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Associations of renal function with urinary excretion of metals: Evidence from NHANES 2003–2012

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ABSTRACT

Background: Urinary metals are considered measures of long-term exposures of metals, such as cadmium (Cd). Some studies indicate reduced renal function may affect the urinary excretion of several metals in general population making assessments difficult.

Objectives: To examine whether reduced renal function is associated with reduced urinary excretion of 12 metals or their metabolites and, in turn, an underestimated measure of Cd in general population.

Methods: We conducted analyses using data from the National Health and Nutrition Examination Survey (NHANES) 2003–2012. Multiple linear regression models were used to examine the associations between urinary metal levels and estimated glomerular filtration rate (eGFR). Restricted cubic spline regression models were used to evaluate the nonlinearity.

Results: Urinary metal levels significantly increased ($p < 0.001$) with increasing eGFR, except for antimony ($p = 0.172$). Urinary levels of arsenic, dimethylarsonic acid, cobalt, molybdenum and tungsten increased linearly with eGFR, while Cd, lead, mercury, barium, cesium and thallium increased nonlinearly ($p < 0.001$) with eGFR. Based on a restricted cubic spline regression model, we found, corresponding to a fixed blood Cd adverse cutpoint of 5 μg/L, predicted urinary Cd cutpoints substantially varied from 0.78–1.21 μg/g for urinary Cd between those aged < 40 years and who had chronic kidney disease and those aged 60 years or over with normal renal function, respectively.

Conclusion: Reduced renal function is associated with reduced urinary metals; and associations are also observed across the eGFR range not just in the reduced range. Urinary abnormal cutpoints of metals are likely dependent on eGFR and age. The associations between urinary exposure of metals and disease risk are likely underestimated without considering the modifying effect of renal function.

1. Introduction

Metals are extensively used and widely distributed in the environment. Their toxic effects on humans are of considerable public health and clinical concern. Some metals, such as cobalt, copper and molybdenum, are essential trace nutrients for normal body functioning, but an excess amount of such metals may cause toxicity (Tchounwou et al., 2012). It has been reported in epidemiological studies that exposure to metals at low levels may lead to damage in multiple organs (Järup, 2003; Tchounwou et al., 2012). Low levels of exposure to cadmium (Cd), lead (Pb), mercury(Hg) and arsenic(As) have been linked to increased risks of cardiovascular disease, kidney disease, skeletal disease and cancer (Hayes, 1997; Järup, 2003; Nigra et al., 2016; Satarug and Moore, 2004; Tellez-Plaza et al., 2013, 2012; Wild et al., 2009).

Many studies have examined the nephrotoxicity of metals (Ekong et al., 2006; Fels, 1999; Roels et al., 1999). Hypercalciuria, impaired renal function, and proteinuria were observed when urinary Cd exceeded 2.0 μg/g creatinine, blood Pb levels were 5 μg/dL or greater, or urinary Hg exceeded 50 μg/g creatinine (Ekong et al., 2006; Roels et al.,

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1999). However, it remains unclear whether low exposure to metals in the general population increases the risk of nephrotoxicity (Lunyera and Smith, 2017). In the general population, some studies found that increased blood Cd or Pb (Fadrowski et al., 2010; Ferraro et al., 2010; Kim et al., 2015, 1996; Navas-Acien et al., 2009), or increased urinary chromium (Cr) or Pb (Tsai et al., 2017) were associated with decreased estimated glomerular filtration rate (eGFR) whereas other studies showed that the increased levels of urinary Cd, Pb, As or dimethylarsonic acid (DMA) were associated with increased eGFR (Buser et al., 2016; Weidemann et al., 2015; Zheng et al., 2015). One possible explanation for this apparent inconsistency is that the majority of previous studies used cross-sectional designs which make the temporal sequence unclear. The positive association might simply be due to reverse causality, i.e. reduced eGFR could result in decreased excretion of Cd and, consequently, increased circulating levels of Cd (Dhingra et al., 2017; Weaver et al., 2016).

Similar to the findings on metals (Buser et al., 2016; Weidemann et al., 2015; Zheng et al., 2015), we previously reported that urinary excretion of triclosan, and possibly bisphenol A, decreased with decreasing renal function in the general population (You et al., 2011). This may indicate a common phenomenon whereby reduced renal function may decrease the urinary excretion of environmental chemicals. In this regard, we hypothesize that reduced renal function may decrease the urinary excretion of all metals in the general population. Urinary levels of metals are also significantly impacted by age (Chaumont et al., 2013; Sun et al., 2016) but precision-based cutpoints for abnormal urinary metals are lacking. To test this hypothesis and to meet this need, we examined urinary excretions of Cd, Pb, Hg, As, DMA, antimony (Sb), Tl, barium (Ba), cesium (Cs), cobalt (Co), molybdenum (Mo), tungsten (Tu) by renal function. In addition, using Cd and Pb as an example, we have estimated the precision-based cutpoints for abnormal urinary Cd or Pb at different age and renal function categories corresponding to the same cutpoint for abnormal blood levels of Cd or Pb.

2. Methods

2.1. Study population

We used data from the 2003–2012 National Health and Nutrition Examination Survey (NHANES) for this analysis. NHANES is a nationally representative survey of the U.S. non-institutionalized civilian population (CDC, 2017). Beginning in 1999, NHANES became a continuous annual survey, with data released in two-year cycles. A complex, multistage, probability sampling design is used to select participants (CDC, 2018). All participants or proxies provided written informed consent. The survey protocol was approved by the Research Ethics Review Board of the National Center of Health Statistics, Centers for Disease Control and Prevention.

NHANES provides continuous environmental chemicals exposure surveillance data. The biomonitoring data on exposure to metals or their metabolites include Cd, Pb, Hg, As, DMA, Sb, Ba, beryllium (Be), Cs, Co, Mo, platinum (Pt), Tl, Tu, uranium (U). There were a total of 27,733 participants aged 20 years or older in the 2003–2012 NHANES study. Approximately one-third of participants were randomly selected for measurement of urinary concentrations of Cd, Pb, Hg, total As, DMA, Ba, Co, Cs, Mo, Sb, Tl, Tu and other metals. Whole blood and spot urine samples were collected in the 2003–2012 NHANES. Specimens were obtained from participants at Mobile Examination Centers, then stored, and shipped to the Division of Environmental Health Sciences Laboratory of the Centers for Disease Control and Prevention (CDC), National Center for Environment Health. Cd, Pb and Hg were measured in whole blood and spot urine specimens. All other metals were only measured in spot urine specimens and were not included in the whole blood profile (CDC, 2009b).

Be, Pt and U were excluded from our analysis because the proportions of measurements below the limit of detection were too high to provide a valid result (CDC, 2009b). We included 12 metals or their metabolites in urine (Cd, Pb, Hg, total As, DMA, Ba, Co, Cs, Mo, Sb, Tl, Tu) and 2 metals in whole blood (Cd and Pb). Pregnant or lactating females were excluded from analysis. The final analysis included 8003 participants who had measurements for both urinary excretion levels of metals and eGFR.

2.2. Measurements of urinary metals

Inductively coupled plasma-mass spectrometry (ICP-MS) was used to measure urinary Cd, Pb, Ba, Co, Cs, Mo, Sb, Tl and Tu. The total urinary mercury concentration was determined by inductively coupled plasma dynamic reaction cell-mass spectroscopy (ICP-DRC-MS). The urinary concentration of DMA was measured by using high performance liquid chromatography (HPLC) to separate the coupled species and ICP-DRC-MS to detect the arsenic species. If the result was below the limit of detection (LOD), the value for that variable was the detection limit divided by the square root of two. The percentage of participants with urinary measures at or above the LOD were: 94.6 for Cd, 95.1 for Pb, 90.7 for Hg, 98.7 for total As, 83.6 for DMA, 97.7 for Ba, 98.7 for Co, 100 for Cs, 99.9 for Mo, 69.1 for Sb, 99.4 for Tl and 85.5 for Tu. Whole blood Cd, Pb and Hg concentrations were determined using inductively coupled plasma mass spectrometry. The percentage of participants with whole blood measures at or above the LOD were: 83.0 for Cd, 99.7 for Pb and 89.7 for Hg.

2.3. Measures of renal function

Serum creatinine was measured using a Jaffe rate method. Serum creatinine was calibrated for 2005–2006 participants; no correction was needed for calibrated serum creatinine in participants in the 2003–2004, and 2007–2012 surveys (CDC, 2008; Selvin et al., 2007). A re-calibration equation for NHANES 2005–2006 surveys was applied:

$$\textit{standard serum creatinine}\ (mg/dL) = -0.016 + 0.978 \times \textit{uncalibrated serum creatinine}\ (mg/dL). \quad (1)$$

Serum creatinine-based eGFR was estimated using the modified 4-variable Modification of Diet in Renal Disease (MDRD) Study equation (Levey et al., 2006) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009):

$$eGFR_{MDRD}\,(mL/min/m^2) = 175.0 \times (S_{cr})^{-1.154} \times age^{-0.203} \times 0.742(if\,female) \times 1.212(if\,black), \quad (2)$$

where *age* was expressed in years and S_{cr} was standard serum creatinine level in milligrams per deciliter;

$$eGFR_{CKD-EPI}\,(mL/min/m^2) = 141 \times min(S_{cr}/\kappa, 1)^{\alpha} \times max(S_{cr}/\kappa, 1)^{-1.029} \times 0.993^{age} \times 1.108(if\,female) \times 1.159(if\,black), \quad (3)$$

where *Scr* is standard serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

We classified the participants into the following three eGFR categories: 1) normal renal function with eGFR ≥90 mL/min/m^2; 2) mildly decreased renal function with eGFR 60–89 mL/min/m^2; and 3) moderately to severely decreased renal function with eGFR < 60 mL/min/m^2 (National Kidney Foundation, 2002).

Urinary creatinine was determined by a Jaffe rate reaction for NHANES 2003–2006 and an enzymatic method for NHANES 2007–2012. The following equations were applied to adjust urinary creatinine in 2003–2006 to compare with urinary creatinine in 2007–2012 (CDC, 2009a):

Urinary creatinine < 75:

$$adjusted\ urinary\ creatinine = [1.02 \times \sqrt{unadjusted\ urinary\ creatinine} - 0.36]^2; \quad (4)$$

Urinary creatinine 75 to < 250:

$$adjusted\ urinary\ creatinine = [1.05 \times \sqrt{unadjusted\ urinary\ creatinine} - 0.74]^2; \quad (5)$$

Urinary creatinine ≥250:

$$adjusted\ urinary\ creatinine = [1.01 \times \sqrt{unadjusted\ urinary\ creatinine} - 0.10]^2. \quad (6)$$

Urinary albumin was measured using solid-phase fluorescence immunoassay. Albuminuria was defined as urinary albumin-to-creatinine ratios of 30–300 mg/g (microalbuminuria) and > 300 mg/g (macroalbuminuria).

2.4. Covariates

A number of covariates were evaluated as potential confounding factors. These include gender, age (years), race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race), educational attainment (less than high school; high school, including general equivalent diploma; some college or above), poverty income ratio (PIR) category [low income (PIR ≤ 1.30), intermediate income (1.30 < PIR ≤ 3.50), and high income (PIR > 3.50)], cigarette smoking (never smoker, former smoker, current smoker), alcohol consumption status (never drinker, former drinker, current drinker) and daily energy intake. Body mass index (BMI, kg/m^2) was determined from the physical examination. Body weight status was classified as underweight, healthy weight, overweight and obese with BMI measures of < 18.5, 18.5–24.9, 25–29.9, and ≥30, respectively. Hypertension was defined as self-reported users of antihypertension medication or measured systolic BP ≥ 140 mmHg, or measured diastolic BP ≥ 90 mmHg. Diabetes was defined as glycated hemoglobin (A1C) ≥6.5% or self-reported current use of insulin or oral hypoglycemic agents. Serum cotinine, a biomarker of tobacco smoke exposure, was measured using an isotope dilution–high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry.

2.5. Statistical analysis

All statistical analyses were performed using the survey analysis procedures in SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) to account for the appropriate weighting and nesting of variables in the multistage clustered, probability sampling design. SURVEYREG procedure was used in linear regression analysis. SURVEYREG and PLM procedures were used in restricted cubic spline regression analysis. All of the reported *p*-values were two-tailed, and statistical significance was set at 0.05.

To investigate the association of renal function with urinary excretion levels of each metal, multiple linear regression models were utilized to calculate geometric means of urinary metal concentration by $eGFR_{MDRD}$ and $eGFR_{CkD\text{-}EPI}$ category, after adjusting for potential confounding factors. Tests for trends were performed by entering the categorical variables as continuous variables in the model. The distribution for urinary metal concentrations were skewed, so these variables were natural log-transformed. Three covariates were also natural log-transformed including urinary creatinine, serum cotinine and urinary albumin-creatinine ratio. Urinary creatinine was included in the models as an independent variable to account for variation in dilution in spot urinary samples, according to previous studies (Barr et al., 2005). Residual plots were used to check and validate the assumptions of linear regression models.

Restricted cubic spline regression was conducted to accommodate nonlinearity in the associations between urinary metal concentrations and eGFR, and between urinary metal concentrations and blood metal levels. Four knots were used in the models, and knots were located at 5th, 35th, 65th and 95th percentiles (Harrell and Frank, 2015, pp. 18–30). In building the relationship between urinary metal and blood metal level, variables X_1, X_2, X_3 of blood metal, X_4 of age (categorical), X_5 of eGFR (categorical) were generated and put in the model and five corresponding parameters were estimated with the restricted cubic spline regression.

Urine metal level (μg/g creatinine) = $\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5$.

$$\begin{aligned}
&(1) X_1 = X;\\
&(2) X_2 = (X-P5)_+^3 - (X-P65)_+^3 * (P95 - P5)/(P95 - P65) + (X-P95)_+^3 \\
&\qquad * (P65 - P5)/(P95 - P65);\\
&(3) X_3 = (X-P35)_+^3 - (X-P65)_+^3 * (P95 - P35)/(P95 - P65) + (X-P95)_+^3 \\
&\qquad * (P65 - P35)/(P95 - P65)\\
&(\text{If } (X - P) \le 0 \text{then } (X - P)_+ = 0;\ \text{If } (X - P) > 0 \text{then } (X - P)_+ \\
&\qquad = (X - P))
\end{aligned} \quad (7)$$

Urinary Cd or Pb (μg/g creatinine) corresponding to the blood Cd or Pb (blood Cd ≥5 μg/L, or Pb ≥ 50 μg/L is considered hazardous by the U.S. Occupational Safety and Health Administration (OSHA) or National Institute of Occupational Safety and Health (NIOSH)) was predicted at different categories of age and renal function groups. Chaumont et al. (2013) showed that after adolescence urinary Cd increased until 60–70 years of age. Sun et al. (2016) found that non-smoking men had peak levels of urinary Cd at approximately 60 years. As such, three categories of ages (< 40, 40–59 and ≥60 years) were used based on the observation that GFR declines with age after 30–40 years, with rate of decline accelerate after age 65–70 years (Glassock and Rule, 2012; Glassock and Winearls, 2009). Three groups of renal functions include moderately to severely reduced, mildly reduced and normal renal function.

Only the results in which eGFR was calculated using the MDRD Study equation was presented since similar results were found when eGFR was calculated using the CKD-EPI equation.

3. Results

Among the 8003 participants, 3612 (42.84%) had normal renal function, 3573 (49.05%) had mildly decreased renal function, and 818 (8.11%) had moderately to severely decreased renal function based on the MDRD equation. Characteristics of participants by the eGFR status are shown in Table 1. Overall, participants with lower eGFR levels were more likely to be male, older, non-Hispanic white, former smokers, former alcohol drinkers, and obese, and to have a lower educational attainment, lower income, a higher BMI, a higher albumin-creatinine ratios, and a lower dietary energy intake. Compared with participants having normal renal function, participants with progressively impaired renal function had higher prevalence of hypertension and diabetes. We found similar results when the CKD-EPI equation was used (Data not shown).

Presented in Table 2 are the associations between renal function using the MDRD Study equation and urinary metals derived from linear regression models in which urinary metals were used as dependent variables. The adjusted geometric means for urinary metal excretion increased with increasing eGFR for all metals. For example, urinary excretion of Cd increased from 0.24 μg/L for those with moderately to severely reduced function to 0.30 μg/L for those with mildly reduced renal function, and to 0.33 μg/mL for those with normal renal function. The *p* for trends were statistically significant for all metals (*p* for trend < 0.001), except for Sb (*p* for trend = 0.172). In the models we additionally adjusted for ln-urinary albumin-creatinine ratio and found similar results (Data not shown). We also have found similar

Table 1
Demographic and characteristics by category of estimated glomerular filtration rate ($eGFR_{MDRD}$) (n = 8003), NHANES 2003–2012.

Participant characteristics[a]	$eGFR_{MDRD}$(mL/min/1.73m^2)			*p* Value[b]
	< 60(n = 818)	60–89(n = 3573)	≥90 (n = 3612)	
Male	359 (36.4)	1870 (50.0)	1826 (50.6)	< 0.0001
Age (years)	67.7(66.4–68.9)	51.2(50.4–51.9)	38.7(38.1–39.3)	< 0.0001
Race/ethnicity				< 0.0001
Mexican American	67(2.5)	429(3.8)	839(13.3)	
Other Hispanic	44(3.4)	256(3.4)	350 (6.73)	
Non-Hispanic White	537(83.3)	2058(80.5)	1191(57.2)	
Non-Hispanic Black	130(6.9)	615(7.5)	932(15.4)	
Other race	40(3.9)	215(4.7)	300(7.5)	
Educational attainment				< 0.0001
Less than high school	279(23.7)	895(14.7)	1101(21.6)	
High school	207(27.2)	834(24.3)	829(23.9)	
Some college or above	329(49.2)	1843(61.0)	1681(54.5)	
Poverty income ratio				< 0.0001
Low	236(21.1)	840(15.2)	1201(26.6)	
Middle	332(45.7)	1249(34.7)	1299(38.7)	
High	187(33.2)	1242(50.0)	821(34.8)	
Cigarette smoking status				< 0.0001
Never smoker	423(53.2)	1811(51.5)	2015(53.7)	
Former smoker	319(37.2)	1052(28.4)	686(19.1)	
Current smoker	76(9.6)	710(20.2)	909(27.2)	
Alcohol consumption status				
Never drinker	151(17.1)	441(10.0)	441(10.5)	< 0.0001
Former drinker	263(29.8)	687(17.2)	504(13.6)	
Current drinker	347(53.0)	2189(72.8)	2283(75.9)	
BMI (kg/m^2)	29.5(28.8–30.1)	28.6(28.2–28.9)	28.3(28.0–28.6)	0.0078
Dietary energy intake (Kcal)	1697.3(1642.4–1752.1)	2132.8(2099.9–2165.7)	2223.0(2184.5–2261.5)	< 0.0001
Weight category				< 0.0001
Underweight	8(0.71)	48(1.4)	79(2.3)	
Healthy weight	200(24.4)	943(29.2)	1113(33.7)	
Overweight	276(35.0)	1296(36.8)	1148(31.5)	
Obese	315(39.8)	1246(32.6)	1224(32.5)	
Albumin-creatinine ratios				< 0.0001
< 30 mg/g	551(73.1)	3161(92.0)	3284(93.3)	
30–300 mg/g	201(21.0)	360(7.1)	290(6.0)	
> 300 mg/g	66(5.9)	51(0.8)	38(0.7)	
Blood pressure				< 0.0001
Normotension	199(29.1)	1302(42.5)	1767(53.3)	
Prehypertension	286(38.4)	1370(40.3)	1198(35.3)	
Hypertension	293(32.5)	759(17.2)	470(11.4)	
Diabetes				< 0.0001
Yes	184(18.8)	389(6.6)	319(6.3)	
No	632(81.2)	3179(93.4)	3284(93.7)	

[a] Value present as unweighted frequency (weighted percentage, %) and weighted mean (95%CI).
[b] Rao-Scott chi-square test for categorical data, and linear regression model for continuous variables.

Table 2
Adjusted geometric means and 95% confidence intervals for urinary excretion rates of 12 metals by category of $eGFR_{MDRD}$, NHANES 2003–2012[a].

Levels in urine (μg/L)	Renal function by $eGFR_{MDRD}$(mL/min/1.73m^2)			*p* for trend
	Moderately to severely reduced < 60	Mildly reduced 60–89	Normal ≥90	
Cadmium	0.24(0.21–0.27)	0.30(0.28–0.32)	0.33(0.31–0.35)	< 0.001
Lead	0.43(0.39–0.46)	0.54(0.50–0.57)	0.61(0.57–0.65)	< 0.001
Mercury	0.29(0.26–0.33)	0.40(0.37–0.44)	0.44(0.41–0.48)	< 0.001
Total arsenic	8.94(7.66–10.45)	9.61(8.63–10.71)	10.38(9.23–11.66)	0.010
Dimethylarsonic acid	3.95(3.55–4.39)	4.22(3.91–4.56)	4.46(4.10–4.86)	0.005
Barium	0.76(0.67–0.86)	1.16(1.06–1.27)	1.32(1.21–1.43)	< 0.001
Cobalt	0.26(0.24–0.29)	0.31(0.29–0.33)	0.35(0.33–0.37)	< 0.001
Cesium	3.40(3.19–3.64)	4.32(4.12–4.53)	4.71(4.47–4.96)	< 0.001
Molybdenum	35.59(32.03–38.35)	40.37(38.97–41.82)	46.73(44.17–49.44)	< 0.001
Antimony	0.062(0.056–0.068)	0.064(0.059–0.069)	0.065(0.061–0.070)	0.172
Thallium	0.12(0.11–0.13)	0.14(0.13–0.15)	0.15(0.14–0.16)	< 0.001
Tungsten	0.07(0.06–0.08)	0.07(0.06–0.08)	0.08(0.07–0.09)	0.002

[a] Covariates included age, gender, educational attainment, race/ethnicity, poverty income ratio, smoking status, alcohol consumption, dietary energy intake, status of blood pressure, status of diabetes, BMI, ln-urinary creatinine and ln-serum cotinine.

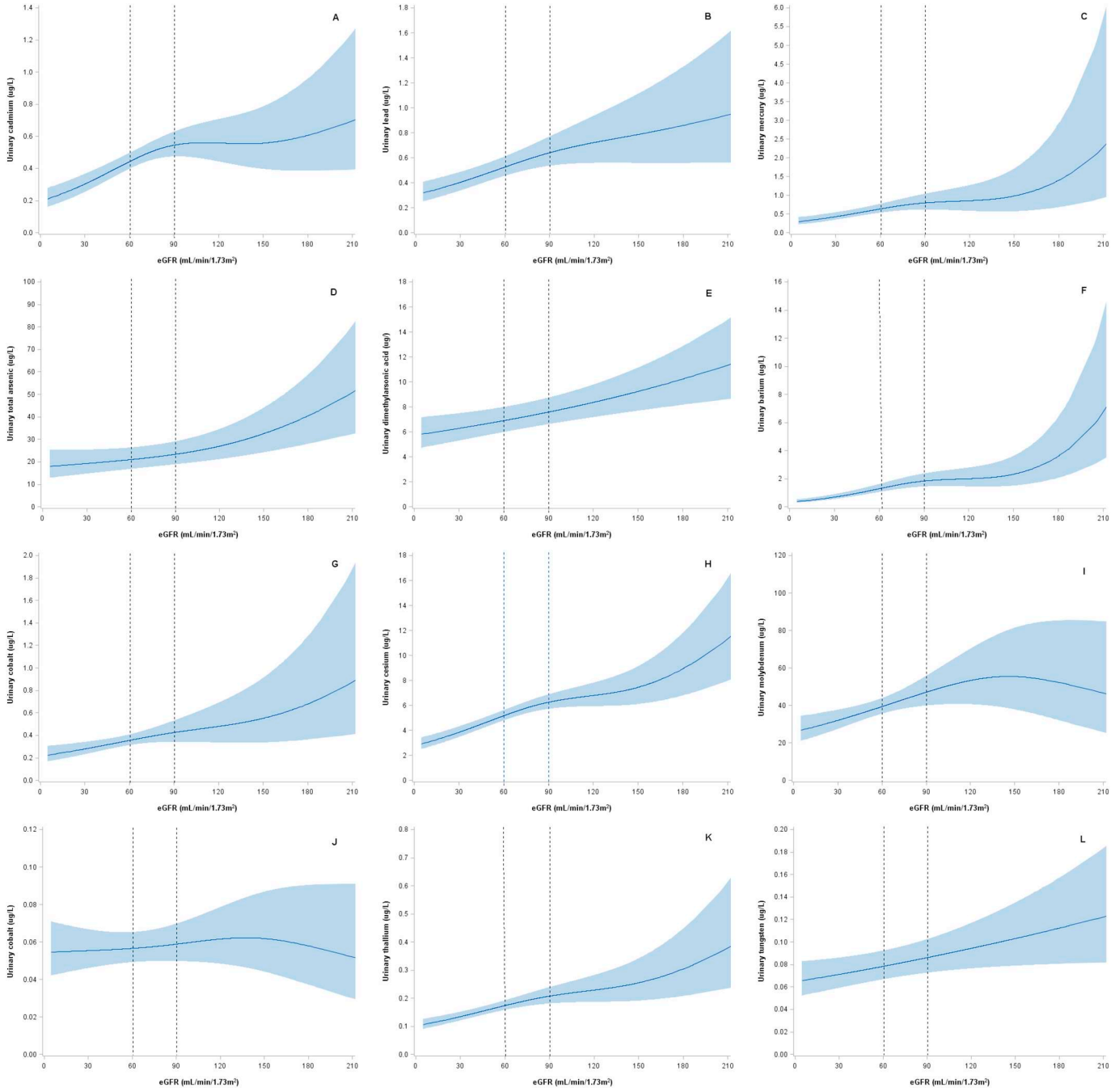

Fig. 1. Predicted spline curves for the associations between urinary metals levels (μg/L) and estimated glomerular filtration rate (mL/min/1.73m^2) using restricted cubic spline regression models. Fig. 1.A-1.L refer to cadmium (Cd), lead (Pb), mercury (Hg), total arsenic (total As), dimethylarsonic acid (DMA), barium (Ba), cobalt (Co), cesium (Cs), molybdenum (Mo), antimony (Sb), thallium (Tl) and tungsten (Tu) respectively. All of the models were significant ($p < 0.001$) except for antimony ($p = 0.172$). The curves for Cd, Pb, Hg, Ba, Cs and Tl were nonlinear whereas the curves for total As, DMA, Co, Mo and Tu were linear.
The middle line shows the weighted spline estimates adjusted for age, gender, educational attainment, race/ethnicity, poverty income ratio, smoking status, alcohol consumption, dietary energy intake, status of blood pressure, status of diabetes, BMI, ln-urinary creatinine and ln-serum cotinine.
Covariates were fixed at their mean levels (for continuous variables) or their reference level (for categorical variables). The outer lines show the 95% confidence intervals. Four knots were used in this restricted cubic spline regression. Knots located at 5th, 35th, 65th and 95th percentiles as suggested by Harrell.

associations when the CKD-EPI equation was used to estimate renal function (Data not shown).

Shown in Fig. 1 are the continuous relationships between urinary excretion rates of metals and eGFR based on restricted cubic spline regression models. Urinary excretion rates of Cd, Pb, Hg, Ba, Cs and Tl were nonlinearly and positively related to eGFR whereas As, DMA, Co, Mo and Tu were linearly and positively associated with eGFR. For Cd, Pb, Hg, Ba, Cs and Tl, it appeared that the slopes of curves were steeper when eGFR was < 90 mL/min/1.73m^2 than those when eGFR was 90 mL/min/1.73m^2 or greater. We also presented scatter-plots as Supplemental Fig. 1. The results from stratified analyses by age, gender and race indicate the relationships between urinary excretion of metals and eGFR remain similar although in some categories, the sample size became relatively small (Supplemental Figs. 2–4).

Using the restricted cubic spline regression models, predicted urinary Cd or Pb was estimated based on blood concentrations of Cd or

Table 3
Predicted cutpoints of urinary cadmium or lead concentration (μg/g) corresponding to blood cadmium fixed at the threshold of 5 μg/L, lead at threshold of 50 μg/L[a].

Age (years)	Renal function [$eGFR_{MDRD}$ (mL/min/1.73m^2)]		
	Moderately to severely reduced ($eGFR_{MDRD} < 60$)	Mildly reduced ($60 \le eGFR_{MDRD} < 90$)	Normal ($eGFR_{MDRD} \ge 90$)
Cadmium			
< 40	0.78	0.84	0.88
40–59	0.97	1.03	1.07
≥60	1.11	1.17	1.21
Lead			
< 40	1.58	1.82	1.93
40–59	1.69	1.93	2.04
≥60	1.79	2.03	2.14

[a] Predicted cutpoints are estimated based on age (years) and renal function categories using restricted cubic spline regression models.

Pb, and categorical variables of age and renal function. The following is the estimated equation:

$$\begin{aligned}\text{Mean of urinary Cd} = &-0.06 + 0.22X_1 + 3.50X_2 - 6.94X_3 \\ &+ 0.06^{*}\text{mildly reduced renal function} \\ &+ 0.10^{*}\text{normal renal function} \\ &+ 0.19^{*}\text{age between forty and fifty nine} \\ &+ 0.33^{*}\text{age above or equal to sixty} \end{aligned} \quad (8)$$

$$\begin{aligned}\text{Mean of urinary Pb} = &-0.30 + 0.50X_1 - 0.20X_2 + 0.43X_3 \\ &+ 0.24^{*}\text{mildly reduced renal function} \\ &+ 0.35^{*}\text{normal renal function} \\ &+ 0.11^{*}\text{age between forty and fifty nine} \\ &+ 0.21^{*}\text{age above or equal to sixty} \end{aligned} \quad (9)$$

Based on the equation, the nine predicted urinary Cd or Pb concentrations (μg/g) in different age and renal function groups are shown in Table 3 corresponding to a fixed blood Cd (5 μg/L) or Pb (50 μg/L) concentration. We found there are substantial variations in predicted urinary Cd or Pb cutpoints. The precision-based cutpoints increased with increasing age and renal function. The variations were larger by age category than by renal function category. The predicted cutpoint of Cd and Pb were 0.78 μg/g and 1.58 μg/g for those aged < 40 years with CKD while Cd and Pb were 1.21 and 2.14 μg/g for those aged 60 years or over who had normal renal function.

4. Discussion

Consistent with our hypothesis, we found that urinary excretion rates of eleven out of twelve metals significantly increased with increasing levels of eGFR. These relationships were non-linear for urinary concentrations of Cd, Pb, Hg, Ba, Cs and Tl and linear for As, DMA, Co, Mo and Tu. In addition, it seems excretion rates of Cd, Pb, Hg, Ba, Cs and Tl were more sensitive to impaired renal function (eGFR < 90 mL/min/1.73m^2). Finally, corresponding to the blood level of Cd at 5 μg/L, Pb at 50 μg/L (a blood cutpoint for hazardous effect of Cd or Pb by OSHA or NIOSH), we found predicted urinary excretion rates of Cd or Pb varied largely by age and renal function category.

In this study, we, for the first time, investigated the associations between urinary excretion rates of six metals (Hg, Ba, Co, Cs, Mo and Tu) and eGFR. We found that urinary excretion levels of all six of these metals were statistically significantly and positively associated with eGFR. Urinary excretion rates of Hg, Ba and Cs were nonlinearly associated with eGFR, while Co, Mo and Tu were linearly associated with eGFR. It is very unlikely that higher exposures to metals protect against reductions in renal function since metals are typically nephrotoxic chemicals. Thus, the more likely explanation is that poor renal function causes urinary excretion of metals to be reduced regardless of exposure levels. Higher eGFR may increase urinary excretion of heavy metals.

Our findings on Cd, Pb, As and DMA are consistent with previous studies also conducted in general populations (Buser et al., 2016; Ferraro et al., 2010; Gao et al., 2018; Navas-Acien et al., 2009; Weidemann et al., 2015; Zheng et al., 2015) which found an inverse association between blood Cd and Pb with renal function in contrast to a positive association between urinary Cd and Pb with renal function (Buser et al., 2016; Ferraro et al., 2010; Gao et al., 2018; Navas-Acien et al., 2009; Weaver et al., 2011a, 2011b; Weidemann et al., 2015; Zheng et al., 2015). Taken together, our new findings and those from previous studies support the hypothesis of reverse causality (Bernard, 2008). Because most metals are mainly eliminated by renal excretion, impaired renal function should logically reduce the elimination of metals. This would lead to the decreased concentrations in urine and, perhaps, increased concentrations in blood (Bernard, 2008). In addition to metals, we also found reduced renal function may reduce the excretions of triclosan and, possibly, bisphenol A (You et al., 2011) indicating that reduced renal function may decrease many urinary excretion of environmental chemicals.

Our results on urinary Cd, Sb and Tl based in the general US population are also in agreement with earlier studies conducted in occupationally-exposed lead workers (Shelley et al., 2012; Weaver et al., 2011a, 2011b). Weaver et al. (2011a) evaluated the association of urinary Cd and eGFR in 712 lead workers. They found eGFR was positively associated with urinary Cd. Weaver et al. (2011b) further reported that higher urine Cd was positively associated with higher creatinine-based eGFRs by using the MDRD Study equation and an equation incorporating serum cystatin C and creatinine. Consistent with the report by Shelley et al. (2012), we found urinary Tl, but not Sb, was statistically significantly associated with eGFR.

In the current study, we found urinary excretion rates of all metals may be affected by renal function. Also, it is well established that renal function reduces with age (Glassock and Rule, 2012; Glassock and Winearls, 2009). Thus, the cutpoints indicating abnormal urinary levels of metals could substantially differ by age and renal function. Although urinary Cd is considered a long-term biomarker of body Cd exposure and a non-invasive biomarker compared to blood Cd (Nordberg et al., 2014, pp. 682–683; Vacchi-Suzzi et al., 2016), blood concentrations of Cd indicate the bioavailable levels in body tissues and organs exposed to Cd (Adams and Newcomb, 2014; Nordberg et al., 2014, pp. 681–682). Using Cd as an example, we found that, corresponding to the same blood concentration of Cd (i.e. 5 μg/L), the predicted urinary cutpoints of Cd varied greatly by age and renal function. Our findings suggest lower urinary Cd does not necessarily indicate lower body internal exposure levels because impaired renal function could reduce renal excretion of Cd. Cd accumulates in kidneys with aging, and, thus, urinary excretion rates of Cd increase with age. A lower urinary level of Cd could be due to a younger age. Thus, age- and renal function-based cutpoints for urinary Cd or other metals could be very critical in health risk assessment.

This is a large-scale population-based study with nationally representative samples. Participation rates were high, which may minimize potential selection biases. Using restricted cubic regression models, we illustrated the relationship with eGFR was linear for several metals, but was nonlinear for the others. When renal function was impaired, excretion levels of Cd, Pb, Hg, Ba, Cs and Tl change more rapidly than when renal function was normal. In the present study, we used eGFR estimated by the MDRD Study equation and the CKD-EPI equation and found similar results. Also, we used uncorrected metals as dependent variables and adjusted for urinary creatinine as a covariate in regression models as recommended previously (Barr et al., 2005; Lang et al., 2008; Melzer et al., 2010). Also, we used the ratio of urinary metals divided by urinary creatinine in the models and found similar

results. Renal excretion of metals is a combination of three processes: glomerular filtration, tubular secretion and tubular reabsorption (Nordberg et al., 2014, pp. 61–62). Cd bound to metallothionein can be easily filtered through the glomeruli and efficiently reabsorbed by the renal tubule (Nordberg, 2009). Physiological variations in renal tubular reabsorption function can cause co-excretion of Cd and low molecular weight proteins such as albumin (Akerstrom et al., 2013; Chaumont et al., 2012; Bernard, 2008). Thus, we adjusted urinary albumin levels as a covariate and found similar results.

The potential limitation of this study is that, as with all prevalent case–control studies, one major concern is that the temporal sequence may not be clear. The cross-sectional design is not appropriate to examine the prospective relationship of metal exposure on renal function. However, it is highly unlikely that high excretion levels of metals protect against kidney damage. As such, it is very likely that renal function levels affect urinary excretion of metals. In addition, the observed associations may be due to serum creatinine-specific kidney function estimates (Weaver et al., 2011b). Weaver et al. (2011b) showed that urine cadmium was not associated with eGFR measures based on serum cystatin C, whereas urine cadmium was positively associated with eGFR estimated with serum creatinine. However, in a later study (Weaver et al., 2014), Weaver et al. found both urinary excretion rates of Cd and Tl were significantly and positively associated with serum cystatin-C-based eGFR. In the current study, we do not have data on metal exposure for participants. However, to date, blood and urine levels have been considered to have substantial advantages over external measures and are often considered to reflect metal exposures. Thus, future studies from animal models and/or human populations are warranted to be specifically designed to address the concerns.

5. Conclusion

Our findings suggest urinary excretion rates of metals decrease (linearly or non-linearly) with declining renal function. Similarly, urinary excretion rates increase (linearly or non-linearly) with higher renal function. The associations between urinary exposure of metals and disease risk are likely underestimated without considering the modifying effect of renal function (Gao et al., 2018). Thus, the modifying effect of renal function on the associations between urinary excretion rates of metals and risk of chronic disease should be considered in future studies (Gao et al., 2018). In addition, urinary cutpoints for abnormal Cd or Pb exposure are age- and renal function-dependent. If confirmed, these findings have very significant public health and clinical implications, particularly given the prevalence of CKD (Coresh et al., 2007; Murphy et al., 2016) and reduced renal function (Yan et al., 2012) are high in the U.S. general population.

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Competing financial interest declaration

None.

Declarations of interest

None.

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