has been a large focus on genetics and health behaviors, but minimal attention has been paid to environmental exposures. In NHANES, a nationally representative sample of US adults, we found that biomarkers of environmental cadmium exposures were inversely associated with LTL, with evidence of a linear dose-response relationship. Participants in the highest quartile of blood cadmium concentration had, on average, 6% shorter LTLs than did those in the lowest quartile, which corresponds to a difference of 147 base pairs. Given our model-based estimate (from multivariate models) of age difference in LTL of 13 base pairs per year, the difference between participants with low and high cadmium exposure of the same chronological age is equivalent to 11 years of calendar age. This difference is quite large; for comparison, the difference in LTL between those with no high school diploma and those with a college degree in a nationally representative sample is between 3% and 4% (47).

We observed a stronger association of LTL with blood cadmium than with urine cadmium. This was unexpected because biomonitoring studies conducted in occupational settings suggested that urine cadmium is a better surrogate for cumulative exposure because it reflects cadmium accumulated in the kidneys and other tissues (68, 69). However, in a recent study conducted in the general population, Adams and Newcomb (70) concluded that there was noticeable overlap between the 2 biomarkers and that blood cadmium concentration is also partly explained by longer-term exposures. Our findings might reflect the fact that LTL and blood cadmium were quantified from the same biological specimen. LTL in blood may not accurately reflect cellular aging of different tissues (24); thus, associations between urine cadmium and LTL in other tissues, such as the kidneys, might be stronger than those found in our study. Alternatively, there may be noise introduced to the urine cadmium estimates because of the correction for molybdenum interference in the analytical method (71). A third possible explanation is that our findings reflect a real difference that deserves further study, indicating that for certain stressors, recent exposure may be more relevant for cross-sectional LTL analyses than cumulative exposure.

Consistent with this idea, we observed a stronger association between LTL and current tobacco smoke exposure (as measured by cotinine) than cumulative smoking history (Web Table 4). Furthermore, a longitudinal study of occupational exposures to fine particulate matter and LTL reported that exposure in the prior month was a more consistent predictor of LTL than was cumulative exposure (72).

Consistent with prior studies, we found no association between blood lead and LTL. Wu et al. (53) examined blood and urine lead as predictors of LTL in a population of highly exposed workers. They found no associations between urine or blood lead levels and LTL in the multivariate models that included their entire sample. They reported an inverse relationship with body lead burden (derived from urine lead measurements) and a positive relationship with blood lead levels and LTL in a subset of workers with high exposures (>40 μg/dL; $n = 87$). Lin et al. (52) examined both placental lead and cadmium concentrations as predictors of placental telomere length in women at delivery. Similar to our findings, they found an inverse association with cadmium and no association with lead. Although we found no association between blood lead and LTL, it remains to be determined whether cumulative lead exposure, as reflected in bone lead measurements, might be associated with LTL, given that lead exposure can also promote reactive oxygen species and oxidative stress (12, 73) and has been associated with multiple aging-related diseases (74, 75).

Our results are biologically plausible because cadmium has been associated with multiple mechanisms that can promote telomere shortening, including oxidative stress, inflammation, and inhibition of DNA repair. Telomeres are particularly sensitive to damage by oxidative stress because of the high guanine content in telomere sequences. Furthermore, reactive oxygen species produce single-strand breaks; in contrast to the majority of genomic DNA, telomeric DNA may be deficient in the repair of single-strand breaks (76). In experimental studies, it has been shown that cadmium contributes to oxidative stress by catalyzing the generation of reactive oxygen species and interfering with antioxidative stress responses (8, 77). Although the relationship between chronic cadmium exposure and oxidative stress is less clear, positive associations between cadmium exposure and biomarkers of oxidative stress have been reported in cross-sectional epidemiologic studies (17, 78). Inflammation may accelerate leukocyte telomere shortening by promoting cell turnover and replicative senescence and by inducing oxidative stress (79). Cadmium can stimulate the production of inflammatory cytokines (13), and chronic cadmium exposure has been associated with higher levels of inflammatory biomarkers in human studies (18, 78). Lastly, cadmium is an established human carcinogen that has been shown to interfere with DNA repair systems, such as the excision, base and nucleotide, and mismatch repair systems (80). These processes could have implications for telomeric maintenance and genomic stability and warrant further research.

Our findings suggest that the established relationship between smoking and LTL (81) might in part be due to the presence of cadmium in tobacco smoke. Cadmium is commonly found in phosphate fertilizers. The tobacco plant efficiently absorbs cadmium from contaminated soil, and consequently cadmium is one of the most abundant compounds in tobacco smoke (66). Although the present study was cross-sectional and thus we were not able to determine whether cigarette smoke determines cadmium exposure which in turn influences LTL, the results from our mediation analysis are consistent with such an explanation. Our findings are also supported by those from an experimental study that separately exposed animals to cadmium or cigarette smoke condensate and found more pronounced telomere shortening in the cadmium-exposed group (51). Future studies should further examine the interplay between environmental, behavioral, and psychosocial factors and LTL because they may exert influence through independent and overlapping pathways. For example, exposure to metals might also moderate or mediate psychosocial effects on LTL. Needham et al. found that low SES was associated with shorter LTL, and this association was partly mediated by smoking (47). In our study, we found that exposure to metals varied by SES, and inclusion of metal biomarkers in the models attenuated the association between SES and LTL (data not shown).

Our main study limitation is the cross-sectional design of the NHANES; thus, we cannot infer a causal association or rule out reverse causation. It is possible that shorter LTLs may lead to enhanced cadmium exposure by altering absorption or metabolism pathways. Future epidemiologic studies should confirm our findings in prospective studies with repeated measures of LTL. Our findings may also be limited by residual confounding by SES because we were unable to account for neighborhood-level SES, although our results were robust to adjustment for individual-level SES indicators. There could also be confounding by other unmeasured variables, such as diet and proportion of different leukocyte subtypes. The latter could contribute to population differences in LTL because prior work has shown that B cells have longer telomere lengths than do T cells in the same individual (56). However, it is unknown if leukocyte composition is associated with low-level exposure to metals. Future epidemiologic studies of LTL should account for this potential confounder.

In conclusion, in the largest study to date of exposure to metals and telomere length, we found a strong and independent association between environmental exposures to cadmium and LTL after adjustment for potential confounders. These findings suggest that environmental toxicants may influence LTL in ways that are comparable to other lifestyle and behavioral factors, such as smoking and SES. Moreover, they shed insight into potentially important and novel biological pathways underlying cadmium toxicity and chronic disease risks that warrant consideration in future studies. Lastly, and possibly most critical for public health, our data are consistent with prior evidence that cadmium exposure can elicit measureable, harmful effects on biological health even at levels well below the current safety standards used by environmental and occupational agencies, which increases the importance of public health measures to reduce cadmium exposures worldwide.

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