Susceptibility to Environmental Heavy Metal Toxicity among Americans with Kidney Disease

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Key Points
- Impaired kidney function is associated with higher lead blood levels yet, simultaneously, lower amounts of urinary lead excretion.
- These findings suggest an increased susceptibility to progressive lead accumulation from even low levels of environmental exposure.
- Further research into the public health consequences of heavy metal exposure is needed, particularly among vulnerable populations.

Abstract

Background The consequences of low levels of environmental heavy metal exposure, as found widely in the United States, in those with impaired renal function remain underexplored.

Methods We examined the cross-sectional association of indices of renal function with lead and cadmium levels in blood and urine among National Health and Nutrition Examination Survey (NHANES) participants. We used the 1999–2002 cycle, which included measures of cystatin C, in order to quantify renal function most precisely and defined chronic kidney disease (CKD) as an estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m².

Results In weighted and adjusted analyses of 5638 participants, lead levels were 0.23 (95% CI, 0.03 to 0.42) μg/dl higher among participants with CKD, and 0.05 (95% CI, 0.01 to 0.09) μg/dl higher per 10 ml/min per 1.73 m² lower eGFR. Cadmium levels were 0.02 (95% CI, 0.01 to 0.03) μg/L higher per 10 ml/min per 1.73 m² lower eGFR. Black race significantly modified the association of lower eGFR with higher circulating lead levels (P interaction < 0.001). A 10 ml/min per 1.73 m² lower eGFR was associated with a 0.13 (95% CI, 0.06 to 0.21) μg/dl higher lead level among Black participants compared with 0.03 (95% CI, −0.04 to 0.11) μg/dl higher level among White participants. Among the 1852 participants with urinary metal measurements, despite higher circulating levels, those with CKD had significantly lower urinary lead levels (−0.16 [95% CI, −0.30 to −0.01] ng/ml) and urinary lead/creatinine ratios (−0.003 [95% CI, −0.004 to −0.001]).

Conclusions CKD is associated with higher blood lead levels, particularly among Blacks, and simultaneously, lower urinary lead levels, consistent with the hypothesis that CKD confers a state of heightened susceptibility to heavy metal environmental exposure by reducing its elimination. Given that low levels of exposure remain highly prevalent in the United States, further efforts to protect patients with CKD from heavy metal toxicity may be warranted.

Introduction

Although environmental and consumer regulations have reduced the overall levels of heavy metal contamination over the last several decades, low levels of exposure remain widespread. In addition to lead paint that remains common in older homes, the aging infrastructure of water systems throughout the United States confers daily exposure to lead for many individuals (1). Similarly, cadmium is in many products, including batteries, pigments, metal coatings, plastics, and cigarette smoke, and exposure occurs through ingestion of contaminated foodstuffs or inhalation (2).

Although low levels of exposure may be of less clinical significance for healthy adults, children are particularly susceptible, in part due to higher proportions absorbed across the gastrointestinal tract and rapid cell metabolism. Whether CKD may confer a similar heightened susceptibility is largely unknown. Studies demonstrating an association between lead (3–7) and cadmium (8,9) and kidney disease have primarily

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been interpreted as causative due to the toxic effect on proximal tubular function. However, the possibility of reverse causality, whereby impaired renal function results in higher circulating blood levels and thus greater long-term toxicity to other organs, has not been fully clarified. Furthermore, because heavy metal toxicity disproportionately affects minoritized racial and ethnic populations, who simultaneously have higher rates of CKD, understanding the hazard from environmental toxins is of public health urgency.

Accordingly, in a representative sampling of US individuals, we describe the associations of renal function with circulating and urinary lead and cadmium levels and whether these associations are consistent across racial and ethnic strata. We hypothesized that renal function would be associated with higher circulating but reduced urinary levels, suggesting reduced excretion, which might be expected to increase long-term toxicity.

**Materials and Methods**

The National Health and Nutrition Examination Survey (NHANES) is a complex, multistage probability sample of the US civilian, noninstitutionalized population designed to assess the health and nutritional status of adults and children. It combines granular historical, physical, and laboratory examinations to provide nationally representative data at 2-year cycles, with no repeat individual measurements. For our primary analyses, we used cycles 1999–2000 and 2001–2002 because they included measures of cystatin C in all participants aged ≥60 years and a 25% random sample of participants aged 12–59 years. Of those with measures of cystatin C, 5638 participants also had measures of lead and cadmium concentrations in blood, and these individuals comprised the primary dataset. All participants provided informed consent, and the NHANES study protocol was approved by the National Center for Health Statistics Research Ethics Review Board.

The 2012 CKD-EPI cystatin C equation was used to calculate participants’ eGFR, which was examined continuously and according to standard definitions of CKD (<60 ml/min per 1.73 m²). Whole blood lead and cadmium concentrations were determined using inductively coupled plasma mass spectrometry. Extreme outliers of lead and cadmium were replaced at the 99.5th percentile (13.5 g/dl for lead and 2.8 µg/L for lead and cadmium, respectively). Levels of lead and cadmium were below the limit of detection among 122 (2%) and 1339 (24%) individuals, respectively, for whom the value was the detection limit (0.2 µg/dl for lead and 0.2 µg/L for cadmium) divided by the square root of two. Additional variables included age, sex, race and ethnicity, family income, number of individuals per household, and citizenship status. For the purpose of this study, self-reported race and ethnicity was categorized into White, Black, Hispanic, and other/unknown. Median household income was categorized as ≤$19,999, $19,999–$34,999, $35,000–$64,999, and ≥$65,000.

Unweighted participant characteristics and estimates of heavy metal concentration are provided according to renal function. We used multivariate linear regression adjusted for all variables above and accounting for the survey sampling scheme to examine the association between eGFR and lead and cadmium levels. Multiyear sample weights were used to obtain unbiased estimates comparable to the US population estimates for all analyses. We used multiplicative interaction terms between Black race and Hispanic ethnicity and eGFR to examine for effect modification, and we provided the stratified results when significant (P<0.05). To estimate heavy metal excretion, we examined spot urinary heavy metal concentrations and metal to creatinine concentrations to account for urinary concentration among 1852 participants with available measures. Secondarily, to explore the effect of newly recommended race free estimates of renal function, we used the 2021 CKD-EPI cystatin and creatinine and the 2021 CKD-EPI creatinine equations in our primary analyses. In addition, to provide more contemporary estimates, we examined the NHANES 2017–2020 cycle, using the 2021 CKD-EPI creatinine equation.

Analyses were performed using JMP Pro 15 and SAS v9.4 (SAS Institute, Cary, NC).

**Results**

Of the 5638 NHANES participants in the 1999–2002 cycles with measured cystatin levels, 17% (n=989) had CKD (Table 1). The unweighted mean (SD) estimates of lead and cadmium in blood were 2.3 (1.9) µg/dl and 0.54 (0.41) µg/L, respectively, and these correlated indirectly with renal function (Figure 1). Compared with those with an eGFR >60 ml/min per 1.73 m², participants with CKD had significantly higher mean levels of lead and cadmium (3 [2.1] versus 2.1 [1.8] µg/dl and 0.65 [0.4] versus 0.51 [0.41] µg/L, respectively).

In weighted and adjusted analyses, a 10 ml/min per 1.73 m² lower eGFR was associated with a 0.05 (95% CI, 0.01 to 0.09) µg/dl higher lead concentration and 0.02 (95% CI, 0.01 to 0.03) µg/L higher cadmium concentration (Table 2). Blood levels of lead, but not cadmium, were significantly

Table 1. Characteristics of 1999–2002 participants

| Characteristics       | Normal Kidney Function (N=4649) | CKD (N=989) |
|-----------------------|---------------------------------|-------------|
| Age, yr               | 46.3 (23.1)                     | 74.6 (10.7) |
| Sex, F                | 50                              | 52          |
| Race                  |                                 |             |
| White                 | 43                              | 66          |
| Black                 | 21                              | 16          |
| Hispanic              | 32                              | 17          |
| Other                 | 3                               | 1           |
| Household income, $   |                                 |             |
| $<19,999              | 24                              | 38          |
| 20,000–34,999         | 20                              | 21          |
| 35,000–64,999         | 23                              | 16          |
| ≥65,000               | 22                              | 13          |
| Diabetes, yes         | 10                              | 23          |
| Household members, n  | 3                               | 2           |
| Citizenship, %        | 88                              | 96          |
| Whole blood lead, µg/dl | 2.1 (1.8)                | 3 (2.1)    |
| Urine lead, ng/ml     | 1.24 (1.43)                     | 1.2 (1.66)  |

Mean (SD) and column percentages provided for continuous and categorical variables, respectively. CKD defined by cystatin C eGFR <60 ml/min per 1.73 m². F, female.
higher among Black participants than among participants from other racial/ethnic groups (Table 2). Furthermore, the magnitude of the association of decreasing eGFR with lead levels was significantly higher among Black participants (multiplicative interaction between Black race and eGFR \(P\) value <0.001). Decrements of 10 ml/min per 1.73 m\(^2\) lower eGFR were associated with a 0.13 (95% CI, 0.06 to 0.21) \(\mu g/dl\) higher lead level among Black participants compared with a 0.03 (95% CI, -0.04 to 0.11) \(\mu g/dl\) higher level among White participants (Figure 2). Cadmium levels were, on average, lower among Hispanic participants, and its association with renal function was not modified by race.

CKD was associated with a 0.23 (95% CI, 0.03 to 0.42) \(\mu g/dl\) higher adjusted lead level (Table 3). CKD was not associated with differences in cadmium concentrations. Among the 1852 participants with measures of urinary metal concentrations, baseline characteristics of those with CKD with and without urinary lead measurements were similar. Compared with those with an eGFR >60 min/ml per 1.73 m\(^2\), those with CKD \((n=302)\) had higher adjusted levels of lead in the blood (0.21 [95% CI, -0.04 to 0.47] \(\mu g/dl\)) but lower levels of urinary lead excretion (0.16 [95% CI, -0.3 to -0.01] \(ng/ml\) lower urine lead concentration and 0.003 [95% CI, -0.004 to -0.001] lower urine lead/creatinine ratio; Table 3). The lower urinary lead excretion observed with CKD was consistent across racial strata (multiplicative interaction \(P\) value >0.05).

Utilizing race free creatinine-based estimates of eGFR resulted in reclassification of CKD \((n=987\) and \(n=561\) for CKD EPI cystatin-creatinine and creatinine only, respectively) but similarly higher blood and lower urinary lead levels in those with CKD compared with normal renal function (Table 3). Mean blood and urine lead levels were significantly lower in more contemporaneous NHANES data (1.04 [0.9] \(\mu g/dl\) and 0.45 [0.6] \(ng/ml\), respectively, in 2017–2020 participants), and although CKD was similarly associated with higher blood lead levels, it was not associated with urinary lead levels.

### Discussion

Individuals with CKD have higher levels of lead in blood and, simultaneously, lower levels of urinary excretion than those with normal renal function. Although lead toxicity has historically been interpreted as a potential cause of CKD, our analysis suggests that at least in part, lead

| Table 2. Adjusted change of baseline characteristics on lead and cadmium levels, weighted to represent the US population |
|---------------------------------------------------------------|
| **Characteristics**                                           | **Adjusted Change of Lead Level, \(\mu g/dl\),** | **Adjusted Change of Cadmium Level, \(\mu g/L\),** |
|                  | (95% Confidence Interval) | \(P\) value | (95% Confidence Interval) | \(P\) Value |
| **Age, yr**       | 0.02 (0.02 to 0.03)       | <0.001     | 0.001 (-0.001 to 0.002)  | 0.29       |
| **Sex, M**        | 0.87 (0.73 to 1.01)       | <0.001     | -0.003 (-0.05 to 0.04)   | 0.91       |
| **Race**          |                           |            |                           |            |
| White             | Ref.                      |            | Ref.                      |            |
| Black             | 0.28 (0.10 to 0.46)       | 0.004      | -0.02 (-0.08 to 0.05)    | 0.65       |
| Hispanic          | 0.02 (-0.2 to 0.24)       | 0.83       | -0.06 (-0.15 to 0.03)    | 0.18       |
| Other             | 0.05 (-0.14 to 0.23)      | 0.6        | 0.16 (0.08 to 0.25)      | <0.001     |
| **Number of household occupants, per one**                   | 0.03 (-0.05 to 0.1)      | 0.46       | -0.01 (-0.02 to 0.01)    | 0.43       |
| **Household monthly income, $**                             |                           |            |                           |            |
| \(\geq19,999\)    | Ref.                      | <0.001     | Ref.                      | <0.001     |
| 20,000-34,999     | -0.01 (-0.24 to 0.23)     |            | -0.05 (-0.11 to 0.02)    |            |
| 35,000-64,999     | -0.09 (-0.27 to 0.09)     |            | -0.11 (-0.19 to 0.03)    |            |
| \(\geq65,000\)    | -0.43 (-0.63 to -0.23)    |            | -0.2 (-0.26 to -0.14)    |            |
| US citizenship, yes| -0.52 (-0.81 to -0.23)    |            | -0.01 (-0.12 to 0.01)    | 0.87       |
| eGFR, per 10 ml/min | -0.05 (-0.09 to -0.01)    | 0.02       | -0.02 (-0.03 to -0.01)   | 0.003      |

Adjusted for age, sex, race and ethnicity, number of household occupants, monthly income, citizenship, and renal function, as estimated from cystatin C calculated GFR. M, male.
toxicity may be a consequence of CKD. Accordingly, that individuals with CKD may have heightened susceptibility to even low levels of environmental exposures that are found widely across the United States warrants further research.

Elevations in blood levels within the range considered normal, and similar to those observed in our analyses, have previously been shown to be associated with negative effects (10). Furthermore, given that lead deposits widely in soft tissue and skeleton (11), such modest elevations may underestimate the biologic consequences of repeated exposures over time. Total body lead accumulation, as can be measured with lead x-ray fluorescence (12–14), has been more closely associated with adverse health outcomes, some of which may develop many years after exposure (15–20).

Given continued environmental exposure to heavy metals in the United States, the hazard for those with CKD is of public health concern (21,22). Recently, we demonstrated that levels of lead found widely in community water systems across the United States, and well below the US Environmental Protection Agency’s surveillance threshold that mandates regulatory action, are associated with lower hemoglobin concentrations and more erythropoietin stimulating agent use among those with advanced kidney disease (23). Given the protean toxic effects of lead, whether low levels of environmental exposure will similarly associate with other diseases in CKD is unknown. Importantly, because studies have demonstrated adverse neurocognitive effects of even low levels of lead exposure, including Parkinson’s, dementia, and depression (24,25), diseases that are highly prevalent in CKD, further studies are needed.

In addition, Black individuals, who tend to have higher rates of lead exposure (26), disproportionately higher rates of CKD (27), and inequitable health care (28), are particularly vulnerable to heavy metal contamination. The significantly stronger effect of decreasing GFR on lead levels observed among Black participants compared with those from other ethnic groups suggests even greater susceptibility. Explanations for such effect modification are not clear. Black individuals tend to have higher rates of iron deficiency and vitamin D deficiency, which increase proportions of lead absorbed across the gastrointestinal tract (29–31). Differences in proximal tubular handling of lead, separate from change in GFR, might similarly contribute to these differences, and a range of polymorphisms in the molecular handling of lead. Ultimately, further studies to identify the mechanisms of heightened lead susceptibility among Black individuals with CKD are warranted.

Our study has important limitations. Most notably, the confounding effect of reverse causality cannot be addressed in this cross-sectional analysis, and the directionality of the CKD/lead association requires further study. Other limitations include the absence of measures of environmental heavy metal exposure. Despite these limitations, given

Table 3. Association of CKD (eGFR ≤ 60 ml/min per 1.73 m²) with levels of lead in blood and urine

| Outcome                                | Adjusted Difference in Blood and Urinary Lead Levels in Those with CKD Compared with Normal Renal Function | NHANES 1999–2002\(^a\) | CKD-EPI 2021 Using Creatinine/Cystatin C | NHANES 2017–2020\(^b\) | CKD-EPI 2021 Using Creatinine/Cystatin C |
|----------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------|----------------------------------------|-------------------------|----------------------------------------|
| Whole blood lead level, µg/dl          | Cystatin 2012                                                                                           | 0.23 (0.03 to 0.42)     | 0.31 (0.09 to 0.53)                    | 0.19 (–0.02 to 0.4)     | 0.12 (0.03 to 0.22)                    |
| Whole blood level in those with urinary lead levels, µg/dl | CKD-EPI 2021 Using Creatinine/Cystatin C                                                               | 0.21 (–0.04 to 0.47)     | 0.1 (–0.26 to 0.46)                    | 0.11 (–0.13 to 0.36)     | 0.22 (0.03 to 0.42)                    |
| Urinary lead, ng/ml                    | CKD-EPI 2021 Using Creatinine/Cystatin C                                                               | –0.16 (–0.3 to –0.01)   | –0.18 (–0.34 to –0.03)                 | –0.18 (–0.3 to –0.06)   | 0.003 (–0.079 to 0.085)                |
| Urinary lead/creatinine ratio          | CKD-EPI 2021 Using Creatinine/Cystatin C                                                               | –0.003 (–0.004 to –0.001) | –0.003 (–0.004 to –0.002)             | –0.003 (–0.004 to –0.002) | 0.00004 (–0.0005 to 0.00066) |

NHANES, National Health and Nutrition Examination Survey.

\(^a\)Adjusted for age, sex, race and ethnicity, number of household occupants, monthly income, citizenship.

\(^b\)Adjusted for age, sex, race and ethnicity. All models are use strata (sdmvstra) and cluster (sdmvpsu) variables. Urinary measures use 4-year heavy metal weights (wtshm4yr). 2017–2020 cohort use MEX exam weights (wtmecppr) for all outcomes.
continued low levels of exposure in the United States, the biologic principles herein are of important public health value.

In conclusion, CKD may confer a heightened susceptibility to low levels of heavy metal exposure found commonly in the United States, particularly among Black individuals. The long-term health effects of environmental heavy metal exposure for those with CKD, and the need for further mitigation strategies, require further study.

Disclosures
J. Danziger reports consultancy for Healthmap Solutions; ownership interest in Healthmap Solutions; and is the regional medical director for Healthmap Solutions. H. Hu reports ownership interest in Advanced Micro Devices, Alphabet, Amazon, Appian Corp., Apple, Costco, Disney, Enphase Energy, Innovative INDL, Kinsale CAP Group, Micron Technology, Netflix, NVIDIA, NOVONIX, Pershing Square, Qualcomm, Taiwan Semiconductor, Wells Fargo, and Zoom; and is Chair of the Scientific Advisory Board for the Marilyn Brachman Hoffman Foundation. K.J. Mukamal reports other interests or relationships with the US Highbush Blueberry Council and Wolters Kluwer. The remaining author has nothing to disclose.

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Author Contributions
J. Danziger was responsible for the conceptualization, data curation, investigation, and methodology, and wrote the original draft of the manuscript; L.E. Dodge was responsible for the formal analysis; and H. Hu and K.J. Mukamal reviewed and edited the manuscript.

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