Urinary and Blood Cadmium and Lead and Kidney Function: NHANES 2007-2012

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25 **ABSTRACT**

26 *Background:* Cadmium (Cd) and lead (Pb) are widespread environmental contaminants that are known
27 nephrotoxins. However, their nephrotoxic effects at low-environmental exposure levels are debated.

28 *Objective:* We examined the association of blood Pb (B-Pb), blood Cd (B-Cd), urinary Pb (U-Pb) and
29 urinary Cd (U-Cd) with estimated glomerular filtration rate (eGFR) and urinary albumin (ALB).

30 *Methods:* We used multivariate linear regression to analyze the association between B-Pb, B-Cd, U-Pb,
31 and U-Cd with eGFR and ALB in adult participants (≥ 20 years of age) in NHANES 2007-2012. The
32 dataset was limited to NHANES individuals with both blood and urinary metal measurements.

33 *Results:* We found a statistically significant inverse association between eGFR and B-Cd and
34 statistically significant positive associations between eGFR and both U-Cd and U-Pb, as well as
35 statistically significant associations between ALB and the 3rd and 4th quartiles of U-Cd.

36 *Conclusions:* The inverse association between eGFR and B-Cd, in conjunction with positive
37 associations between eGFR and ALB with U-Cd, suggest that U-Cd measurement at low levels of
38 exposure may result from changes in renal excretion of Cd due to kidney function and protein excretion.
39 However, renal effects such as hyperfiltration from Cd-mediated kidney damage or creatinine-specific
40 Cd effects cannot be excluded with this cross-sectional design.

41

42 INTRODUCTION

43 Chronic kidney disease (CKD) is a leading cause of death in the United States (Levey *et al.*,
44 2009). The estimated prevalence of CKD among people in the United States 20 years of age and older is
45 greater than 10% (Zhang and Rothenbacker 2008). High blood pressure (McCarley and Burrows-
46 Hudson 2006) and diabetes (Baumgarten and Gehr 2011; Collins *et al.*, 2013) are known risk factors for
47 CKD; furthermore, exposure to chemical substances can also play a role in the development of this
48 disease (Franchini *et al.*, 2005; Gingsberg 2012; Soderland *et al.*, 2010).

49 Cadmium (Cd) and lead (Pb) are two environmental pollutants that exhibit nephrotoxic activity,
50 frequently evidenced by decreased GFR and increased levels of albumin loss in urine (ALB) (ATSDR
51 2007, 2012). Cadmium is a widespread industrial and environmental pollutant, with food and tobacco
52 being the primary sources of exposure in the United States (ATSDR, 2012). Lead is widespread in the
53 environment and exposure can occur through contact with air, tobacco smoke, household dust, soil,
54 water, food, and commercial products (ATSDR, 2007). Cadmium and Pb nephrotoxicity effects are
55 dose-dependent (Bernard, 2008). Studies of workers with chronic Cd exposure (Chaumont *et al.*, 2012;
56 Jarup *et al.*, 1998) have estimated that urinary Cd (U-Cd) in the range of 4-10 µg/g creatinine is
57 associated with increased microproteinuria (non-albumin proteins passing from the blood through the
58 glomeruli into the urinary tract), and the U.S. Occupational Safety and Health Administration considers
59 3 µg Cd/g of creatinine as the safety standard for U-Cd (OSHA, 1993).

60 Studies over the past decade have reported a statistically significant association of low-level
61 environmental Pb and/or Cd exposure with renal dysfunction in the general population using both cross-
62 sectional (Navas-Acien *et al.*, 2009; Ferraro *et al.*, 2010) and prospective cohort (Kim *et al.*, 1996; Yu *et al.* 2004) study designs.

64 Recently, however, the potential nephrotoxic effects of low-level Cd exposure have been called
65 into question. Weaver *et al.* (2011a, b) reported an association of higher U-Cd with increased eGFR;

66 further studies have confirmed this association, describing a pattern of increased B-Cd and decreased U-
67 Cd associated with decreased eGFR, as well as positive associations between U-Cd and ALB and select
68 other urinary proteins (Akerstrom et al., 2013; Chaumont et al., 2012). These findings suggest that the
69 reported associations between low-level metal exposure and perturbations in renal activity are not a
70 simple causal relationship, but represent a more complex interplay between Cd effects on the kidney and
71 the renal function's effects on the accumulation and excretion of Cd. Based on analyses of the types of
72 proteins excreted and non-creatinine based markers of kidney function, several studies have suggested
73 that the patterns of association between eGFR and U-Cd and B-Cd may be a consequence of reverse
74 causality, with kidney function driving measured levels of B-Cd and U-Cd, rather than an effect of Cd
75 on the kidneys (Akerstrom *et al.*, 2013; Chaumont *et al.*, 2012; Evans and Elinder, 2011; Haddam *et al.*,
76 2011).

77 Lead nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and
78 interstitial fibrosis (Diamond 2005). Studies of rats fed with a continuous high dose of lead (5000 ppm)
79 showed a statistically significant increased eGFR compared to controls after 3 months, followed by a
80 decreased eGFR at 6, 9 and 12 months. The decreased eGFR reached statistical significance relative to
81 the control only after 12 months of exposure. Histologically, the kidneys presented proximal tubule
82 inclusion bodies, interstitial fibrosis, tubular atrophy, and focal glomerular sclerosis (Khalil-Manesh *et*
83 *al.*, 1992). A study from the same group on rats fed with a continuous low dose of lead (100 ppm)
84 showed a statistically significantly increased eGFR at 3 months compared to controls, but the eGFR at 6,
85 9, and 12 months was comparable to controls (Kalil-Manesh *et al.*, 1993). No morphological changes
86 were observed in the kidney.

87 To weigh in on these recent hypotheses, we investigated the associations between Cd and Pb
88 blood and urine levels with renal dysfunction in NHANES 2007-2012. We assessed whether the
89 association of blood and urine Pb- and particularly Cd-levels with eGFR and albuminuria is consistent

with the patterns described by Akerstrom *et al.* (2013) and others, which have called into question the direct causal relationship of low level metal exposure leading to reduced kidney function. To facilitate the comparison of the potential associations between renal outcomes with blood metals and urine metals, we restricted our analyses to adult participants (≥ 20 years of age) who had both urinary and blood measures of Pb and Cd. Our analyses confirm findings from recent studies of a positive relationship between U-Cd and eGFR, associated with a concurrent inverse relationship between B-Cd and eGFR at low levels of Cd exposure using current NHANES data. Furthermore, we report a previously unidentified positive relationship between U-Pb and eGFR.

102 **METHODS**

103 ***Study Population***

104 NHANES is a cross-sectional, nationally representative survey of the non-institutionalized
105 civilian population of the United States conducted by the National Center for Health Statistics (NCHS),
106 Centers for Disease Control and Prevention (CDC) (NCHS 2008). Beginning in 1999, the survey was
107 conducted continuously and released in 2-year cycles. For our study we merged the publicly available
108 files for NHANES cycles 2007-2008, 2009-2010, and 2011-2012 using the NCHS recommendations
109 (NCHS 2013a, b). The survey employs a multistage stratified probability sample based on selected
110 counties, blocks, households, and persons within households. The NHANES 2007-2010 and 2011-2012
111 study protocols are approved by the National Center for Health Statistics Institutional Review Board
112 (Protocol #2005-2006 and Protocol #2011-17, respectively
113 <http://www.cdc.gov/nchs/nhanes/irba98.htm>).

114 In the 2007-2008, 2009-2010, and 2011-2012 data sets, urinary concentrations of cadmium and
115 lead were measured in a randomly selected one-third subsample. For our analysis, we included all
116 participants who had measurements for U-Cd, U-Pb, B-Cd, and B-Pb. Pregnant and breastfeeding
117 women were excluded.

118

119 ***Exposure Measurements***

120 Whole blood Pb and Cd concentrations were determined using inductively coupled plasma mass
121 spectrometry. Cd and Pb in spot urine specimens were measured by inductively coupled plasma-mass
122 spectrometry using a multi-element analytical technique. Levels below the limit of detection were
123 entered as the limit of detection divided by the square root of two. Blood Cd, B-Pb, U-Cd, and U-Pb
124 were categorized as weighted quartiles based on the distribution of blood and urine metal levels among
125 the study population, resulting in approximately the same number of participants within each quartile. A
126 total of 973 of the 4875 participants had B-Cd values below the limit of detection (LOD 2007–2012:

0.20 µg/l), so these were considered the referent lowest Cd quartile. The LOD for B-PB was 0.25 µg/dl, for U-PB was 0.1 µg/l for NHANES 2007-2010 and 0.08 µg/l for NHANES 2011-2012, for U-Cd was 0.042 µg/l for NHANES 2007-2010 and 0.056 µg/l for NHANES 2011-2012. The percent of participants at or above the LOD were: 99.61 for B-Pb, 96.55 for U-Pb and 91.87 for U-Cd,

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132 ***Renal Outcomes***

Urinary albumin (ALB) was measured in spot urine samples by solid-phase fluorescence immunoassay. The lower limit of detection for the assay is 0.3 µg/mL. Urinary creatinine was measured by the modified kinetic Jaffe' method. The ratio of albumin to creatinine (ACR) was reported in milligrams per gram and categorized by using 30 mg/g as a cutoff; albuminuria is considered to be present when ACR is greater than 30 mg/g (Levey *et al.*, 2003). ACR was not normally distributed, thus it was natural log-transformed and the results were re-transformed by exponentiation of the β coefficients and presented as percent differences estimated by comparing each of the upper three quartiles to the lowest quartile using the formula $100 \times (e^{\beta} - 1)$.

Estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation 1 : $eGFR \text{ (mL/minute/1.73 m}^2\text{)} = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ if female} \times 1.159 \text{ if non-Hispanic-black}$, where SCr is 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. Analyses using the Modification of Diet in Renal Disease Study formula for the eGFR held the same significant

associations (data not shown). Chronic Kidney Disease was defined as $\text{eGFR} < 60 \text{ mL/minute/1.73m}^2$ (Levey *et al.*, 2009).

Covariates

We obtained information about age (continuous, years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican-American, Other Hispanic, or Other), and education (less than high school, completed high school, or more than high school) from the household interview. Alcohol consumption (amount consumed per week, categorized as no alcohol, 1-4 drinks/week, of >4 drinks/week) and self-reported smoking status (current smoker, former smoker, or never smoker) were obtained from the physical examination and associated questionnaire. Body mass index (BMI) was obtained from the physical examination and calculated by dividing measured weight in kilograms by measured height in meters squared. Body weight status was classified as normal/underweight, overweight, and obese with BMI measures of <25 , $25-29.9$, and ≥ 30 , respectively. Diabetes status was defined as glycated hemoglobin (A1C) $\geq 6.5\%$, or self-reported current use of insulin or oral hypoglycemic agents. Hypertension was defined as self-reported current use of an antihypertensive medication, or systolic BP ≥ 140 mmHg, or diastolic BP ≥ 90 mmHg. The self-reported weak/failing kidney was obtained from the Kidney Conditions questionnaire.

Serum creatinine was measured by the modified kinetic method of Jaffe. Urinary creatinine was determined using a Jaffe rate reaction measured with a CX3 analyzer. To account for variation in dilution in spot urinary samples, urinary creatinine was entered into the models as an independent variable, as suggested by previous studies (Barr *et al.* 2005; Ikeda *et al.* 2003). Because the distribution of this variable was not normal, we log-transformed it in analyses. Serum cotinine, a biomarker of environmental tobacco smoke, was categorized as weighted quartile based on the distribution among the study population. In our analyses we did not exclude participants with self-reported diagnosis of kidney cancer. However, analyses including, also, as independent variable the self-report diagnosis of kidney

cancer (obtained from the medical questionnaire), did not change the the results of our primary analyses (data not shown).

Statistical analysis

Sample weights were used for analyses to account for the complex sampling design and non-response of NHANES. Weights for combined NHANES survey cycles were calculated according to NHANES guidelines (NCHS 2008b). Because urinary heavy metals are measured only in a subsample of the participants, specific urinary metal subset sample weights were used in the models with U-Pb and U-Cd. All other analyses used the exam sample weights. We estimated sampling errors using the Taylor series linearized method. We used multivariate linear regression to calculate adjusted β -coefficients, using models without (Model 1) and with (Model 2) inclusion of B-Cd (for Pb analyses) and B-Pb (for Cd analyses). We looked at the interaction terms between the metal concentrations (ln-transformed) and the covariates included in the models. The only statistically significant interaction was found with age, which supports the known association between age and decreasing kidney function.

We also assessed the collinearity between blood and urine metal measures using Pearson correlation coefficients and multicollinearity diagnostic statistics (tolerance and variance inflation factors [VIF]). A value of $VIF \geq 10$ often indicates multicollinearity. No covariates were multicollinear with each other. There was a moderate correlation between blood and urine measures as indicated by the Spearman correlation coefficients ($r = 0.56$, $p < 0.001$ for B-Pb and U-Pb; $r = 0.27$, $p < 0.0001$ for B-Pb and U-Cd; $r = 0.46$, $p < 0.001$ for B-Cd and U-Cd; and $r = 0.17$, $p < 0.0001$ for B-Cd and U-Pb).

SAS 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses and SAS-Callable SUDAAN 10 (Research Triangle Institute, Research Triangle Park, NC) was used to account for the NHANES complex sample design. P-values were presented at the significance level < 0.05 . Statistical

195 tests for linear trends were conducted by modeling quartiles as an ordinal variable using integer values
196 and p-value for trend based on Wald test.

197

198 RESULTS

199 The geometric mean age for the 4,875 study participants was 44.1 years, and there was an
 200 approximately equal representation of men and women. The geometric mean B-Cd concentrations was
 201 0.35 µg/L and the geometric mean B-Pb level was 1.23 µg/dL. The geometric mean U-Cd
 202 concentrations was 0.22µg/L and the geometric mean U-Pb level was 0.45 µg/L. 418 individuals had
 203 eGFR <60 mL/minute/1.73 m² (weighted percentage 6.13%) a filtration rate indicative of CKD, and 584
 204 individuals (weighted percentage 8.79%) presented with urinary albumin/creatinine ratio (ACR) ≥
 205 30mg/g, a ratio indicating potential albuminuria. Table 1 presents additional characteristics of the study
 206 populations.

207 Table 2 presents the mean change in eGFR with quartile levels of B-Cd, B-Pb, U-Cd, and U-Pb,
 208 with the β values representing the change in eGFR (mL/minute/1.73 m²) comparing the three highest
 209 quartiles to their respective referent lowest quartile. The two highest B-Cd quartiles (Q3 and Q4)
 210 showed statistically significant inverse associations with eGFR levels, with a statistically significant
 211 increase in the strength of association moving from lowest quartile (Q1) to Q4 indicating evidence of
 212 dose-response (Models 1 and 2).

213 Blood Pb Q3 and Q4 were inversely associated with eGFR (Model 1), with a similarly
 214 significant increase in the strength of association moving from Q1 to Q4; when B-Cd was added (model
 215 2), B-Pb Q4 was still significantly associated, but the statistically significant trend moving from Q1 to
 216 Q4 was lost. Conversely, U-Cd and U-Pb Q3 and Q4 showed statistically significant positive
 217 associations with eGFR (Models 1 and 2). There was a significant increase in the strength of association
 218 moving from Q1 to Q4 for U-Pb in models 1 and 2 and for U-Cd in model 1, with a marginally
 219 significant association in U-Cd model 2 (p = 0.06).

Table 3 presents the percent change in ALB with quartile levels of B-Cd, B-Pb, U-Cd and U-Pb.

Overall, we found that U-Cd Q2, Q3 and Q4 were associated with statistically significantly higher excretion of ALB, both with (model 2) and without (model 1) inclusion of B-Pb in the model, with evidence of a dose-response relationship (p trend <0.001). No significant associations were found between B-Cd, U-Cd, or U-Pb and ALB in any of the models. Analyses without urinary creatinine as independent variable confirm the similar statistic association of U-Cd with ALB (Supplemental Table 1)

As complementary analyses, we used log natural-transformed urinary and blood Cd and Pb levels. These analyses showed similar results to those using weighted quartiles in all participants (Table 4).

232 DISCUSSION

233 In our study, we found that with increased eGFR, there is increased U-Cd and U-Pb excretion.
 234 Conversely, eGFR was inversely associated with increased B-Cd and B-Pb. To our knowledge, this is
 235 the first study to demonstrate both the positive associations of U-Cd and U-Pb and the inverse
 236 associations of B-Cd and B-Pb with eGFR using the most recent NHANES data, a larger and more
 237 nationally representative dataset than that which has been used by previous studies describing these
 238 interesting associations.

239 Our findings are also consistent with studies conducted on previous NHANES cycles. Navas-
 240 Acien *et al.*, (2009) investigated associations of B-Cd and B-Pb with CKD in 14,778 adults (≥ 20 years
 241 of age) using NHANES 1999-2006. They found that the fully adjusted highest quartiles of both B-Cd
 242 and B-Pb were statistically significantly associated with higher odds of CKD (OR=1.32, 95% CI: 1.04,
 243 1.68 and OR=1.56, 95% CI: 1.17, 2.08, respectively). Additionally, they found higher odds ratios for
 244 ACR in the third and fourth quartiles of B-Cd (OR=1.32, 95% CI: 1.07, 1.64 and OR=1.92, 95% CI:
 245 1.53, 2.43, respectively) but no association with B-Pb (Navas-Acien *et al.*, 2009). Ferraro *et al.*, (2010),
 246 in addition to studying the association between B-Cd and CKD in a subset of participants in the same
 247 NHANES dataset (1999-2006) that had both U-Cd and B-Cd measurements, further investigated the role
 248 of U-Cd in renal outcomes. Using B-Cd as a dichotomous variable ($\leq 1 \mu\text{g/L}$ and $> 1 \mu\text{g/L}$), they
 249 confirmed the positive association between B-Cd and CKD (OR=1.48, 95% CI: 1.01, 2.17) as well as
 250 with ACR (OR=1.41 95% CI: 1.10, 1.82). When investigating U-Cd, they found an inverse, though not
 251 statistically significant, association with CKD in individuals with U-Cd levels $> 1 \mu\text{g/g}$ creatinine
 252 compared to those with U-Cd $\leq 1 \mu\text{g/g}$ creatinine (OR=0.70, 95% CI: 0.47, 1.04) (Ferraro *et al.*, 2010).
 253 Therefore, our results of positive associations between U-Cd and inverse associations of B-Cd and B-Pb
 254 with eGFR are consistent with the previous findings related to CKD, as reduced eGFR is an indicator of
 255 CKD.

256 While the cross-sectional nature of our study design prevents definitive assessment of the causal
257 directionality underlying any associations described, the positive relationship between eGFR and U-Cd,
258 and the inverse association between eGFR and B-Cd may be consistent with the hypothesis of reverse
259 causality put forward by Chaumon *et al.*, (2012) and Akerstrom *et al.*, (2013), among others. Reverse
260 causality predicts that reduced eGFR will decrease the total filtration of the chemical substances and
261 consequently lead to decreased levels in the urine and increased levels in the blood.

262 Furthermore, the association we observed between U-Cd and ALB may point to a co-excretion
263 function of the kidney, as suggested in recent studies (Akerstrom *et al.*, 2013; Chaumont *et al.*, 2012;
264 Evans and Elinder 2011; Haddam *et al.*, 2011). Haddam *et al.*, (2011) found that urinary albumin did
265 not correlate with B-Cd, but was consistently associated with U-Cd through a relationship that was
266 unaffected by age, smoking, or diuresis. However, the authors do note that co-excretion of retinol-
267 binding protein (RBP) may be influencing the association between albumin and U-Cd (Haddam *et al.*,
268 2011). Chaumont *et al.* (2012) in a cross-sectional study of 736 adolescents reported associations
269 between B-Cd, B-Pb, U-Cd, and U-Pb with concentrations of urinary albumin and the low-molecular
270 weight (LMW) proteins RBP and β 2-microglobulin (β 2m). They argued that the overall evidence favors
271 a non-causal association originating from the co-excretion of Cd- or Pb-binding proteins with LMW
272 proteins; because of evidence that Cd and Pb primarily circulate while bound to LMW proteins, the
273 observed associations at low exposures might simply reflect the inter-individual variations in the renal
274 uptake of proteins sharing the same affinity for tubular binding sites (Chaumont *et al.*, 2012). Two
275 mechanisms leading to protein-metal co-excretion were proposed: 1) the physiological variation in
276 fractional uptake of proteins by proximal tubules when ALB is low, which may account for the non-
277 threshold linear relationships between U-RBP and U-Cd and between U- β 2m and U-Pb found in the
278 adolescents with no increase of ALB; or 2) competitive inhibition of LMW protein reabsorption by

279 ALB, which is the only protein whose concentration can markedly increase in tubular fluid in the
 280 absence of renal failure (Chaumon *et al.*, 2012). Akerstrom *et al.*, (2013) in a study among 30 non-
 281 smoking healthy adults found U-Cd excretion was positively associated with ALB excretion as well as
 282 urinary LMW protein α -1-microglobulin (A1M). They also found significant positive associations of
 283 urinary flow with excretion of U-Cd, ALB, and U-A1M, suggesting that the association in individuals
 284 with low-level exposure to Cd is unlikely caused by Cd toxicity but instead results from normal
 285 variation in renal function, including changes in urinary flow that may influence the urinary excretion of
 286 both Cd and proteins in the same direction.

287 Other plausible hypotheses are also supported by our findings. The first, suggested by Weber *et*
 288 *al.* (2011b), is that low-level Cd and Pb exposure can lead to glomerular hyperfiltration, which can be
 289 indicative of kidney damage. While prospective studies on the nephrotoxic effects of low-level Cd
 290 exposure are lacking, several studies conducted among the general population reported an association of
 291 higher B-Pb with lower glomerular filtration rate using both cross-sectional and prospective designs
 292 (Fadrowski *et al* 2010; Kim *et al.*, 1996; Muntner *et al.*, 2003; Staeesen *et al.*, 1990, 1992; Yu *et al.*,
 293 2004). In our study, we describe a similar association between B-Pb and eGFR. However, we believe
 294 that the positive association we found is not necessarily reflective of the same causal relationship
 295 described in prospective studies, which establishes the nephrotoxic potential of low-level Pb exposure,
 296 because of the differences in Pb levels between our study and the others. While still classified as “low-
 297 level exposure,” Yu *et al.* (2004) and Kim *et al.* (1996) both report mean B-Pb levels between 2.5 and 8
 298 times greater than those described in this study.

299 Another alternative hypothesis was proposed by Weaver *et al.* (2011a) in a study investigating
 300 low-level U-Cd and eGFR in 712 lead workers. Multivariate linear analyses showed that higher ln-
 301 transformed U-Cd was associated with lower serum creatinine, higher calculated creatinine clearance,
 302 and higher eGFR (β coefficient for eGFR=8.7 mL/min/1.73m², 95% CI: 5.4, 12.1). In a follow-up

analysis of the same population, Weaver *et al.*, (2011b) confirmed their previous findings between ln-transformed U-Cd and higher creatinine-based eGFR. In this follow-up study, they also examined the association between U-Cd and serum cystatin C measures to try and elucidate a potential mechanism for their previous finding of an inverse association. They found that U-Cd was not associated with cystatin C outcomes, thus suggesting that the association seen between U-Cd and eGFR may be a “creatinine-specific mechanism rather than a kidney function mechanism” (Weaver *et al.*, 2011b). In our analyses, we could not confirm Weaver *et al.*,’s suggestion of a creatinine-based mechanism for the inverse association between U-Cd and renal outcomes because cystatin C measurement is not available in NHANES 2007-2012.

This study used the NHANES 2007-2012 dataset, a large, national survey whose findings are generalizable to the U.S. adult non-institutionalized population. Although there are strengths to this study including its large sample-size and random sampling, there are important limitations to note. The cross-sectional design is unable to definitively assess questions of causality (and reverse causality), although it can be beneficial in refining and supporting hypotheses. While our findings are consistent with the hypothesis of reverse causation, the relationship of blood and urinary Cd concentrations at low levels of exposure with kidney dysfunction is a complex one that cannot be fully assessed using cross-sectional data alone. Further mechanistic studies using animal models and human prospective cohort research are necessary to assess this relationship.

The use of blood and urine Cd and Pb levels as markers for exposure is further complicated by the deposition of these metals within the body; Cd selectively accumulates in the renal cortex, which has over 50% of the body burden of cadmium (ATSDR 2012), whereas Pb accumulates in bone, with bone Pb levels accounting for over 90% of the total body burden (ATSDR 2007). Therefore, the levels of B-Cd and blood and urine Pb may not be the best indications of total body burden. Furthermore, the use of a single spot urine sample for U-Cd and U-Pb is a limitation in our analyses. The pattern observed in

the association between U-Pb and eGFR should also be assessed with the caveat that a single-spot U-Pb measure is not a very reliable assay. Urinary Pb measures are reflective of Pb that has diffused from the plasma and excreted through the kidneys, and these measures can be useful when collected for long-term biomonitoring. A single spot urine sample, as assessed in this study, may be unreliable because it can be subjected to biological variations. However, the use of a single spot measure may be acceptable when there is a creatinine excretion correction factor included in analyses (Barbosa et al. 2005). Therefore, while the use of a single-spot U-Pb measure may be limited, we have tried to lessen this impact by including urinary creatinine in the analysis. Finally, although we controlled for many of the known factors associated with renal outcomes, other genetic and environmental factors may have influenced our findings.

CONCLUSION

Despite the continuous decrease in blood Cd and Pb levels in the U.S. population, we confirmed the previously reported associations between B-Cd and B-Pb levels with adverse renal outcomes. However, the inverse direction of the associations of U-Cd and U-Pb may suggest that, at this low-level exposure, the results may also be attributed to a reverse causation action: a decreased glomerular filtration will result in a build-up of Cd and Pb in the blood, with a contemporarily decrease of urinary excretion of Cd and Pb. If these associations are due to reverse causation, they may be important both from a clinical and public health prospective because subjects with decreased glomerular filtration may retain the compounds, which may potentially exacerbate their toxic effects in the kidney and other organs.

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517 **Table 1: Sample size (N) and weighted characteristics of adult participants (≥ 20 years of age) with**
 518 **blood lead, blood cadmium, urinary lead and urinary cadmium in NHANES 2007-2012.**
 519

	n	Weighted
Urinary Cadmium ($\mu\text{g/L}$), GM (SE)	4875	0.22 (0.00)
Urinary Cadmium ($\mu\text{g/L}$), Mean (Lower 95%, Upper 95%)		0.35 (0.34, 0.37)
Urinary Lead ($\mu\text{g/L}$), GM (SE)	4875	0.45 (0.01)
Urinary Lead ($\mu\text{g/L}$), Mean (Lower 95%, Upper 95%)		0.70 (0.64, 0.76)
Blood Cadmium ($\mu\text{g/L}$), GM (SE)	4871	0.35 (0.01)
Blood Cadmium ($\mu\text{g/L}$), Mean (Lower 95%, Upper 95%)		0.51 (0.49, 0.52)
Blood Lead ($\mu\text{g/dL}$), GM (SE)	4871	1.23 (0.02)
Blood Lead ($\mu\text{g/dL}$), Mean (Lower 95%, Upper 95%)		1.58 (1.49, 1.67)
Age (Years), GM (SE)	4875	44.10 (0.49)
BMI(kg/m^2), GM (SE)	4875	27.88 (0.13)
Serum Cotinine (ng/mL), GM (SE)	4875	0.31 (0.03)
Serum Creatinine (mg/dL), GM (SE)	4875	0.85 (0.00)
eGFR (mL/minute/1.73 m^2) GM (SE)	4875	91.95 (0.58)
Urinary Creatinine (mg/dL), GM (SE)	4874	92.16 (1.44)
Urinary Albumin	4874	7.42 (0.16)
Urinary Albumin/Urinary Creatinine Ratio	4874	8.05 (0.16)
Sex		
Men	2481	49.53 (0.67)
Women	2394	50.47 (0.67)
CKD		
Yes, % (SE)	418	6.13 (0.46)
No, % (SE)	4457	93.87 (0.46)
ACR		
Yes, % (SE)	584	8.79 (0.51)
No, % (SE)	4290	91.21 (0.51)
Hypertension*		
Yes, % (SE)	1831	32.08 (0.85)
No, % (SE)	3044	67.92 (0.85)

Diabetes**

Yes, % (SE)	556	8.03 (0.48)
No, % (SE)	4319	91.97 (0.48)

Body Weight

Underweight/Normal weight,, % (SE)	1462	32.31 (1.09)
Overweight, % (SE)	1615	33.26 (1.17)
Obese, % (SE)	1798	34.43 (1.03)

Self-reported Smoking Status

Current Smoker, % (SE)	1031	21.01 (0.84)
Former Smoker, % (SE)	1205	24.87 (0.96)
Never Smoked, % (SE)	2639	54.12 (1.15)

Self-reported Alcohol Consumption

No Alcohol, % (SE)	1588	27.08 (1.04)
1-4 drinks per week, % (SE)	2889	64.65 (1.34)
>4 drinks per week, % (SE)	398	8.26 (0.64)

Education Status

Less than High School % (SE)	1347	18.23 (1.08)
Completed High School % (SE)	1092	22.42 (1.07)
More than High School % (SE)	2436	59.35 (1.60)

Race/ethnicity

White (Non-Hispanic) % (SE)	2203	69.30 (2.08)
Non-Hispanic Black % (SE)	990	10.86 (1.083)
Mexican-American % (SE)	744	7.87 (1.08)
Other Hispanic % (SE)	533	5.75 (0.85)
Other % (SE)	405	6.22 (0.66)

Weak/Failing Kidney

Yes, % (SE)	128	2.31 (0.35)
No, % (SE)	4738	97.69 (0.35)

520 Hypertension was defined as self-reported current use of an antihypertensive medication, or systolic BP $\geq$ 140 mmHg, or
521 diastolic BP $\geq$ 90 mmHg. **Diabetes status was defined as glycated hemoglobin (A1C) > 6.5% or self-reported current use of
522 insulin or oral hypoglycemic agents
523

Table 2: Adjusted β -coefficient (95% CIs) of eGFR (mL/minute/1.73 m²) by blood cadmium, blood lead, urinary cadmium, and urinary lead.

	Model 1^a	Model 2^b
B-Cd Quartile^c		
B-Cd Q1	0.00	0.00
B-Cd Q2	-1.08 (-2.96, 0.80)	-0.91 (-2.75, 0.93)
B-Cd Q3	-2.44 (-4.79, -0.09)	-2.11 (-4.40, 0.18)
B-Cd Q4	-4.29 (-6.48, -2.10)	-3.66 (-5.81, -1.50)
<i>p</i> trend	0.01	0.03
B-Pb Quartile^c		
B-Pb Q1	0.00	0.00
B-Pb Q2	-1.35 (-3.10, 0.41)	-1.17 (-2.91, 0.57)
B-Pb Q3	-2.02 (-4.00, -0.05)	-1.62 (-3.60, 0.36)
B-Pb Q4	-3.27 (-5.39, -1.16)	-2.67 (-4.78, -0.56)
<i>p</i> trend	0.02	0.08
U-Cd Quartile^c		
U-Cd Q1	0.00	0.00
U-Cd Q2	1.01 (-0.80, 2.83)	1.36 (-0.45, 3.17)
U-Cd Q3	1.92 (0.20, 3.64)	2.43 (0.71, 4.15)
U-Cd Q4	2.69 (0.34, 5.03)	3.55 (1.22, 5.89)
<i>p</i> trend	0.12	0.03
U-Pb Quartile^c		
U-Pb Q1	0.00	0.00
U-Pb Q2	3.72 (2.11, 5.33)	3.99 (2.40, 5.59)
U-Pb Q3	5.59 (3.77, 7.41)	5.96 (4.13, 7.78)
U-Pb Q4	7.73 (5.71, 9.76)	8.51 (6.46, 10.55)
<i>p</i> trend	<0.01	<0.01

^aModel 1: adjusted for age, race/ethnicity, sex, diabetes, alcohol intake, education, smoking status, body weight, hypertension, weak/failing kidney, serum cotinine, and ln urinary creatinine (for the urinary models only)

^bModels 2: included the variables in model 1 and blood lead (ln µg/dL) for blood cadmium and urinary cadmium models; and blood cadmium (ln µg/dL) for blood lead and urinary lead models

^cBlood Cadmium Quartiles (µg/L): Q1: <0.20; Q2: 0.20-0.31; Q3: 0.32-0.57; Q4: >0.57; Blood Lead Quartiles (µg/dL): Q1: ≤0.79; Q2: 0.80-1.20; Q3: 1.21-1.82; Q4: >1.82; Urinary Cadmium Quartiles (µg/L): Q1: <0.111; Q2: 0.111-0.216; Q3: 0.217-0.421; Q4: >0.421; Urinary Lead Quartiles (µg/L): Q1: ≤0.25; Q2: 0.26-0.46; Q3: 0.47-0.79; Q4: >0.79.

Table 3: Percent differences (95% CIs) in ALB by blood cadmium, blood lead, urinary cadmium, and urinary lead.

	Model 1^a	Model 2^b
B-Cd Quartile^c		
B-Cd Q1	referent	referent
B-Cd Q2	-2.27 (-11.57, 7.90)	-2.57 (-11.84, 7.68)
B-Cd Q3	1.51 (-7.23, 11.18)	0.90 (-7.69, 10.41)
B-Cd Q4	10.30 (-3.44, 25.86)	8.98 (-4.88, 24.86)
<i>p</i> trend	0.31	0.38
B-Pb Quartile^c		
B-Pb Q1	referent	referent
B-Pb Q2	-3.05 (-13.06, 8.33)	-4.02 (-13.76, 6.93)
B-Pb Q3	-7.23 (-17.30, 4.08)	-9.24 (-19.43, 2.22)
B-Pb Q4	9.86 (-2.96, 24.61)	6.29 (-6.39, 20.80)
<i>p</i> trend	0.02	0.02
U-Cd Quartile^c		
U-Cd Q1	referent	referent
U-Cd Q2	18.06 (6.18, 31.26)	17.82 (6.08, 31.00)
U-Cd Q3	32.05 (20.08, 45.21)	31.52 (19.48, 44.77)
U-Cd Q4	44.34 (26.74, 64.38)	43.48 (26.24, 63.07)
<i>p</i> trend	<0.001	<0.001
U-Pb Quartile^c		
U-Pb Q1	referent	referent
U-Pb Q2	6.82 (-5.07, 20.20)	5.97 (-5.73, 19.12)

U-Pb Q3	2.63 (-8.52, 15.14)	1.61 (-9.34, 13.88)
U-Pb Q4	14.00 (-0.10, 30.21)	11.29 (-2.08, 26.49)
<i>p</i> trend	0.09	0.17

^aModel 1: adjusted for age, race/ethnicity, sex, diabetes, alcohol intake, education, smoking status, body weight, hypertension, weak/failing kidney, serum cotinine, and ln urinary creatinine (for the urinary models only)

^bModel 2: included the variables in model 1 and blood lead (ln µg/dL) for blood cadmium model; blood cadmium (ln µg/dL) for blood lead model; or blood lead (ln µg/dL) and blood cadmium (ln µg/dL) for the urinary lead or urinary cadmium quartiles.

^cBlood Cadmium Quartiles (µg/L): Q1: <0.20; Q2: 0.20-0.31; Q3: 0.32-0.57; Q4: >0.57; Blood Lead Quartiles (µg/dL): Q1: ≤0.79; Q2: 0.80-1.20; Q3: 1.21-1.82; Q4: >1.82; Urinary Cadmium Quartiles (µg/L): Q1: <0.111; Q2: 0.111-0.216; Q3: 0.217-0.421; Q4: >0.421; Urinary Lead Quartiles (µg/L): Q1: ≤0.25; Q2: 0.26-0.46; Q3: 0.47-0.79; Q4: >0.79.

Table 4: Adjusted β -coefficient (95% CI) of eGFR (mL/minute/1.73 m²) and ALB (mg/g creatinine) by log-natural transformed blood cadmium, blood lead, urinary cadmium, and urinary lead

	eGFR β -coefficient (95% Ci)	ALB Percent change (95%CI)	
	Model 2 ^a	Model 2 ^a	Model 2 ^b
All Participants			
Ln B-Cd	-1.57 (-2.76, -0.28)	9.09 (2.43, 16.30)	
Ln B-Pb	-1.59 (-2.75, -0.42)	2.02 (-4.40, 8.76)	
Ln U-Cd	1.75 (0.81, 2.70)	19.84 (14.11, 25.86)	8.55 (5.13, 12.08)
Ln U-Pb	3.77 (2.88, 4.65)	3.46 (-1.78, 8.98)	0.80 (-2.86, 4.71)

^aModel adjusted for age, race/ethnicity, sex, diabetes, alcohol intake, education, smoking status, body weight, hypertension, weak/failing kidney, serum cotinine, ln urinary creatinine (for the urinary models only); and blood lead (ln $\mu\text{g/dL}$) for blood cadmium and urinary cadmium models or blood cadmium (ln $\mu\text{g/dL}$) for blood lead and urinary lead models.

^bModel without urinary creatinine.