University of Cincinnati

Date: 6/16/2017

I, Mary Avendt-Reeber M.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Chronic Kidney Disease and Heavy Metal Exposure in Children

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This work and its defense approved by:

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Committee member: Jane Khoury, M.S
Committee member: Mark Mitsnefes, M.D.
Chronic Kidney Disease and Heavy Metal Exposure in Children

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
requirements for the degree of
Master in Clinical and Translational Research
in the Department of Environmental Health
Division of Epidemiology

by

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M.D., Wayne State University, May 2011
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Committee Chair:
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Abstract:

Background:

Recent adult studies have shown even low level exposure to arsenic (As) in drinking water was associated with kidney dysfunction. These low levels were found in the upper quartile observed in children by the National Health and Nutrition Examination Survey (NHANES). Limited studies exist for evaluating renal function and As in children. One study observed a positive association between As and estimated glomerular filtration rate (eGFR) in children when analyzing NHANES data from 2009-2012. However, this study did not account for the impact of other heavy metals, ie cadmium (Cd), mercury (Hg), and lead (Pb) on renal function. Another method of assessing renal dysfunction is urine albumin to creatinine ratio (ACR).

Objective:

To assess the association between urinary As, Cd, Hg, and Pb and renal function in children.

Methods:

NHANES data from 2003-2014 for individuals 12-20 were evaluated in this cross-sectional study. Independent variables included measurements of urine heavy metals of As, Cd, Hg, and Pb normalized to urinary creatinine. Outcome measurements were ACR and eGFR as determined by Schwartz et al. for participants aged 12-17 and by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) for those aged 18-20. Multivariable linear regression models were utilized to assess the association between both ACR and eGFR and urinary concentrations of As, Cd, Hg, and Pb. These models were adjusted for age, gender, race, ethnicity, blood pressure, body mass index, serum hemoglobin A1C, and serum cotinine.

Results:

A total of 2897 kids aged 12-20 had available data to determine eGFR and urinary As, Cd, Hg, and Pb concentrations. Median eGFR was 105 ml/min/1.73m² (IQR 89-123). Mean heavy metal concentrations, normalized to urinary creatinine, were: As 10.74 µg/g, Cd 0.15 µg/g, Hg 0.45 µg/g, and Pb 0.46 µg/g. Multivariate analysis showed an increase in ACR of 3.77 for every log unit increase in urinary Cd which approached statistical significance (p=0.06). Multivariate analyses showed an increase in eGFR of 1.7 ml/min/1.73m² for each log unit increase in total urinary As (p = 0.04), an increase of 2.4 ml/min/1.73m for each log unit increase in Cd (p = 0.009), an increase of 1.2 ml/min/1.73m for each log unit increase in Hg (p = 0.04), and an increase of 3.6 for each log unit increase in Pb (p=<0.001). There was no significant association seen between urinary Hg and eGFR.

Conclusion:

A positive association was once again seen with low level exposure of As and eGFR in children. Similar associations were observed with Cd and Pb as well. Investigation of ACR showed a positive relationship between Cd and ACR which approached statistical significance. The positive relationship seen with eGFR may be due to impairment of excretion or due to hyperfiltration. Thus, further prospective studies using additional, more sensitive, markers of renal injury are needed.
Acknowledgements

I would like to acknowledge the members of my thesis committee: Erin Haynes, Dr.P.H., Mark Mitsnefes, M.D., M.S., and Jane Khoury, Ph.D. for their support and guidance. This study was funded by a T32 training grant from the National Institute of Health (T32DK007695).
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Figure 1. Flow diagram of included participants with exclusion criteria.
1. Introduction

The effects chronic kidney disease (CKD) can have on a person and a society are quite substantial. The diagnosis of CKD brings with it increased all-cause mortality and morbidity from cardiovascular disease, growth impairment, anemia, and cognitive impairment [1]. The prevalence of CKD in children has increased to 75 per million population in the last 15 years [2]. With the burden of CKD both on an individual level and global economy, preventative measures must be taken. Modifiable risk factors need to be identified.

Exposure to large amounts of heavy metals, such as arsenic, lead, cadmium, or mercury, have been associated with kidney injury [3]. In 2001, the U.S. Environmental Protection Agency’s (EPA) standard for arsenic concentration lowered from 50 to 10 µg/L [4]. The Strong Heart Study was conducted in the American southwest among a population of American Indian adults with a high prevalence of diabetes and obesity. This study used albuminuria as a marker of kidney dysfunction and found increasing amounts of albuminuria with increasing amounts of arsenic in the urine [5]. However, another study conducted in American children by Weidemann et al used estimated glomerular filtration rates (eGFR) as a marker of kidney function [6]. In this study, an increase in eGFR was seen, associated with increasing concentrations of urinary arsenic, in children participating in the National Health and Nutrition Examination Survey (NHANES) from 2009-2012 [6]. This study adjusted its model for standard potential chronic kidney disease (CKD) risk factors such as BMI, serum cotinine, hypertension, and diabetes; however, it did not account for other heavy metal exposures.

The aim of the current study is to fully utilize the NHANES data to assess the association between arsenic, cadmium, mercury, and lead and kidney function in children. Kidney injury resulting from exposure to large amounts of heavy metals has been described in numerous case reports and the presumed site of injury is the proximal tubule[7]. Injury to the proximal tubule can result in acute tubular necrosis with proteinuria and decrease in eGFR. Thus, we picked two outcome measures of kidney function: eGFR and albumin to creatinine ratio (ACR). We hypothesized that increasing amounts of arsenic,
cadmium, mercury and lead in the urine would be associated with worsening of ACR and eGFR, that is increased ACR and decreased eGFR.

Methods

We utilized data from NHANES cycles 2003 to 2014 for children 12 to 20 years of age in which urine heavy metals were assessed. NHANES is a continuous nationally representative survey conducted by the Centers for Disease Control and Prevention (CDC). The study protocols were approved by the National Center for Health Statistics institutional review board. Consent was obtained orally and in writing from all participants older than 18 years of age. Assent was obtained for those aged 12-17 years.

Over 60,000 participants were surveyed in these six cohorts from 2003 to 2014. Figure 1 depicts the inclusion and exclusion criteria which resulted in a total of 2897 kids included in our analysis.

Urinary heavy metal measures

Urine samples were collected on NHANES participants aged 6 years and older. Samples were transported on dry ice to the Environmental Health Sciences Laboratory at the National Center for Environmental Health in Atlanta, GA. Samples were stored at or below -20°C prior to be analyzed within 3 weeks of collection. Total urine arsenic concentrations were determined by using inductively coupled-plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS). The level of detection (LOD) was not the same for all 6 cycles. For urinary cadmium, mercury, and lead, samples were collected from NHANES participants aged 6 years of older in a similar fashion. The LOD for each heavy metal and the percentage of collections above the LOD are listed below in Table 1. For samples below the LOD, a value, which was equal to LOD divided by the square root of 2, was substituted. To correct for degree of dilution of urine, all metal concentrations were normalized to urinary concentrations of creatinine.
Markers of kidney function

Serum specimens were collected from individuals and shipped to Collaborative Laboratory Services in Ottumwa, IA. Random spot urine samples were processed, stored, and shipped to University of Minnesota, Minneapolis, MN. Serum and urine creatinine were determined by the Jaffe rate method. Urine albumin measurement was performed using solid-phase fluorescent immunoassay [8].

For the first marker of kidney function, estimated GFR (eGFR), two equations utilizing serum creatinine were used. For participants aged less than 18 years, the Chronic Kidney Disease in Children (CKiD) bedside GFR calculation (0.413*height in centimeters/serum creatinine) [9]. For participants aged 18 years and older, eGFR was determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. For the second marker of kidney function, urine albumin to creatinine ratios (ACRs) were calculated as mg/g.

Covariates

Basic demographic data, including age, gender, race, and ethnicity, were collected by questionnaire. General guidelines on standard procedures were followed for obtaining anthropometric measurements [11]. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Blood pressures were taken on all participants aged 8 years and older and was obtained following 5 minutes of sitting. The mean of at least 3 blood pressure readings both systolic and diastolic were calculated and indexed to the 95th percentile for gender, age, and height [12]. Tobacco exposure was determined by serum cotinine levels measured by an isotope-dilution high performance liquid chromatography (HLPC) and atmospheric pressure chemical ionization tandem mass spectrometric method. Serum glycohemoglobin A1c which was measured on participants aged 12 and older by HLPC.
Statistical Analysis

Analyses were performed using SAS 9.3 statistical software package. Given the large scale and complexity of the NHANES data collection survey procedures were performed as linear regression. All analyses included the recommended factors for variance estimation; stratum, primary sampling unit and sampling weight as recommended by the NHANES Analytic Guidelines [13]. This was implemented by using the SAS survey programs. Statistical significance was set at alpha = 0.05, and all p-values were two sided.

All numerical measurements were analyzed as continuous variables. The concentrations of metals normalized to urine concentration of creatinine were log-transformed, base for analysis due to the distribution violating the assumption of normality. Association between each heavy metal and the marker of kidney dysfunction, either eGFR or ACR was first conducted in a univariate analysis. Next we adjusted for covariates in a stepwise manner. In model 1, we adjusted for age, gender, race/ethnicity. Model 2 adjusted for age, gender, race/ethnicity, BMI, serum cotinine, systolic blood pressure index (SBPI), diastolic blood pressure index (DBPI), and glycohemoglobin A1c. Model 3 adjusted for age, gender, race/ethnicity, BMI, serum cotinine, SBPI, DBPI, glycohemoglobin A1c, and log values of the other urine heavy metal normalized to urinary creatinine. For the association with ACR a sensitivity analysis was run with urine albumin as the dependent variable and unadjusted heavy metals as the independent variables correcting for urinary creatinine. This was due to the fact that both ACR and heavy metals were divided by urinary creatinine in the primary analysis, which may potentially increase the associations.

Results

A total of 2897 participants 12 to 20 years of age had met criteria for inclusion in this study (Figure 1). Information for basic demographics and laboratory values are shown below in Table 2. Of note the mean age was just under 16 years, and the mean eGFR was well within the normal range of greater than 90
ml/min/1.73m² at 105.2 ml/min/1.73m². The mean ACR was also within the normal range of below 30 mg/g at 22.76 mg/g.

When using eGFR as an outcome of kidney function, we found a statistically significant association with urinary arsenic, cadmium, mercury, and lead (Table 3). This association was true even after adjusting for age, sex, race/ethnicity, blood pressure, glycohemoglobin A1c, serum cotinine, and concentrations of the other 3 heavy metals. With every log-unit increase urine arsenic normalized to creatinine, there was on average a 1.66 ml/min/1.73m² increase in eGFR. With every log-unit increase in urine cadmium normalized to creatinine, there was on average a 2.37 ml/min/1.73m² increase in eGFR. With every log-unit increase in urine mercury normalized to creatinine, there was an increase of eGFR by 1.15 ml/min/1.73m² on average. With every log-unit increase in urine lead normalized to creatinine, there was an increase in eGFR of 3.61 ml/min/1.73m².

When using ACR as an outcome of kidney function, we did not find a statistically significant association with urinary arsenic, cadmium, mercury, or lead (Table 4). Although we did find the association between the log-unit of urinary cadmium normalized to creatinine and ACR approached statistical significance (p of 0.06) when adjusted for age, gender, race/ethnicity, BMI, serum cotinine, indexed systolic and diastolic blood pressures, glycohemoglobin A1c, and other heavy metals. This relationship showed an increase in ACR by 3.77 mg/g for every log-unit increase in urinary cadmium normalized to urinary creatinine. The sensitivity analysis showed similar results for the association of heavy metals with urinary albumin.

**Discussion**

The heavy metals in this analysis, arsenic, cadmium, mercury, and lead, were chosen because they have been associated with kidney injury in large quantities [7]. However, the exact effect on the kidneys at low levels of concentration has not been fully elucidated. Individuals are exposed to these heavy metals in a numerous ways. The more toxic, inorganic form of arsenic, can be found in contaminated groundwater or food such as apple juice and rice. Exposure to cadmium can occur with contact with fossil fuel,
phosphate fertilizers, and during incineration of solid waste. Individuals can be exposed to mercury during the smelting process in gold production and from coal-fired power plants. Sources of lead are more commonly known to the public with lead-based paint, cigarette smoke, and contaminated water from lead pipes.

The majority of studies of the effect heavy metals have on the kidney have occurred in adults, but the vulnerability of children make them an especially important cohort to investigate. Because of their smaller size, their exposures occur at a higher proportion to their weight and body surface area. Children’s metabolic processes may be immature to properly breakdown toxins to inactive metabolites. These characteristics make children particularly sensitive and vulnerable to environmental toxins.

As mentioned earlier, there have been contradicting results from studies regarding arsenic. For example, while the Strong Heart Study showed increasing urine arsenic concentrations were cross-sectionally associated with increased albuminuria[5], the authors found an adjusted odds ratio of 0.7 for the prevalence of CKD when comparing the 75th to the 25th quartiles of urine arsenic concentrations [14]. However, the investigators of the Strong Heart Study concluded that a reduced prevalence in CKD is associated with increasing urine inorganic arsenic concentrations because inorganic arsenic may impair the kidneys ability to excrete inorganic urine or it may be due to hyperfiltration [14]. The results of our study may suggest low doses of heavy metals may lead to reduced excretion. This has been termed reverse causality. In other words, exposure to these heavy metals are leading to kidney injury and subsequent impairment in excretion of the heavy metals. Thus the association of excreted heavy metals in the urine and eGFR would be positive. This was hypothesized in the previous NHANES study by Weidemann et al [6]. This could be mitigated by analyzing the amount of heavy metal in the exposure rather than the amount excreted, but this type of study design would be unethical in human subjects.

The possible explanation for this positive relation between urinary heavy metals and eGFR may be due to hyperfiltration. Hyperfiltration occurs in the early stages of CKD when the eGFR is actually elevated.
The stress the increased GFR cannot be sustained and eventually results in kidney damage. Elevated ACR is the marker of damage due to hyperfiltration. Hyperfiltration has been a proposed mechanism of kidney injury in children for these four heavy metals [15]. With our analysis of ACR, we did see a positive association between cadmium and ACR which approached statistical significance. This was not true for arsenic, mercury, or lead in our study, however.

Studies regarding the other heavy metals have also yielded mixed results. For example, in the case of cadmium, one European study showed no association between blood or urine cadmium levels an serum cystatin C level in a cohort of 200 children living near a lead smelter [16]. However, the MINIMat study of Bangladesh found an increase in urinary cadmium of 0.5 µg/L was associated with a decrease in eGFR of 2.6 ml/min/1.73m² in girls [17]. Studies looking into the renal damage from placement of amalgam, known to contain mercury, have been shown to both be associated and not associated with increase in albuminuria at follow up 5-7 years later [18, 19]. Similar mixed conclusions have been seen with studies of lead exposure in children. European studies investigating blood lead levels and eGFR in children have shown both positive and negative associations [15, 16].

**Conclusion**

In conclusion, our analysis of urinary arsenic, cadmium, mercury, and lead show an association with increase in eGFR. However, this association is seen only with a log-unit increase in the concentration of the heavy metal. When analyzing renal dysfunction by ACR, we found an association with increasing ACR that approached statistical significance only for cadmium. No association was observed for arsenic, mercury, or lead. While others have postulated the increase in GFR with increasing urinary concentration of heavy metals is due to reverse causality, this seems unlikely. Studies utilizing blood levels of heavy metals have continued to show mixed results. Further studies are needed over larger ranges of exposure to fully elucidate the relationship between heavy metal exposure and kidney injury in children.
Figure 1. Flow diagram of included participants with exclusion criteria.

Sample


Exclusion Criteria

Participants aged > 20 years (n=10,218)

Participants > 12 years with measured urine As, Cd, Cr, Hg, and Pb (n=15680)

Participants with measured blood pressures (n=3101)

Participants with positive pregnancy test (n=29)

Participants with measured serum creatinine, cotinine, and glycohemoglobin A1c levels (n=2897)

Participants with no anthropometric measurements (n=31)

NHANES, National Health and Nutrition Exam Survey; As, arsenic; Cd, cadmium; Hg, mercury; Pb, lead.
Table 1. Level of detection for urinary heavy metals and percentage of samples above level of detection.

<table>
<thead>
<tr>
<th>Survey Cohort</th>
<th>Arsenic LOD (µg/L)</th>
<th>Percentage below LOD (%)</th>
<th>Cadmium LOD (µg/L)</th>
<th>Percentage below LOD (%)</th>
<th>Mercury LOD (µg/L)</th>
<th>Percentage below LOD (%)</th>
<th>Lead LOD (µg/L)</th>
<th>Percentage below LOD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-4</td>
<td>0.6</td>
<td>1%</td>
<td>0.03</td>
<td>9%</td>
<td>0.11</td>
<td>19%</td>
<td>0.07</td>
<td>15%</td>
</tr>
<tr>
<td>2005-6</td>
<td>0.74</td>
<td>0.7%</td>
<td>0.03</td>
<td>10%</td>
<td>0.06</td>
<td>7%</td>
<td>0.07</td>
<td>2%</td>
</tr>
<tr>
<td>2007-8</td>
<td>0.74</td>
<td>0.4%</td>
<td>0.03</td>
<td>10%</td>
<td>0.06</td>
<td>0%</td>
<td>0.07</td>
<td>2%</td>
</tr>
<tr>
<td>2009-10</td>
<td>0.74</td>
<td>0.5%</td>
<td>0.042</td>
<td>11%</td>
<td>0.06</td>
<td>0%</td>
<td>0.10</td>
<td>3%</td>
</tr>
<tr>
<td>2011-2</td>
<td>1.25</td>
<td>4%</td>
<td>0.056</td>
<td>22%</td>
<td>0.04</td>
<td>4%</td>
<td>0.08</td>
<td>4%</td>
</tr>
<tr>
<td>2013-4</td>
<td>0.26</td>
<td>0%</td>
<td>0.036</td>
<td>18%</td>
<td>0.13</td>
<td>34%</td>
<td>0.03</td>
<td>1%</td>
</tr>
</tbody>
</table>

LOD, level of detection
Table 2. Demographic and laboratory values for participants. n=2897

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.75</td>
<td>2.45</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.89</td>
<td>19.72</td>
<td>28.4</td>
<td>215.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.69</td>
<td>10.14</td>
<td>134.8</td>
<td>200.1</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.19</td>
<td>6.14</td>
<td>13.43</td>
<td>62.08</td>
</tr>
<tr>
<td>Systolic BP index</td>
<td>0.83</td>
<td>0.08</td>
<td>0.62</td>
<td>1.12</td>
</tr>
<tr>
<td>Diastolic BP index</td>
<td>0.53</td>
<td>0.15</td>
<td>0.07</td>
<td>1.2</td>
</tr>
<tr>
<td>Glycohemoglobin A1c (%)</td>
<td>5.21</td>
<td>0.40</td>
<td>3.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Serum Cotinine (ng/mL)</td>
<td>18.99</td>
<td>63.77</td>
<td>0.01</td>
<td>564</td>
</tr>
<tr>
<td>Estimated GFR (ml/min/1.73m²)</td>
<td>105.2</td>
<td>21.47</td>
<td>38.16</td>
<td>198.11</td>
</tr>
<tr>
<td>Urine Albumin:Creatinine (mg/g)</td>
<td>22.76</td>
<td>86.01</td>
<td>0.22</td>
<td>1957.75</td>
</tr>
<tr>
<td>Urine Total Arsenic (µg/L)</td>
<td>15.16</td>
<td>46.88</td>
<td>0.4</td>
<td>1470</td>
</tr>
<tr>
<td>Urine Arsenic/Creatinine (µg/g)</td>
<td>10.74</td>
<td>40.73</td>
<td>0.22</td>
<td>1441.18</td>
</tr>
<tr>
<td>Urine Cadmium (ng/mL)</td>
<td>0.15</td>
<td>0.31</td>
<td>0.03</td>
<td>14.94</td>
</tr>
<tr>
<td>Urine Cadmium/Creatinine (µg/g)</td>
<td>0.10</td>
<td>0.14</td>
<td>0.01</td>
<td>6.47</td>
</tr>
<tr>
<td>Urine Mercury (ng/mL)</td>
<td>0.64</td>
<td>1.13</td>
<td>0.04</td>
<td>21.43</td>
</tr>
<tr>
<td>Urine Mercury/Creatinine (ng/mL)</td>
<td>0.45</td>
<td>0.90</td>
<td>0.02</td>
<td>33.48</td>
</tr>
<tr>
<td>Urine Lead (ng/mL)</td>
<td>0.65</td>
<td>1.49</td>
<td>0.02</td>
<td>71.7</td>
</tr>
<tr>
<td>Urine Lead/Creatinine (ng/mL)</td>
<td>0.46</td>
<td>0.96</td>
<td>0.02</td>
<td>28</td>
</tr>
</tbody>
</table>

Std dev, standard deviation; GFR, glomerular filtration rate;
Table 3. Change in eGFR associated with one log$_e$-unit change in concentrations of urine heavy metals adjusted for urinary creatinine.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Unadjusted Model</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β(sterr)</td>
<td>p-value</td>
<td>β(sterr)</td>
<td>p-value</td>
</tr>
<tr>
<td>Arsenic</td>
<td>2.41 (0.69)</td>
<td>0.0001</td>
<td>2.28 (0.69)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cadmium</td>
<td>4.96 (0.80)</td>
<td>&lt;0.0001</td>
<td>4.08 (0.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mercury</td>
<td>2.81 (0.52)</td>
<td>&lt;0.0001</td>
<td>2.47 (0.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lead</td>
<td>5.02 (0.71)</td>
<td>&lt;0.0001</td>
<td>5.30 (0.66)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; change in eGFR measured as ml/min/1.73m$^2$.

Model 1 adjusted for age, gender, and race/ethnicity. Model 2 is adjusted for age, gender, race/ethnicity, body mass index, serum cotinine, systolic blood pressure index, diastolic blood pressure index, and glycohemoglobin A1c. Model 3 is adjusted for age, gender, race/ethnicity, body mass index, serum cotinine, systolic blood pressure index, diastolic blood pressure index, glycohemoglobin A1c, and the log values of the other heavy metals.
Table 4. Change in urine albumin: creatinine associated with one log\(_e\)-unit change in concentrations of urine heavy metals adjusted for urinary creatinine.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Unadjusted Model</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β(sterr)</td>
<td>p-value</td>
<td>β(sterr)</td>
<td>p-value</td>
</tr>
<tr>
<td>Arsenic</td>
<td>-3.11 (2.66)</td>
<td>0.19</td>
<td>-2.64 (2.26)</td>
<td>0.25</td>
</tr>
<tr>
<td>Cadmium</td>
<td>3.43 (2.85)</td>
<td>0.23</td>
<td>3.77 (2.51)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mercury</td>
<td>0.35 (1.76)</td>
<td>0.84</td>
<td>0.41 (1.64)</td>
<td>0.80</td>
</tr>
<tr>
<td>Lead</td>
<td>0.46 (3.90)</td>
<td>0.91</td>
<td>-0.22 (4.00)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Change in urine albumin/creatinine measured in milligram per gram.

Model 1 adjusted for age, gender, and race/ethnicity. Model 2 is adjusted for age, gender, race/ethnicity, body mass index, serum cotinine, systolic blood pressure index, diastolic blood pressure index, and glycohemoglobin. Model 3 is adjusted for age, gender, race/ethnicity, body mass index, serum cotinine, systolic blood pressure index, diastolic blood pressure index, glycohemoglobin A1c, and the log values of the other heavy metals.

Table 5. Change in log urine albumin associated with one log\(_e\)-unit change in concentrations of urine heavy metals.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Unadjusted Model</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β(sterr)</td>
<td>p-value</td>
<td>β(sterr)</td>
<td>p-value</td>
</tr>
<tr>
<td>Arsenic</td>
<td>-0.07 (0.03)</td>
<td>0.02</td>
<td>-0.06 (0.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.13 (0.04)</td>
<td>0.004</td>
<td>0.11 (0.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mercury</td>
<td>0.02 (0.03)</td>
<td>0.45</td>
<td>0.02 (0.03)</td>
<td>0.54</td>
</tr>
<tr>
<td>Lead</td>
<td>-0.01 (0.04)</td>
<td>0.86</td>
<td>-0.01 (0.04)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Change in urine albumin/creatinine measured in milligram per gram.

Model 1 adjusted for age, gender, and race/ethnicity. Model 2 is adjusted for age, gender, race/ethnicity, body mass index, serum cotinine, systolic blood pressure index, diastolic blood pressure index, and glycohemoglobin. Model 3 is adjusted for age, gender, race/ethnicity, body mass index, serum cotinine, systolic blood pressure index, diastolic blood pressure index, glycohemoglobin A1c, and the log values of the other heavy metals.
4. *National primary drinking water regulations; arsenic and clarifications to compliance and new source contaminants monitoring final rule*, F. Register, Editor. 2001, Environmental Protection Agency. p. 6976-7066.