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Original Contribution

Blood Cadmium and Lead and Chronic Kidney Disease in US Adults: A Joint Analysis

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Environmental cadmium and lead exposures are widespread, and both metals are nephrotoxic at high exposure levels. Few studies have evaluated the associations between low-level cadmium and clinical renal outcomes, particularly with respect to joint cadmium and lead exposure. The geometric mean levels of blood cadmium and lead were 0.41 μg/L (3.65 nmol/L) and 1.58 μg/dL (0.076 μmol/L), respectively, in 14,778 adults aged ≥20 years who participated in the National Health and Nutrition Examination Survey (1999–2006). After adjustment for survey year, sociodemographic factors, chronic kidney disease risk factors, and blood lead, the odds ratios for albuminuria (≥30 mg/g creatinine), reduced estimated glomerular filtration rate (eGFR) (<60 mL/minute/1.73 m^2), and both albuminuria and reduced eGFR were 1.92 (95% confidence interval (CI): 1.53, 2.43), 1.32 (95% CI: 1.04, 1.68), and 2.91 (95% CI: 1.76, 4.81), respectively, comparing the highest with the lowest blood cadmium quartiles. The odds ratios comparing participants in the highest with the lowest quartiles of both cadmium and lead were 2.34 (95% CI: 1.72, 3.18) for albuminuria, 1.98 (95% CI: 1.27, 3.10) for reduced eGFR, and 4.10 (95% CI: 1.58, 10.65) for both outcomes. These findings support consideration of cadmium and lead as chronic kidney disease risk factors in the general population and provide novel evidence of risk with environmental exposure to both metals.

albuminuria; cadmium; creatinine; glomerular filtration rate; kidney diseases; lead; metals; nutrition surveys

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey.

Chronic kidney disease affects 13% of US adults (1). The prevalence of chronic kidney disease (1) and its major risk factors, including diabetes mellitus (2, 3), hypertension (4), and obesity (5, 6), is increasing. Therefore, identification of novel risk factors, particularly those that are preventable or may interact with traditional risks, is important. Cadmium and lead are established nephrotoxicants at high exposure levels (7–13), environmental exposure to low levels of both metals is widespread (14, 15), and they accumulate in the body resulting in chronic endogenous exposure (7, 16). An increasing body of epidemiologic evidence supports the contribution of environmental lead exposure to chronic kidney disease, even at the low levels currently observed in the United States and other developed countries (15, 17, 18). However, few studies have evaluated the association between low-level, environmental cadmium exposure and clinical renal outcomes (19–22). Data on the impact of cadmium and lead coexposure on chronic kidney disease are also quite scarce (20–22). The objective of this study was to evaluate the associations of blood cadmium and lead, separately and jointly, with albuminuria and the estimated glomerular filtration rate (eGFR) in US adults who participated in the National Health and Nutrition Examination Survey (NHANES) (1999–2006).

MATERIALS AND METHODS

Study population

NHANES (1999–2006), conducted by the US National Center for Health Statistics, used a complex multistage

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sampling design to obtain a representative sample of the civilian, noninstitutionalized US population (23). The NHANES (1999–2006) study protocols were approved by the National Center for Health Statistics Institutional Review Board. Oral and written, informed consents were obtained from all participants. For the present analysis, we used data from 18,986 adults, aged ≥20 years, who participated in the NHANES (1999–2006) interviews and physical examinations. The overall participation rate was 70%. We excluded 1,097 pregnant women, 908 participants missing blood cadmium or lead measurements, 582 participants missing urine albumin or creatinine or serum creatinine levels, 1,006 participants missing information on alcohol consumption, and 615 participants missing other variables of interest, leaving 14,778 participants for this study. Participants included in the final analyses were similar to the overall NHANES (1999–2006) sample in sociodemographic characteristics (age, sex, race/ethnicity, education), body mass index, smoking status, systolic blood pressure, and hematologic indices.

Blood cadmium and lead determinations

Blood cadmium and lead were measured at the Environmental Health Laboratory of the Centers for Disease Control and Prevention's National Center for Environmental Health (23). Extensive quality control procedures were followed, including confirmation that collection and storage materials were not contaminated with background lead or cadmium. Cadmium and lead in whole blood were measured with a SIMAA 6000 simultaneous multielement atomic absorption spectrometer (Perkin-Elmer, Waltham, Massachusetts) with Zeeman background correction in 1999–2002 and with an inductively coupled plasma-mass spectrometer in 2003–2006. The limit of detection for blood cadmium was 0.3 μg/L (2.67 nmol/L) in NHANES (1999–2002) and 0.2 μg/L (1.78 nmol/L) in NHANES (2003–2006). For blood lead, the limit of detection was 0.3 μg/dL (0.015 μmol/L) in NHANES (1999–2004) and 0.25 μg/dL (0.012 μmol/L) in NHANES (2005–2006). Blood cadmium levels were below the limits of detection in 21.7% and 16.6% of the study participants in NHANES (1999–2002) and NHANES (2003–2006), respectively. Blood lead levels were below the limit of detection in 0.4% and 0.2% of the study participants in NHANES (1999–2004) and NHANES (2005–2006), respectively. In the final study population of 14,778 herein, blood cadmium and lead were below the limit of detection in 2,823 (19.1%) and 43 (0.3%) participants, respectively. For participants with blood cadmium or lead below the limit of detection, a level equal to the limit of detection divided by the squared root of 2 was imputed (14, 24). National Institute of Standards and Technology whole-blood standard reference materials were used for external calibration (25, 26). The interassay coefficients of variation ranged from 3.2% to 9.4% for blood cadmium and from 1.3% to 7.0% for blood lead.

Measures of chronic kidney disease

Urinary albumin was measured in spot urine samples by solid-phase fluorescence immunoassay. The limit of detection for urinary albumin was 0.3 μg/L, and a total of 15 (0.16%) participants were below the limit of detection in the final study population of 14,778. Urinary creatinine was measured by the modified kinetic Jaffé method. The ratio of albumin to creatinine was reported in milligrams per gram and categorized by using 30 mg/g as a cutoff (23).

Serum creatinine was measured by using a kinetic rate Jaffé method with a Hitachi model 704 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Indiana). Serum creatinine concentrations were calibrated to standard creatinine, and eGFR was calculated by using the Modification of Diet in Renal Disease Study formula: eGFR (mL/minute/1.73 m^2) = 175 × (standardized serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × 0.742 if the individual was female and × 1.212 if the individual was black (27).

Other variables

Information on age, sex, race/ethnicity, education, menopausal status, smoking, and alcohol consumption was based on self-report (23). Body mass index was calculated by dividing the measured weight in kilograms by the measured height in meters squared. Serum cotinine was measured by an isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric method. On the basis of 3 blood pressure measurements obtained during the medical examination, hypertension was defined as a mean systolic blood pressure of ≥140 mm Hg, a mean diastolic blood pressure of ≥90 mm Hg, or a self-reported physician's diagnosis or antihypertensive medication use. Diabetes mellitus was defined as a fasting glucose of ≥126 mg/dL (6.99 mmol/L), a nonfasting glucose of ≥200 mg/dL (11.1 mmol/L), or a self-reported physician's diagnosis or medication use.

Statistical analysis

All statistical analyses were performed by using the survey package in the R statistical language to account for the complex sampling design and weights in NHANES (1999–2006) (28). The distributions of blood cadmium and lead were right skewed and log transformed for the analyses. The odds ratios for albuminuria (≥30 mg/g creatinine), reduced eGFR (<60 mL/minute/1.73 m^2), and both albuminuria and reduced eGFR were estimated, comparing each of the 3 highest quartiles of blood cadmium and lead, in separate models, with the lowest quartile using logistic regression. Prevalence ratios were estimated from the logistic models as the ratio of the predicted probabilities for each outcome comparing the 3 highest quartiles with the lowest one. Ninety-five percent confidence intervals for the prevalence ratios were generated by the bootstrap percentile method using 1,000 resamples (29). Quartile cutpoints were based on weighted distributions in the whole study sample. Statistical models were initially adjusted for survey year, age (restricted cubic spline transformation), sex, race/ethnicity, and body mass index. Models were further adjusted for education, smoking (never/former/current), serum cotinine, alcohol (never/former/current), hypertension, diabetes mellitus, and

Table 1. Characteristics of Participants by Albuminuria and Reduced Estimated Glomerular Filtration Rate Status, National Health and Nutrition Examination Survey, 1999–2006[a,b]

	Albuminuria (≥30 mg/g Creatinine)		Reduced eGFR (<60 mL/minute/1.73 m^2)	
	Yes (n = 1,834)	No (n = 12,944)	Yes (n = 1,668)	No (n = 13,110)
Age, years	55.8 (0.6)	45.7 (0.3)	67.6 (0.5)	44.7 (0.3)
Sex, % male	46.8 (1.5)	50.0 (0.4)	38.4 (1.4)	50.8 (0.4)
Race/ethnicity, % white	66.2 (2.0)	74.4 (1.3)	85.3 (1.2)	72.6 (1.4)
Education, % >high school	45.3 (1.7)	56.4 (1.0)	46.0 (2.1)	56.3 (1.0)
Body mass index, kg/m^2	29.5 (0.3)	28.1 (0.1)	28.7 (0.2)	28.2 (0.1)
Smoking, %				
Former smoker	29.8 (1.2)	25.1 (0.6)	36.3 (1.6)	24.5 (0.6)
Current smoker	24.1 (1.1)	24.9 (0.7)	11.7 (1.1)	26.1 (0.7)
Cotinine, ng/mL[c]	0.57 (0.44, 0.74)	0.57 (0.49, 0.68)	0.16 (0.12, 0.20)	0.65 (0.55, 0.77)
Alcohol intake, %				
Former drinker	14.2 (1.1)	8.5 (0.5)	15.2 (1.4)	8.4 (0.5)
Current drinker	52.2 (1.7)	65.2 (1.3)	43.9 (2.2)	65.9 (1.3)
Hypertension, %	62.7 (1.6)	33.3 (0.7)	71.2 (1.5)	33.0 (0.7)
Diabetes mellitus, %	29.2 (1.4)	6.4 (0.3)	20.3 (1.5)	7.3 (0.3)
Blood cadmium, μg/L[c]	0.49 (0.47, 0.51)	0.40 (0.39, 0.42)	0.48 (0.46, 0.50)	0.40 (0.39, 0.42)
Blood lead, μg/dL[c]	1.86 (1.79, 1.94)	1.55 (1.52, 1.59)	2.06 (1.98, 2.15)	1.54 (1.50, 1.57)
Albuminuria, mg/g[c]			14.5 (13.1, 16.1)	7.1 (6.9, 7.3)
eGFR, mL/minute/1.73 m^2	78.7 (0.8)	85.6 (0.4)		

Abbreviation: eGFR, estimated glomerular filtration rate.

[a] Système International conversion factors: To convert cotinine and cadmium to nmol/L, multiply by 5.675 and 8.896, respectively; to convert lead to μmol/L, multiply by 0.0483.

[b] Values are expressed as mean or percent (standard error) except where noted otherwise.

[c] Values are expressed as the geometric mean (95% confidence interval).

menopausal status. Cadmium models were further adjusted for blood lead levels, and lead models were further adjusted for blood cadmium levels.

Next, the odds ratios for each outcome associated with cadmium and lead modeled as log-transformed continuous variables were calculated for the overall population and for subgroups defined by sex, age groups, race, smoking status, hypertension, diabetes mellitus, and quartiles of the other metal. In these analyses, odds ratios represent the effect associated with an increase from the 25th to the 75th percentile of each metal distribution (i.e., from 0.2 to 0.6 μg/L (3-fold increase) for cadmium; from 1.1 to 2.4 μg/dL (>2-fold increase) for lead), and the $P_{interaction}$ was estimated by using the Wald test. Other interaction approaches based on quartiles of both cadmium and lead and on the product of the 2 log-transformed metals were also evaluated.

RESULTS

Blood cadmium and lead levels

In this population, the geometric means of blood cadmium and blood lead were 0.41 μg/L (3.65 nmol/L) and 1.58 μg/dL (0.076 μmol/L), respectively (Web Figure 1, dashed vertical line). (This information is described in the first of 2 supplementary figures; each is referred to as ''Web Figure'' in the text and is posted on the *Journal*'s website (http://aje.oxfordjournals.org/).) Blood cadmium and lead levels were higher in older participants, in participants with less education, and in current and former smokers. Blood lead levels were also higher in men, in current and former alcohol drinkers, and in participants with hypertension. Blood cadmium and lead levels were moderately correlated with one another (Spearman's correlation coefficient = 0.34).

Chronic kidney disease outcomes

The weighted prevalence of albuminuria (≥30 mg/g creatinine), reduced eGFR (<60 mL/minute/1.73 m^2), and both outcomes was 9.1%, 8.7%, and 2.1%, respectively. Participants with albuminuria or reduced eGFR were older and less likely to have a high school education, had a higher body mass index, and were more likely to be former smokers and former alcohol drinkers, to have hypertension and diabetes mellitus, and to have higher blood cadmium and lead levels (Table 1).

Blood cadmium and lead and chronic kidney disease

The odds ratios of albuminuria and reduced eGFR associated with blood cadmium and lead quartiles, adjusted initially for sociodemographic factors and subsequently also for chronic kidney disease risk factors, are shown in Table 2, models 1 and 2. After further adjustment for the other metal, the odds ratios remained similar (Table 2, model 3). For

albuminuria, fully adjusted odds ratios comparing the highest versus the lowest blood cadmium and lead quartiles were 1.92 (95% confidence interval (CI): 1.53, 2.43) and 1.19 (95% CI: 0.96, 1.47), respectively. The fully adjusted prevalence ratios of albuminuria comparing the 3 highest with the lowest quartile were 1.09 (95% CI: 0.90, 1.34), 1.30 (95% CI: 1.03, 1.64), and 1.84 (95% CI: 1.45, 2.38) for blood cadmium and 0.83 (95% CI: 0.66, 1.05), 0.92 (95% CI: 0.74, 1.15), and 1.17 (95% CI: 0.92, 1.47) for blood lead.

For reduced eGFR, fully adjusted odds ratios comparing the highest versus the lowest blood cadmium and lead quartiles were 1.32 (95% CI: 1.04, 1.68) and 1.56 (95% CI: 1.17, 2.08), respectively (Table 2, model 3). The fully adjusted prevalence ratios of reduced eGFR comparing the 3 highest with the lowest quartile were 0.90 (95% CI: 0.70, 1.15), 1.05 (95% CI: 0.80, 1.37), and 1.32 (95% CI: 1.00, 1.75) for blood cadmium and 1.10 (95% CI: 0.81, 1.54), 1.36 (95% CI: 1.01, 1.82), and 1.56 (95% CI: 1.17, 2.04) for blood lead.

For participants with albuminuria and reduced eGFR (each participant had both outcomes), the fully adjusted odds ratios comparing the 3 highest with the lowest quartile were 1.37 (95% CI: 0.80, 2.35), 1.91 (95% CI: 1.11, 3.27), and 2.91 (95% CI: 1.76, 4.81) for blood cadmium and 1.53 (95% CI: 0.85, 2.77), 1.57 (95% CI: 0.83, 2.98), and 2.39 (95% CI: 1.31, 4.37) for blood lead. The corresponding fully adjusted prevalence ratios for having both albuminuria and reduced eGFR comparing the 3 highest with the lowest quartile were 1.37 (95% CI: 0.85, 2.31), 1.91 (95% CI: 1.21, 3.15), and 2.91 (95% CI: 1.81, 4.94) for blood cadmium and 1.53 (95% CI: 0.82, 3.13), 1.56 (95% CI: 0.89, 2.97), and 2.40 (95% CI: 1.43, 4.65) for blood lead.

Subgroup and joint cadmium-lead analyses

After multivariable adjustment, associations of blood cadmium and lead, modeled as continuous variables, with albuminuria and reduced eGFR were present in the overall population and most subgroups (Table 3). The adjusted prevalences of albuminuria, reduced eGFR, and both albuminuria and reduced eGFR were substantially increased among participants in higher quartiles of both metals compared with participants in lower quartiles (Web Figure 2). The odds ratios comparing participants in the highest quartile of both metals with those in the lowest quartile of both metals were 2.34 (95% CI: 1.72, 3.18) for albuminuria, 1.98 (95% CI: 1.27, 3.10) for reduced eGFR, and 4.10 (95% CI: 1.58, 10.65) for both albuminuria and reduced eGFR. The corresponding prevalence ratios were 2.19 (95% CI: 1.51, 3.17) for albuminuria, 1.98 (95% CI: 1.26, 3.43) for reduced eGFR, and 4.09 (95% CI: 1.77, 14.98) for both albuminuria and reduced eGFR. In models based on the product of the 2 log-transformed metals, the interaction between blood cadmium and lead was statistically significant for albuminuria ($P = 0.003$) but not for reduced eGFR ($P = 0.17$) or both outcomes ($P = 0.22$).

DISCUSSION

In this large, representative sample of US adults, increased blood cadmium and lead levels were strong, independent risk factors for the prevalence of albuminuria, reduced eGFR, and both outcomes together. On the basis of odds ratios, participants in the highest quartile of blood cadmium were almost 2 times more likely to have albuminuria, 32% more likely to have reduced eGFR, and almost 3 times more likely to have both albuminuria and reduced eGFR compared with those in the lowest blood cadmium quartile. Participants in the highest quartile of blood lead were 19% more likely to have albuminuria, 56% more likely to have reduced eGFR, and more than 2 times more likely to have both outcomes compared with those in the lowest blood lead quartile. For both metals, the associations remained present across most subgroups defined by sex, age, race, smoking status, hypertension, diabetes mellitus, and different exposure levels of the other metal. Importantly, coexposure to both metals was a very strong determinant of chronic kidney disease, with a 4-fold increased odds of having both albuminuria and reduced eGFR comparing participants in the highest exposure quartiles with those in the lowest exposure quartiles of both metals.

Cadmium and lead are widespread environmental toxicants (7, 11–14). The primary sources of cadmium exposure in the general population are cigarette smoke, food (shellfish, organ meats, grains, and vegetables, particularly root vegetables, as a result of soil pollution from cadmium-containing phosphate fertilizers), and industrial releases from smelting and fuel combustion (12). Exposure to lead has decreased substantially in developed countries because of public health measures banning lead in gasoline, paint, and solder (13). However, the body burden of lead in adults, resulting from past exposures, can be a source of endogenous exposure, particularly in women (16). Exogenous exposure continues to occur through industrial and combustion sources, lead paint, folk remedies, glazed pottery, and sometimes drinking water (30, 31). Moreover, certain populations are disproportionately exposed to lead, especially inner city residents of low socioeconomic status and workers in small or mobile workplaces, such as radiator repair shops and construction sites (13, 32). In the human body, cadmium accumulates in the renal cortex where >50% of the body burden is stored (7), and lead accumulates in bone which contains >90% of the body burden in adults (16). Biologic half-lives of cadmium in the renal cortex and of lead in bone are on the order of decades. Blood cadmium and lead reflect current exogenous exposure, as well as chronic endogenous exposure from accumulated body burdens.

Our findings are consistent with the limited data available on low-level cadmium exposure and clinical renal function measures in adults. Age-standardized rate ratios for kidney dialysis or transplantation were 1.4 (95% CI: 0.8, 2.0) and 1.9 (95% CI: 1.3, 2.5) in Swedish populations residing 2–10 and <2 km, respectively, from industrial cadmium sources compared with reference populations residing >10 km from these sources (19). In a cross-sectional study of Swedish women residing in an area not characterized by cadmium pollution (median blood cadmium = 0.38 μg/L (3.38 nmol/L)), higher blood cadmium was associated with lower creatinine clearance and eGFR based on serum cystatin C after adjustment for sociodemographic factors, chronic kidney disease risk factors, and blood lead (median = 2.2 μg/dL (0.106

Table 2. Odds Ratios for Albuminuria (≥30 mg/g Creatinine) and Estimated Glomerular Filtration Rate (<60 mL/minute/1.73 m^2) by Blood Cadmium and Lead Levels ($N = 14,778$), National Health and Nutrition Examination Survey, 1999–2006[a]

	Study Participants		Model 1[b]		Model 2[c]		Model 3[d]	
	Cases, no.	Noncases, no.	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Albuminuria (≥30 mg/g creatinine)								
Blood cadmium, μg/L (median)								
≤0.2 (0.2)	274	3,074	1.00	Referent	1.00	Referent	1.00	Referent
>0.2–0.4 (0.3)	535	4,239	1.05	0.85, 1.30	1.12	0.91, 1.39	1.10	0.89, 1.36
>0.4–0.6 (0.5)	426	2,491	1.26	1.01, 1.57	1.39	1.13, 1.72	1.32	1.07, 1.64
>0.6 (1.0)	599	3,140	1.83	1.51, 2.21	2.07	1.65, 2.59	1.92	1.53, 2.43
P_{trend}[e]				<0.001		<0.001		<0.001
Blood lead, μg/dL (median)								
≤1.1 (0.8)	280	2,962	1.00	Referent	1.00	Referent	1.00	Referent
>1.1–1.6 (1.3)	324	2,843	0.84	0.69, 1.04	0.86	0.69, 1.08	0.83	0.66, 1.04
>1.6–2.4 (1.9)	452	3,282	0.90	0.75, 1.08	0.98	0.81, 1.19	0.92	0.76, 1.12
>2.4 (3.2)	778	3,857	1.19	1.00, 1.43	1.31	1.06, 1.62	1.19	0.96, 1.47
P_{trend}				<0.001		<0.001		<0.001
Reduced eGFR (<60 mL/minute/1.73 m^2)								
Blood cadmium, μg/L (median)								
≤0.2 (0.2)	188	3,160	1.00	Referent	1.00	Referent	1.00	Referent
>0.2–0.4 (0.3)	503	4,271	0.87	0.70, 1.08	0.94	0.75, 1.17	0.91	0.73, 1.13
>0.4–0.6 (0.5)	475	2,442	0.99	0.77, 1.28	1.13	0.88, 1.44	1.05	0.82, 1.34
>0.6 (1.0)	502	3,237	1.09	0.86, 1.37	1.47	1.15, 1.87	1.32	1.04, 1.68
P_{trend}				0.09		<0.001		0.002
Blood lead, μg/dL (median)								
≤1.1 (0.8)	147	3,095	1.00	Referent	1.00	Referent	1.00	Referent
>1.1–1.6 (1.3)	274	2,893	1.08	0.79, 1.47	1.13	0.82, 1.55	1.10	0.80, 1.51
>1.6–2.4 (1.9)	468	3,266	1.25	0.92, 1.69	1.41	1.03, 1.92	1.36	0.99, 1.85
>2.4 (3.2)	779	3,856	1.41	1.07, 1.86	1.66	1.25, 2.21	1.56	1.17, 2.08
P_{trend}				<0.001		<0.001		<0.001

Abbreviation: eGFR, estimated glomerular filtration rate.

[a] Système International conversion factors: To convert cadmium to nmol/L, multiply by 8.896; to convert lead to μmol/L, multiply by 0.0483.

[b] Model 1 was adjusted for survey year, age (years modeled as the restricted cubic spline with 5 knots), sex, race/ethnicity, and body mass index (kg/m^2).

[c] Model 2 included the variables in model 1 and education (<high school, high school, >high school), smoking status (never, former, current), cotinine (log_{10} ng/mL), alcohol intake (never, former, current), hypertension (yes, no), diabetes mellitus (yes, no), and menopausal status (yes, no).

[d] Model 3 included the variables in models 1 and 2 and blood lead (log_{10} μg/dL) for cadmium quartile models or blood cadmium (log_{10} μg/L) for lead quartile models.

[e] Values for $P_{linear\ trend}$ were obtained by including log-transformed blood cadmium or lead levels as continuous variables in the regression model; for model 3, the P_{trend} values were obtained from one model for each outcome in which both metals were entered as log-transformed continuous variables.

μmol/L)), which was also significant in these models (22). β_2-Microglobulin is an established early marker for cadmium-related proximal tubular damage (7, 33). Albuminuria, a clinically relevant biomarker of early kidney damage (34), has been measured less often in cadmium exposed populations. In the setting of low cadmium exposure, urinary cadmium was associated with albuminuria in a small study of diabetics in a population from Australia (35), but not in 2 other small studies from China (36) and the United States (37). In the Cadmibel Study in Belgium, a change in urinary cadmium was associated with change in albuminuria over a 5-year follow-up period (21). However, blood cadmium (mean, 1.12 μg/L (9.96 nmol/L)) in the Cadmibel Study was not associated with measured or calculated creatinine clearances after adjusting for blood lead (mean, 9.4 μg/dL (0.454 μmol/L)), which remained significantly associated with

Table 3. Odds Ratios[a] for Albuminuria (≥30 mg/g Creatinine) and Estimated Glomerular Filtration Rate (<60 mL/minute/1.73 m^2) Comparing the 75th and the 25th Percentiles[b] of Blood Cadmium (Equivalent to a 3-Fold Increase) and Blood Lead (>2-Fold Increase) by Characteristics of Participants ($N = 14,778$), National Health and Nutrition Examination Survey, 1999–2006[c]

	Albuminuria (≥30 mg/g Creatinine)						eGFR (<60 mL/minute/1.73 m^2)					
	Cadmium			Lead			Cadmium			Lead		
	Odds Ratio	95% Confidence Interval	$P_{interaction}$[d]	Odds Ratio	95% Confidence Interval	$P_{interaction}$	Odds Ratio	95% Confidence Interval	$P_{interaction}$	Odds Ratio	95% Confidence Interval	$P_{interaction}$
Overall	1.37	1.18, 1.59		1.20	1.09, 1.33		1.26	1.09, 1.47		1.31	1.16, 1.47	
Sex												
Men	1.32	1.10, 1.58	0.41	1.10	0.97, 1.24	0.09	1.16	0.95, 1.42	0.26	1.13	0.96, 1.33	0.03
Women	1.43	1.21, 1.67		1.30	1.12, 1.52		1.35	1.12, 1.64		1.44	1.22, 1.69	
Age, years												
<50	1.26	1.03, 1.53	0.007	0.97	0.82, 1.16	0.001	1.13	0.83, 1.54	0.16	1.24	0.96, 1.61	0.13
50–65	1.32	1.08, 1.61		1.24	1.03, 1.50		1.52	1.22, 1.90		1.31	1.01, 1.70	
>65	1.91	1.59, 2.29		1.59	1.31, 1.93		1.52	1.21, 1.91		1.59	1.40, 1.81	
Race												
White	1.41	1.20, 1.66	0.52	1.22	1.08, 1.39	0.04	1.29	1.10, 1.52	0.64	1.31	1.16, 1.48	0.03
Black	1.31	1.00, 1.71		1.47	1.21, 1.79		1.39	1.02, 1.89		1.61	1.28, 2.03	
Mexican American	1.16	0.90, 1.49		1.05	0.87, 1.27		1.23	0.82, 1.85		1.54	1.29, 1.84	
Other	1.34	0.95, 1.89		1.00	0.74, 1.36		0.93	0.53, 1.61		0.99	0.62, 1.58	
Smoking												
Never	1.43	1.12, 1.84	0.31	1.19	1.03, 1.37	0.98	0.95	0.77, 1.16	0.002	1.28	1.08, 1.50	0.84
Former	1.52	1.21, 1.91		1.22	0.98, 1.51		1.76	1.33, 2.32		1.36	1.14, 1.61	
Current	1.20	0.96, 1.51		1.21	0.99, 1.47		1.39	0.95, 2.03		1.31	1.00, 1.72	
Hypertension												
Yes	1.42	1.21, 1.67	0.41	1.32	1.14, 1.52	0.03	1.42	1.17, 1.72	0.03	1.40	1.19, 1.64	0.10
No	1.31	1.07, 1.59		1.06	0.92, 1.21		1.03	0.82, 1.29		1.15	0.97, 1.36	
Diabetes mellitus												
Yes	1.22	0.97, 1.52	0.24	0.99	0.83, 1.19	0.02	1.22	0.93, 1.59	0.74	1.24	0.96, 1.60	0.60
No	1.42	1.20, 1.67		1.27	1.14, 1.41		1.28	1.09, 1.49		1.32	1.18, 1.49	
Lead quartiles (μg/dL)												
≤1.1	1.27	0.99, 1.64	0.43				0.85	0.57, 1.26	0.02			
>1.1–1.6	1.23	0.95, 1.60					1.48	1.05, 2.08				
>1.6–2.4	1.54	1.20, 1.98					1.08	0.85, 1.38				
>2.4	1.48	1.20, 1.82					1.56	1.29, 1.89				
Cadmium quartiles (μg/L)												
≤0.2				0.98	0.81, 1.19	0.02				1.12	0.87, 1.45	0.39
>0.2–0.4				1.06	0.87, 1.27					1.26	0.98, 1.60	
>0.4–0.7				1.50	1.19, 1.88					1.45	1.19, 1.76	
>0.7				1.28	1.09, 1.51					1.40	1.16, 1.69	

Abbreviation: eGFR, estimated glomerular filtration rate.

[a] Odds ratios comparing the 75th percentile with the 25th percentile of the blood cadmium or lead distribution assuming a log-linear relation. Odds ratios were adjusted for survey year, age (years modeled as restricted cubic spline with 5 knots), sex, race/ethnicity, body mass index (kg/m^2), education (<high school, high school, >high school), smoking status (never, former, current), cotinine (log_{10} ng/mL), alcohol intake (never, former, current), hypertension (yes, no), diabetes mellitus (yes, no), menopausal status (yes, no), and blood lead (log_{10} μg/dL) or blood cadmium (log_{10} μg/L).

[b] The 25th and the 75th percentiles correspond to 0.2 and 0.6 μg/L, respectively, for cadmium and 1.1 and 2.4 μg/dL, respectively, for lead.

[c] Système International conversion factors: To convert cadmium to nmol/L, multiply by 8.896; to convert lead to μmol/L, multiply by 0.0483.

[d] Estimated including an interaction term between log-transformed blood cadmium or lead levels and the corresponding group of categories and using the Wald test.

both creatinine clearance measures in these models (20). Our results are also consistent with the larger body of literature showing associations between low-level environmental lead exposure and clinical renal outcomes in cross-sectional studies (17), including earlier NHANES data (15, 38), as well as in prospective studies (18, 39, 40). Importantly, we provide novel data on the adverse renal impact of lead and cadmium coexposure in the general population, indicating that simultaneous assessment of both metals is needed to fully evaluate their public health impact.

The renal pathology induced by high-level chronic exposure to either cadmium or lead is characterized by proximal tubular atrophy associated with interstitial fibrosis and vascular changes (7, 10, 41–43). The molecular mechanisms implicated in toxicity from these metals also share several similarities. Both metals are divalent cations that inhibit sulfhydryl group-containing enzymes (44). Substantial experimental evidence implicates oxidative stress via oxidation-reduction–inactive metal pathways for both lead and cadmium, resulting in increased reactive oxygen species that lead to depletion of nitric oxide and secondary upregulation of endothelial nitric oxide synthase (42, 45, 46). Changes in intracellular calcium homeostasis (47, 48) and activation of protein kinase C may also be involved (42, 48). Alterations in cell adhesion molecules in renal proximal tubules and endothelium appear to be important mechanisms for cadmium-related nephrotoxicity (49) and may be involved in lead nephrotoxicity as well (50). In addition, both metals have been implicated in hypertension, even at low levels of exposure (51, 52). Differences between the 2 metals include cadmium induction of metallothionein synthesis and the presence of β_2-microglobulinuria in cadmium exposure (7, 33). In addition, many mechanisms and effects have been observed primarily at higher levels of exposure. Despite these differences, similarities in kidney target areas and mechanisms of toxicity add concern regarding the renal impact from coexposure to these metals.

Limitations of our study should be considered. Reverse causation (i.e., increased metal levels related to reduced renal excretion) cannot be excluded as an explanation for our results because of the cross-sectional study design. However, the adverse impact of low-level lead exposure on renal function has been observed in prospective studies (18, 39, 40) and in study population subsets with normal and minimally decreased glomerular filtration rate (18, 39), making reverse causation less likely. Although equivalent longitudinal data are lacking for cadmium, renal excretion of absorbed cadmium is only 0.007% of total body burden per day (12). Our findings could also be limited by difficulty in fully adjusting for potential confounders, including socioeconomic status, tobacco smoke, alcohol intake, or other environmental factors. However, the associations persisted after adjustment for education, race/ethnicity, smoking status, serum cotinine levels, alcohol intake, and the other metal. Our analysis may underestimate the consequences of cadmium and lead exposure due to the known limitations of albuminuria- and creatinine-based eGFR as markers of kidney damage (53, 54). Thus, the increased odds ratios observed in models of participants with both outcomes may reflect, in part, improved specificity in outcome assessment. The eGFR based on serum cystatin C or other serum markers individually or in combination with creatinine (55) may be of value in future research on metals-related nephrotoxicity. Also, blood cadmium levels were low with a substantial proportion below the limit of detection; most participants had levels over a limited range of values. Finally, our study outcomes are associated with increased mortality and frequent comorbidities. Cross-sectional surveys may differentially miss severe cases of chronic kidney disease and may be subject to selection and survival biases. Among the strengths of our study, we note the large sample size, providing power to examine effect modification, and the adjustment for a variety of sociodemographic and traditional kidney disease risk factors. Additional strengths of the NHANES (1999–2006) include representation of the US noninstitutionalized, civilian population, a rigorous study protocol, extensive quality control, and high-quality, standardized laboratory procedures.

In conclusion, we found consistent associations of blood cadmium and lead levels with albuminuria and reduced eGFR and with both endpoints combined. Because few studies have examined the impact of low-level cadmium exposure on clinical renal outcomes, this work provides important evidence regarding the potential for nephrotoxicity from cadmium at levels currently present in general populations in the United States and other developed countries. Furthermore, although exposure to multiple environmental nephrotoxicants is common, few publications have assessed the impact of joint exposure on clinical renal outcomes. We found that lead and cadmium coexposure was a very strong determinant of chronic kidney disease. Given widespread and correlated exposures to these metals and the increasing worldwide burden of chronic kidney disease, these data have substantial public health implications and add to the concern of cardiovascular (51, 56) and cognitive (57) toxicity from chronic low levels of exposure in the general population. Although additional prospective studies in patients with chronic kidney disease are needed to fully characterize the impact of low-level metal exposure on the development and progression of chronic kidney disease, our findings provide strong support for consideration of these metals as chronic kidney disease risk factors. Furthermore, these data underscore the need to monitor and reduce cadmium and lead exposures in the general population and to assess modifiable exposures clinically in chronic kidney disease patients.

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