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Toxicology

# Lead and kidney: Concentrations, variabilities, and associations across the various stages of glomerular function

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ABSTRACT

Data (N = 9882) from National Health and Nutrition Examination Survey for 2003–2014 for US adults aged ≥20 years were analyzed to evaluate the variabilities in concentrations of blood and urine lead across various stages of glomerular function. Those who had estimated glomerular filtration rate (eGFR) > 90 mL/min/1.73 $m^2$ were defined to be in glomerular function stage 1 (GF-1), those who had eGFR between 60 and 90 mL/min/1.73 $m^2$ were defined to be in GF-2, those who had eGFR between 45 and 60 mL/min/1.73 $m^2$ were defined to be in GF-3A, those who had eGFR between 15 and 45 mL/min/1.73 $m^2$ were defined to be in GF-3B/4. There were consistent increases in adjusted geometric means (AGM) for both blood and urine lead from GF-1 to GF-3A even though increases were not uniform from one GF stage to another. For the total population, AGMs for blood lead were 1.23, 1.78, 2.25, and 2.25 μg/dL for GF-1, GF-2, GF-3A, and GF-3B/4 respectively. AGMs for urine lead were 0.49, 0.61, 0.68, and 0.47 μg/L for GF-1, GF-2, GF-3A, and GF-3B/4 respectively. Thus, from GF-3A to GF-3B/4, AGMs for both blood and urine lead decreased. However, percent increases from GF-1 to GF-3A for urine lead were smaller than for blood lead and percent decreases from GF-3A to GF-3B/4 for urine lead were larger than for blood lead. Females had lower AGMs than males for both blood and urine lead. Also, smoker-nonsmoker differences for blood lead narrowed as kidney function deteriorated but smoker-nonsmoker differences for urine cadmium lead as kidney function deteriorated. Smokers had sharper increases in AGMs for blood and urine lead than nonsmokers from GF-1 to GF-3A but at GF-3B/4, this difference was reduced to 0.17 μg/dL.

## 1. Introduction

Lead, along with cadmium and mercury are among the most toxic metals. Humans can be exposed to lead in a variety of occupational and non-occupational settings. Humans are also exposed to lead via smoking. Sources of exposure to lead, mechanisms involved in lead toxicity, and some of the adverse health effects associated with lead have been described in a review article by Jaishanker et al. [1]. Other recent publications that have documented adverse health effects of lead include those by Obeng-Gyasi [2], Lanphear et al. [3], and Geier et al. [4,5].

Human lead exposure traces back to the dawn of industrial activity. Exposure is known to be associated with increased risk of kidney disease [6]. Also, a positive association between urinary lead levels and eGFR was reported by Buser et al. [7]. More recently, associations between lead levels and reduced kidney function have been reported by Harari et al. [8]. Navas-Acien et al. [9] reported adjusted elevated odds of albuminuria defined as ≥30 mg/g creatinine (1.31; 95% C.I. 1.06–1.62) for fourth quartile of blood lead compared to first quartile, and for eGFR < 60 mL/min/1.73 $m^2$ to be 1.66 (95% C.I. 1.25–2.21) for US adults aged ≥20 years.

Potential mechanism involved in nephrotoxicity induced by toxic metals including lead are: tubular transport of these metals by apical uptake, basolateral uptake, apical export, and basolateral export [10,11]. For example, organic anion transporters 1 and 3 play a role in basolateral uptake of Hg [12].

Health of the kidneys is usually determined by how well the kidneys are able to filter the blood by removing excess wastes and fluids. The process of kidneys filtering excess wastes and fluids from the blood is called the glomerular filtration (https://www.healthlinkbc.ca/health-topics/aa154102). Estimated GFR (eGFR) is usually used to estimate a person's GFR. In order to compute eGFR for a person, in addition to his/her age, gender, and race/ethnicity, observed concentrations of creatinine and/or cystatin C in serum are needed. Among the several equations that are available to compute eGFR, Modification of Diet in Renal Disease (MDRD) equation developed by Levey et al. [13] and Chronic Kidney Disease Epidemiology (CKD-EPI) equation also developed by Levey et al. [14] are most often used. The full spectrum of eGFR values is classified in five stages that indicate relative health of the kidney/glomerular function (GF). In GF-1 or the first stage of GF, a person may have some protein in urine but normal eGFR of > 90 mL/min/1.73 $m^2$; in GF-2, a person may have some kidney damage with mild decrease in GFR with eGFR values between 60 and 89 mL/min/1.73 $m^2$; in GF-3A, a person may have mild to moderate decrease in eGFR with eGFR values between 45 and 59 mL/min/1.73 $m^2$; in GF-3B, a person has moderate to severe decrease in eGFR with eGFR values between 30 and 44 mL/

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**Table 1**
Unweighted sample sizes by gender, race/ethnicity for US adults aged > =20 year with matching data for urine and blood lead. Data from National Health and Nutrition Examination Survey 2003–2014.

| | Glomerular Function Stage | | | | |
|---|---|---|---|---|---|
| | GF-1 | GF-2 | GF-3A | GF-3B/4 | Total |
| Total | 5710 | 3263 | 563 | 286 | 9822 |
| Males | 2853 | 1792 | 262 | 137 | 5044 |
| Females | 2857 | 1471 | 301 | 149 | 4778 |
| Non-Hispanic white | 2179 | 1911 | 365 | 179 | 4634 |
| Non-Hispanic Black | 1296 | 599 | 105 | 48 | 2048 |
| Hispanic | 1700 | 551 | 65 | 43 | 2359 |
| Others | 535 | 202 | 28 | 16 | 781 |
| Nonsmoker | 3748 | 2447 | 480 | 228 | 6903 |
| Smoker | 1962 | 816 | 83 | 58 | 2919 |

min/1.73 $m^2$; in GF-4, a person has severely decreased eGFR with eGFR values between 15 and 29 mL/min/1.73 $m^2$; in GF-5, a person's kidneys are supposed to have failed with eGFR values < 15 mL/min/1.73 $m^2$ (https://www.kidney.org/sites/default/files/docs/11-10-1813_abe_patbro_gfr_b.pdf, https://renal.org/information-resources/the-uk-eckd-guide/ckd-stages/). A person in GF-5 is identified as being in end stage renal disease.

It is well understood that deteriorating renal function, including renal disease caused by toxic metals themselves, can affect excretion of metals in advancing renal disease. It is hard to know what to do about that well understood problem in epidemiologic studies. Consequently, this study was undertaken to evaluate the variabilities in concentrations of blood and urine lead across various stages of glomerular function. The data from National Health and Nutritional Examination Survey (NHANES, www.cdc.gov/nchs/nhanes/index.htm) for 2003–2014 for US adults aged ≥20 years were selected for this purpose.

## 2. Materials and methods

Data from NHANES for the years 2003–2014 for US adults aged ≥20 years were downloaded on demographics, body measures, blood pressure, urine and blood lead, glycohemoglobin, serum and urine creatinine, and serum cotinine and match merged by the ID of NHANES participants. Data for urine lead were available for only one third of all NHANES participants for every NHANES cycle. Data for blood lead were available for all NHANES participants for 2003–2012 but for only for half of all participants for 2013 − 2014. Non-missing matching data for both blood and urine lead were available for 9882 participants after excluding females who were pregnant, those who had eGFR < 15 mL/min/1.73 $m^2$ and for whom data on smoking status, body mass index, fasting, and poverty income ratio were missing. Sample size details are provided in Table 1. Percent observations ≥ the limit of detection (LOD) were 95.8% for urine lead and 99.9% for blood lead. All observations below LOD were imputed as LOD/Sqrt(2).

CKD-EPI equation [14] was used to compute eGFR based on the observed values of serum creatinine. For the purpose of this study, those who had eGFR > 90 mL/min/1.73 $m^2$ were defined to be in glomerular function stage 1 (GF-1), those who had eGFR between 60 and 90 mL/min/1.73 $m^2$ were defined to be in GF-2, those who had eGFR between 45 and 60 mL/min/1.73 $m^2$ were defined to be in GF-3A, those who had eGFR between 30 and 45 mL/min/1.73 $m^2$ were defined to be in GF-3B, and those who had eGFR < 30 mL/min/1.73 $m^2$ were defined to be in GF-4. However, to have adequate sample size, data for GF-3B and GF-4 were integrated.

### 2.1. Statistical analysis

All data for this study were analyzed by using SAS University Edition software (www.sas.com). All analyses used appropriate sampling weights and incorporated variables that defined sampling design of NHANES. These variables represented stratification and clustering used in NHANES. Specifically, SAS Procs FREQ and SURVEYREG were used to do all analyses including fitting regression models, computing unadjusted (UGM) and adjusted geometric means (AGM). In order to evaluate the associations of blood and urine lead with eGFR, data on eGFR were converted to quartiles of almost equal sizes within each glomerular function stage. Data on lower and upper limits of eGFR associated with quartiles in each GF stage are given in Table 2.

#### 2.1.1. Unadjusted distributions of blood and urine lead across stages of glomerular function

UGMs for matching urine and blood lead data were computed by using SAS Proc SURVEYREG for each stage of glomerular function and pairwise comparisons were made by *t*-test with adjustments made for multiple comparisons by Tukey-Kremer method. These results are given in Table 3.

#### 2.1.2. Adjusted distributions of blood and urine lead across stages of glomerular function

Regression models were fitted for each glomerular function stage for both urine and blood lead. Since, there were four glomerular function stages, a total of 8 regression models were fitted. Log10 transformed values of blood and urine lead were used as dependent variables. All models included independent variables as follows: gender (male, female), race/ethnicity (non-Hispanic white or NHW, non-Hispanic black or NHB, all Hispanics or HISP, other unclassified race/ethnicities or OTHR), smoking status (nonsmoker, smoker with smokers defined as those who had serum cotinine values ≥ 10 ng/mL, eGFR quartiles (Q1, Q2, Q3, Q4), age, log10 transformed values of body mass index, fasting time in hours, survey year to adjust for changes over time, diabetes status (no, yes), and hypertension status (no, yes). Models for urine lead also included urine creatinine as an independent variable. For the purpose of this study, those who reported being current users of insulin and/or diabetic pills and/or had glycohemoglobin levels ≥ 6.5% were considered defined to be diabetic. All those with average systolic blood pressure > 130 mm Hg and/or diastolic blood pressure > 80 mm Hg were considered to be hypertensive. Results for AGMs are given in Table 4.

#### 2.1.3. Associations between blood and urine lead and independent variables

Results for the associations that blood and urine lead had with other independent variables are given in Table 5.

**Table 2**
Lower and upper limits of estimated glomerular filtration rate (eGFR) in mL/min/1.73 $m^2$ used to construct quartiles for eGFR within each stage of glomerular function. Data from National Health and Nutrition Examination Survey 2003–2014.

| Quartiles | GF-1 | | GF-2 | | GF-3A | | GF-3B/4 | |
|---|---|---|---|---|---|---|---|---|
| | Lower Limit | Upper Limit | Lower Limit | Upper Limit | Lower Limit | Upper Limit | Lower Limit | Upper Limit |
| Q1 | ≥90.000 | < 98.655 | ≥60.000 | < 70.750 | ≥45.000 | < 50.300 | ≥15.000 | < 30.900 |
| Q2 | ≥98.655 | < 107.320 | ≥70.750 | < 78.7000 | ≥50.300 | < 54.300 | ≥30.900 | < 37.500 |
| Q3 | ≥107.320 | < 117.600 | ≥78.700 | < 84.760 | ≥54.300 | < 57.300 | ≥37.500 | < 41.800 |
| Q4 | ≥117.600 | | ≥84.760 | < 90.000 | ≥57.300 | < 60.000 | ≥41.800 | < 45.000 |

**Table 3**
Unadjusted geometric means with 95% confidence intervals for blood lead in μg/dL and urine lead in μg/L for US adults aged > =20 years by gender, race/ethnicity, and smoking status by stages of glomerular function. Data from National Health and Nutrition Examination Survey.2003–2016.

| | Glomerular Function Stage | | | | |
|---|---|---|---|---|---|
| | GF-1 | GF-2 | GF-3A | GF-3B/4 | SSD[a] |
| **Blood Lead** | | | | | |
| Total | 1.05 (1.02 – 1.09) | 1.42 (1.37 – 1.47) | 1.74 (1.63 – 1.87) | 1.87 (1.70 – 2.05) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01), GF-1 < GF-3B (p < 0.01), GF-2 < GF-3A (p < 0.01), GF-2 < GF-3B (p < 0.01) |
| Males | 1.28 (1.22 – 1.33) | 1.65 (1.58 – 1.72) | 1.98 (1.72 – 2.27) | 2.30 (2.06 – 2.58) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01), GF-1 < GF-3B (p < 0.01), GF-2 < GF-3A (p < 0.01), GF-2 < GF-3B (p < 0.01) |
| Females | 0.88 (0.85 – 0.90) | 1.20 (1.15 – 1.25) | 1.59 (1.46 – 1.73) | 1.63 (1.46 – 1.83) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01), GF-1 < GF-3B (p < 0.01), GF-2 < GF-3A (p < 0.01), GF-2 < GF-3B (p < 0.01) |
| Nonsmoker | 0.93 (0.90 – 0.96) | 1.32 (1.27 – 1.37) | 1.64 (1.49 – 1.79) | 1.82 (1.64 – 2.02) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01), GF-1 < GF-3B (p < 0.01), GF-2 < GF-3A (p < 0.01), GF-2 < GF-3B (p < 0.01) |
| Smokers | 1.32 (1.26 – 1.39) | 1.78 (1.69 – 1.88) | 2.50 (1.98 – 3.15) | 2.13 (1.85 – 2.44) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01), GF-1 < GF-3B (p < 0.01), GF-2 < GF-3A (p < 0.01) |
| **Urine Lead** | | | | | |
| Total | 0.43 (0.41 – 0.44) | 0.51 (0.49 – 0.53) | 0.53 (0.49 – 0.57) | 0.44 (0.40 – 0.49) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01), GF-3A > GF-3B (p = 0.03) |
| Males | 0.50 (0.48 – 0.53) | 0.61 (0.58 – 0.65) | 0.60 (0.54 – 0.67) | 0.48 (0.39 – 0.59) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01) |
| Females | 0.36 (0.35 – 0.38) | 0.41 (0.39 – 0.44) | 0.49 (0.43 – 0.55) | 0.42 (0.37 – 0.49) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01) |
| Nonsmokers | 0.38 (0.36 – 0.39) | 0.48 (0.45 – 0.50) | 0.51 (0.46 – 0.56) | 0.43 (0.39 – 0.49) | GF-1 < GF-2 (p < 0.01), GF-1 < GF-3A (p < 0.01) |
| Smokers | 0.56 (0.53 – 0.60) | 0.66 (0.60 – 0.72) | 0.76 (0.59 – 0.98) | 0.50 (0.40 – 0.64) | GF-1 < GF-2 (p < 0.01) |

[a] Statistically significant with p-values adjusted for multiple comparisons by Tukey-Kremer method.

## 3. Results

### 3.1. Unadjusted geometric means (UGM) of blood and urine lead across stages of glomerular function

UGMs for blood lead consistently increased from GF-1 through GF-3B/4 for the total population, males, females, and nonsmokers (Table 3). UGMs were found to be in order GF-1 < GF-2 < GF-3A < GF-3B/4 and all pairwise differences except those between GF-3A and GF-3B/4 were statistically significant ($p < 0.01$, Table 3). For example, UGMs for nonsmokers were 0.93, 1.32, 1.64, and 1.82 μg/dL. For smokers, UGMs increased from GF-1 through GF-3A (from 1.32 to 2.50 μg/dL) but decreased for GF-3B/4 to 2.13 μg/dL.

UGMs for urine lead consistently increased from GF-1 through GF-3A but then, decreased for GF-3B/4 for the total population, males, females, smokers, and nonsmokers (Table 3). For example, for females, UGMs were found to be 0.36, 0.41, 0.49, and 0.42 μg//L for GF-1, GF-2, GF-3A, and GF-3B/4 respectively. However, pairwise differences were found to be statistically significant between GF-1 and GF-2, and GF-1 and GF-3A ($p < 0.01$). In addition, for the total population, GF-3A (0.53 μg/L) > GF-3B/4 (0.44 μg/L, Table 3, $p = 0.03$).

### 3.2. Adjusted geometric means (AGM) of blood and urine lead across stages of glomerular function

AGMs for blood lead consistently increased from GF-1 through GF-3A and then, decreased for GF-3B/4 for the total population, males, females, NHW, NHB, HISP, nonsmokers, and eGFR Q2, Q3, and Q4 (Table 4). For example, for females, AGMs were 1.03, 1.53, 1.95, and 1.79 μg//dL for GF-1, GF-2, GF-3A, and GF-3B/4 respectively (Table 4). For nonsmokers, OTHR, and eGFR Q1, AGMs consistently increased from GF-1 through GF-3B/4.

Males had statistically significantly higher AGMs for blood lead for every GF stage ($p < 0.01$, Table 4). For example, for GF-1, AGMs for blood lead for males and females were 1.47 vs. 1.03 μg/dL respectively. NHW had statistically significantly lower AGMs than NHB for GF-1, GF-2, and GF-3A and then HISP for GF-1. For example, for GF-1, AGMs for blood lead were 1.11, 1.24, and 1.27 μg/dL for NHW, NHB, and HISP respectively ($p < 0.01$, Table 4). Nonsmoker had statistically significantly lower AGMs than smokers ($p < 0.1$) for GF-1, GF-2, and GF-3A. For example, for GF-3A, AGMs were 1.79 vs. 2.82 μg/dL for nonsmoker and smokers respectively ($p < 0.01$, Table 4). AGMs for quartiles of eGFR did not differ for any GF stage.

Irrespective of gender, race/ethnicity, smoking status, and eGFR quartiles, AGMs for urine lead consistently increased from GF-1 through GF-3A and then decreased for GF-3B/4 (Table 4). For example, for NHB, AGMs for GF-1, GF-2, GF-3A, and GF-3B/4 were 0.42, 0.58, 0.69, and 0.44 μg/L respectively.

Males had statistically significantly higher AGMs than females for GF-1 and GF-2 ($p \leq 0.02$, Table 4). For example, for GF-2, AGMs for males and females were 0.64 and 0.59 μg/L respectively ($p = 0.02$). Nonsmoker had statistically significantly lower AGMs than smokers ($p < 0.1$) for GF-1 and GF-2 ($p < 0.01$). For example, for GF-1, AGMs for smokers and nonsmokers were 0.56 and 0.43 μg/L respectively ($p < 0.01$, Table 4). For both GF-1 and GF-2, eGFR Q1 had lower AGMs than Q2, Q3, and Q4. For example, for GF-2, urine lead AGMs were 0.53, 0.60, 0.64, and 0.68 μg/L for Q1, Q2, Q3, and Q4 respectively ($p < 0.01$).

### 3.3. Associations of blood and urine lead with independent variables across the stages of glomerular function

Adjusted levels of both blood and urine lead were found to be positively associated with age for every GF stage ($p < 0.01$, Table 5). BMI was negatively associated with the levels of blood lead for GF-1 ($\beta = -0.42455$, $p < 0.01$) and GF-2 ($\beta = -0.28917$, $p < 0.01$) and with the

**Table 4**
Adjusted geometric means with 95% confidence intervals for blood lead in μg/dL and urine lead in μg/L for US adults aged > =20 years by gender, race/ethnicity, smoking status, and quartiles of eGFR by stages of glomerular function. Data from National Health and Nutrition Examination Survey.2003–2016.

| | Glomerular Function Stage | | | |
|---|---|---|---|---|
| | GF-1 | GF-2 | GF-3A | GF-3B/4 |
| **Blood Lead** | | | | |
| Total | 1.23 (1.19 – 1.27) | 1.78 (1.70 – 1.86) | 2.25 (1.95 – 2.60) | 2.15 (1.92 – 2.41) |
| Males (M) | 1.47 (1.41 – 1.53) | 2.08 (1.98 – 2.18) | 2.60 (2.22 – 3.04) | 2.58 (2.27 – 2.94) |
| Females (F) | 1.03 (0.99 – 1.06) | 1.53 (1.45 – 1.61) | 1.95 (1.64 – 2.31) | 1.79 (1.57 – 2.04) |
| Non-Hispanic Whites (NHW) | 1.11 (1.07 – 1.15) | 1.67 (1.62 – 1.72) | 2.22 (1.99 – 2.49) | 2.15 (1.94 – 2.38) |
| Non-Hispanic Blacks (NHB) | 1.24 (1.19 – 1.29) | 1.97 (1.86 – 2.08) | 2.69 (2.32 – 3.11) | 2.31 (1.96 – 2.72) |
| Hispanics (HISP) | 1.27 (1.22 – 1.33) | 1.67 (1.57 – 1.77) | 1.86 (1.33 – 2.59) | 1.73 (1.37 – 2.18) |
| Others (OTHR) | 1.30 (1.18 – 1.43) | 1.85 (1.64 – 2.08) | 2.31 (1.87 – 2.86) | 2.49 (1.78 – 3.48) |
| Nonsmoker (NSM) | 1.05 (1.01 – 1.08) | 1.50 (1.44 – 1.56) | 1.79 (1.62 – 1.99) | 2.07 (1.83 – 2.33) |
| Smoker (SM) | 1.44 (1.38 – 1.51) | 2.12 (1.98 – 2.27) | 2.82 (2.15 – 3.70) | 2.24 (1.91 – 2.62) |
| Quartile 1 (Q1) | 1.19 (1.13 – 1.24) | 1.72 (1.61 – 1.83) | 2.15 (1.82 – 2.54) | 2.40 (2.06 – 2.80) |
| Quartile 2 (Q2) | 1.25 (1.19 – 1.30) | 1.79 (1.68 – 1.91) | 2.28 (1.93 – 2.70) | 2.12 (1.78 – 2.53) |
| Quartile 3 (Q3) | 1.23 (1.16 – 1.29) | 1.85 (1.73 – 1.97) | 2.23 (1.87 – 2.67) | 2.14 (1.80 – 2.53) |
| Quartile 4 (Q4) | 1.25 (1.20 – 1.31) | 1.78 (1.68 – 1.88) | 2.35 (1.87 – 2.95) | 1.96 (1.61 – 2.38) |
| SSD[a] | M > F($p < 0.01$), NHW < NHB ($p < 0.01$), NHW < HISP ($p < 0.01$), NHW < OTHR ($p < 0.01$), NSM < SM ($p < 0.01$), | M > F($p < 0.01$), NHW < NHB ($p < 0.01$), NSM < SM ($p < 0.01$) | M > F($p < 0.01$), NHW < NHB ($p = 0.04$), NSM < SM ($p < 0.01$) | M > F ($p < 0.01$) |
| **Urine Lead** | | | | |
| Total | 0.49 (0.46 – 0.52) | 0.61 (0.57 – 0.65) | 0.68 (0.58 – 0.79) | 0.47 (0.40 – 0.55) |
| Males (M) | 0.51 (0.48 – 0.55) | 0.64 (0.59 – 0.68) | 0.69 (0.58 – 0.83) | 0.49 (0.40 – 0.60) |
| Females (F) | 0.47 (0.44 – 0.49) | 0.59 (0.54 – 0.64) | 0.66 (0.56 – 0.79) | 0.45 (0.38 – 0.53) |
| Non-Hispanic Whites (NHW) | 0.45 (0.42 – 0.48) | 0.59 (0.57 – 0.62) | 0.67 (0.57 – 0.77) | 0.52 (0.45 – 0.60) |
| Non-Hispanic Blacks (NHB) | 0.42 (0.40 – 0.45) | 0.58 (0.55 – 0.62) | 0.69 (0.56 – 0.84) | 0.44 (0.36 – 0.53) |
| Hispanics (HISP) | 0.58 (0.55 – 0.62) | 0.62 (0.57 – 0.66) | 0.68 (0.53 – 0.87) | 0.40 (0.29 – 0.55) |
| Others (OTHR) | 0.51 (0.46 – 0.57) | 0.66 (0.54 – 0.80) | 0.68 (0.53 – 0.87) | 0.53 (0.35 – 0.82) |
| Nonsmoker (NSM) | 0.43 (0.40 – 0.45) | 0.54 (0.51 – 0.57) | 0.57 (0.52 – 0.62) | 0.45 (0.39 – 0.52) |
| Smoker (SM) | 0.56 (0.52 – 0.60) | 0.69 (0.63 – 0.76) | 0.81 (0.58 – 1.11) | 0.49 (0.38 – 0.64) |
| Quartile 1 (Q1) | 0.43 (0.39 – 0.46) | 0.53 (0.49 – 0.57) | 0.63 (0.54 – 0.74) | 0.47 (0.38 – 0.57) |
| Quartile 2 (Q2) | 0.47 (0.44 – 0.50) | 0.60 (0.55 – 0.66) | 0.69 (0.60 – 0.80) | 0.47 (0.38 – 0.59) |
| Quartile 3 (Q3) | 0.50 (0.47 – 0.53) | 0.64 (0.58 – 0.69) | 0.68 (0.55 – 0.83) | 0.46 (0.37 – 0.58) |
| Quartile 4 (Q4) | 0.57 (0.54 – 0.61) | 0.68 (0.64 – 0.73) | 0.71 (0.54 – 0.94) | 0.47 (0.37 – 0.61) |
| SSD[a] | M > F ($p < 0.01$), NHW < HISP ($p = 0.03$), NHW < OTHR ($p < 0.01$), NHB < HISP ($p < 0.01$), NHB < OTHR ($p < 0.01$), NSM < SM ($p < 0.01$), Q1 < Q2 ($p = 0.04$), Q1 < Q3 ($p < 0.01$), Q1 < Q4 ($p < 0.01$), Q2 < Q4 ($p < 0.01$), Q3 < Q4 ($p < 0.01$) | M > F ($p = 0.02$), NSM < SM ($p < 0.01$), Q1 < Q2 ($p = 0.04$), Q1 < Q3 ($p < 0.01$), Q1 < Q4 ($p < 0.01$), Q2 < Q4 ($p = 0.046$) | | |

[a] Statistically significant differences, p-values were adjusted for multiple comparisons by Tukey-Kremer method.

**Table 5**
Adjusted regression coefficients with p-values associated with age, log10 transformed values of body mass index (BMI), poverty income ratio (PIR), fasting time, survey year, and diabetes and hypertension status for log10 transformed vales of blood and urine lead by stages of glomerular function (GF) for US adults aged > =20 years. Data from National Health and Nutrition Examination Survey 1999–2014.

| | Glomerular Function Stage | | | |
|---|---|---|---|---|
| | GF-1 | GF-2 | GF-3A | GF-3B/4 |
| **Blood Lead** | | | | |
| Age | 0.00951 (< 0.01) | 0.00776 (< 0.01) | 0.00436 (< 0.01) | 0.00396 (< 0.01) |
| Log10(BMI) | −0.42455 (< 0.01) | −0.28917 (< 0.01) | −0.13588 (0.30) | −0.32850 (0.25) |
| PIR | −0.00734 (0.01) | −0.01096 (0.02) | −0.01812 (0.11) | −0.00432 (0.70) |
| Hypertensive | 0.01227 (0.29) | 0.00395 (0.75) | 0.02580 (0.40) | 0.07546 (< 0.01) |
| Diabetic | −0.10360 (< 0.01) | −0.10315 (< 0.01) | −0.12784 (< 0.01) | −0.02918 (0.36) |
| Fast | 0.00075 (0.28) | 0.00125 (0.21) | −0.00005 (0.98) | 0.00057 (0.83) |
| Survey Year | −0.04222 (< 0.01) | −0.04158 (< 0.01) | −0.03221 (< 0.01) | −0.03289 (< 0.01) |
| **Urine Lead** | | | | |
| Age | 0.01200 (< 0.01) | 0.01056 (< 0.01) | 0.00802 (< 0.01) | 0.00794 (< 0.01) |
| Log10(BMI) | −0.23745 (< 0.01) | −0.24096 (< 0.01) | −0.36053 (0.02) | −0.07651 (0.69) |
| PIR | −0.01041 (< 0.01) | −0.01270 (0.01) | −0.01217 (0.34) | 0.00951 (0.52) |
| Hypertensive | −0.00326 (0.77) | −0.01777 (0.22) | −0.00078 (0.98) | 0.09238 (0.01) |
| Diabetic | −0.03785 (0.02) | −0.05226 (< 0.01) | −0.06925 (0.04) | −0.01356 (0.76) |
| Fast | −0.00362 (< 0.01) | −0.00336 (0.01) | −0.00242 (0.29) | −0.00302 (0.32) |
| Survey Year | −0.06441 (< 0.01) | −0.05765 (< 0.01) | −0.05336 (< 0.01) | −0.04733 (< 0.01) |
| Urine Creatinine | 0.00301 (< 0.01) | 0.00312 (< 0.01) | 0.00265 (< 0.01) | 0.00339 (< 0.01) |

**Table 6**
Percent change in adjusted geometric means from GF-1 and GF-3A and from GF-3A to GF-3B/4 for blood lead and urine lead. Data from National Health and Nutrition Examination Survey 1999−201.

| | For Blood Lead | | For Urine Lead | |
|---|---|---|---|---|
| | Change from GF-1 to GF-3A | Change from GF-3A to GF-3B/4 | Change from GF-1 to GF-3A | Change from GF-3A to GF-3B/4 |
| Total | 83.3 | −4.5 | 36.3 | −29.3 |
| Males | 77.4 | −0.8 | 41.6 | −32.3 |
| Females | 89.5 | −8.0 | 49.0 | −22.2 |
| Non-Hispanic White | 100.8 | −3.4 | 62.0 | −36.5 |
| Non-Hispanic Black | 117.1 | −14.2 | 16.9 | −41.0 |
| Hispanic | 45.8 | −7.0 | 32.1 | −21.3 |
| Others | 77.7 | 7.9 | 33.8 | −21.3 |
| Nonsmoker | 71.7 | 15.2 | 44.3 | −39.2 |
| Smoker | 95.7 | −20.8 | 47.5 | −25.7 |
| Q1 | 81.3 | 11.7 | 48.7 | −31.6 |
| Q2 | 83.1 | −6.8 | 36.3 | −31.5 |
| Q3 | 82.0 | −4.3 | 24.6 | −34.1 |
| Q4 | 87.0 | −16.4 | 38.9 | −30.8 |

levels of urine lead for GF-1 (β= - 0.23745, p < 0.01), GF-2 (β= - 0.24096, p < 0.01), and GF-3A (β= - 0.36053, p = 0.02). Being hypertensive was associated with higher levels of blood lead (β = 0.07546, p < 0.01) as well as urine lead for GF-3B/4 (β = 0.09238, p < 0.01). Being diabetic was associated with lower levels of blood and urine lead for GF-1, GF-2, and GF3A (p ≤ 0.04, Table 5). Adjusted levels of both blood and urine lead decreased over 1999–2014 (p < 0.01) for every GF stage (Table 5).

## 4. Discussion

There was no doubt that there was a consistent change from GF-1 to GF-3A for both blood and urine lead due to increased uptake of lead as kidney function deteriorated from GF-1 to GF-3A (Table 6). For blood lead, increase from GF-1 to GF-3A varied from 45.8% for Hispanics to 117.1% for non-Hispanic blacks (Table 6). These increases, however, for urine lead were much smaller from 16.9% for non-Hispanic blacks to 62% for non-Hispanic whites. Decreases from GF-3A to GF-3B/4, possibly due to reduced re-absorption of lead, for blood lead were from 3.4% for non-Hispanic white to 20.8% for smokers. Decreases from GF-3A to GF-3B/4 for urine lead were from 21.3% for Hispanics to 41% for non-Hispanic blacks. Thus, it must be noted that percent increases from GF-1 to GF-3A for urine lead were smaller than for blood lead (36.3% vs 83.3%, Table 6) and percent decreases from GF-3A to GF-3B/4 for urine lead were larger than for blood lead (29.3% vs. 4.5%, Table 6, Fig. 1, Panel A).

The increases from GF-1 to GF-3A for blood lead for males and females were comparable (Fig. 1, Panel B) but while for males, there was almost no decrease from GF-3A to GF-3B/4 (2.60 to 2.58 μg/dL), decrease for females was about 20% from 1.95 to 1.79 μg/dL. It may be that reduction in reabsorption among females is larger than among males. However, decrease among males and females from GF-3A to GF-3B/4 for urine lead was similar (Fig. 1, Panel C).

There have been quite a few studies that have reported on the effect of factors like gender, race/ethnicity, and smoking status on the concentration levels of blood and urine lead. However, almost all of these studies reported their results for the data that were not stratified by GF stages contrary to what was done for this study. Since, the sample sizes for GF-1 and GF-2 of 5710 and 3263 respectively were overwhelmingly larger than the sample sizes of 563 and 286 (Table 1) for GF-3A and GF-3B/4 respectively, it should be expected that the results of studies unstratified by GF stages should be more like the results we had for the models fitted for GF-1 and GF-2. In a study [15] that used NHANES data for blood lead for 2003–2012, US males aged 20–64 years were found to have higher adjusted blood lead levels than females aged 20–64 years (1.66 for males vs. 1.13 μg/dL for females). Adjusted levels of 1.47 μg/dL for males and 1.03 μg/dL for this study for GF-1 are closer to the results obtained by Jain [15] than the results for any other GF stage. The results by Jain [15] are too far apart from the results, for example for GF-3A (2.60 μg/dL for males vs. 1.95 μg/dL for females) or GF-3B/4 (2.58 μg/dL for males vs. 1.79 μg/dL for females). Richter et al. [16] used NHANES data for 1999–2008 and showed males aged ≥ 19 years to have higher levels of blood lead than females aged ≥19 years. Kim et al. [17] and Bonberg et al. [18] also showed males to have higher blood lead levels than females.

For blood lead, curves for NHB and NHW keeps diverging from GF-1 to GF-3A but than from GF-3A onwards, they start coming closer together signifying a larger decrease among NHB than NHW (Fig. 1, Panel D). For urine lead, however, curves for NHB and NHW almost coincide with each other (Fig. 2, Panel A). The steep drop for urine lead for HISP from GF-3A to GF-3B/4 from 0.68 to 0.40 μg/L is worth noticing (Fig. 2, Panel A).

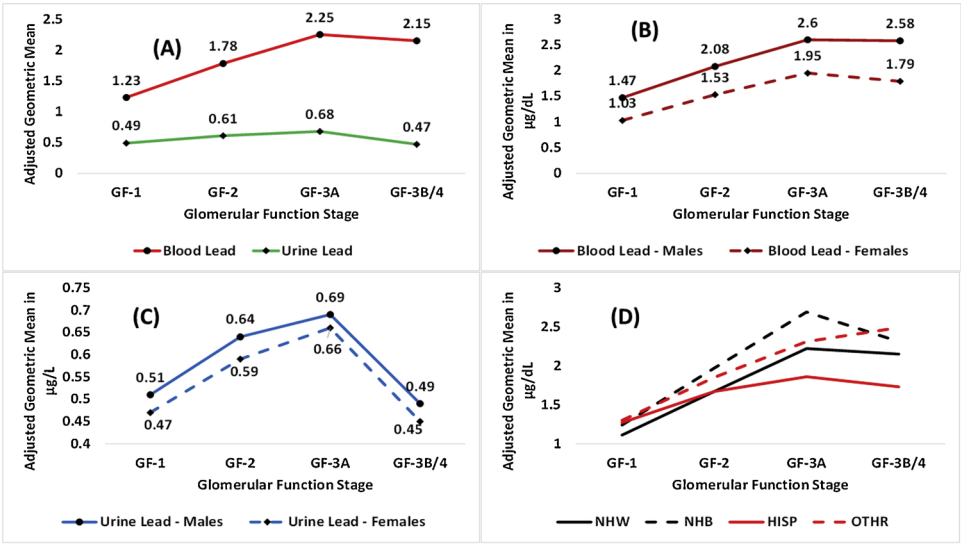


**Fig. 1.** Adjusted geometric means by stages of glomerular function (GF-1, GF-2, GF-3A, and GF-3B/4) for (A) for the total population for blood lead in µg/dL and urine lead in µg/L, (B) for males and females for blood lead in µg/dL, (C) for males and females for urine lead in µg/L, and (D) for non-Hispanic white, non-Hispanic black, Hispanics, and other unclassified race/ethnicities for blood lead in µg/dL.

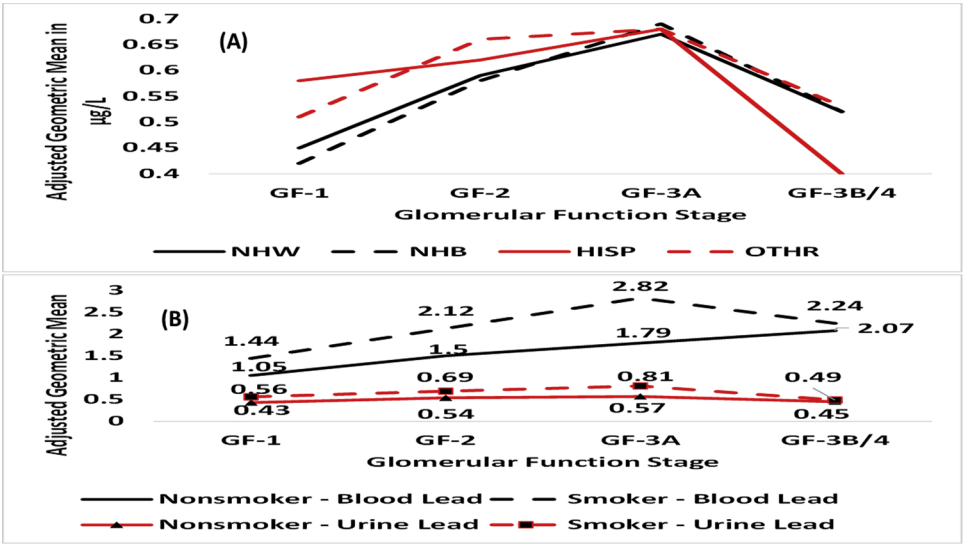


**Fig. 2.** Adjusted geometric means by stages of glomerular function (GF-1, GF-2, GF-3A, and GF-3B/4) for (A) for non-Hispanic white (NHW), non-Hispanic black (NHB), Hispanics (HISP), and other unclassified race/ethnicities (OTHR) for urine lead in µg/L, (B) for smokers and nonsmokers in blood lead in µg/dL and urine lead in µg/L.

For this study, NHW were found to have lower levels of blood lead than NHB for GF-1 and GF-2, NHW had lower levels of blood lead than HISP at GF-1, and NHW as well as NHB were found to have lower levels of urine lead than HISP at GF-1 (Table 4). Richter et al. [16] also reported NHW to have lower levels of blood lead than NHB and Mexican Americans. Jain [15] reported adjusted levels of blood lead to be 1.22 and 1.42 µg/dL for NHW and NHB respectively which are close to the adjusted levels of 1.11 and 1.24 µg/dL for NHW and NHB respectively at GF-1 but substantially lower than the adjusted levels of 2.15 and 2.31 µg/dL for NHW and NHB respectively at GF-3B/4.

Nonsmoker, probably was one of the demographic groups for which there was a straight forward increase in blood lead from 1.05 to 2.07 µg/dL (Fig. 2, Panel B). Increases in blood lead for smokers from GF-1 to GF-3A were substantially sharper than for nonsmokers but at GF-3B/4, smokers had only an advantage of 0.13 µg/dL over nonsmokers compared to the advantage of 1.03 µg/dL they had at GF-3A (Fig. 2, Panel B). Thus, smokers spill lead in urine much faster than nonsmokers in advance kidney failure. Similar trends were observed for urine lead also. Compared to the decrease of 0.32 µg/L from GF-3A to GF-3B/4 for smokers, the decrease for nonsmokers was 0.12 µg/L.

Jain [15] reported adjusted levels of blood lead among US 20–64 year old smokers and nonsmokers to be 1.54 and 1.22 µg/dL, the adjusted levels that were close to the adjusted levels of 1.44 and 1.05 µg/dL found for smokers and nonsmokers respectively at GF-1 (Table 4). Richter et al. [16] also reported blood lead levels to be higher among smokers than nonsmokers. Quite a few other studies [18–24] have reported association between elevated lead levels and mainstream and/or passive smoking.

Positive association between age and the levels of blood lead as observed for this study was also reported by Jain [15] and Richter et al. [16]. For this study, at least at GF-1 and GF-2, body mass index was observed to be negatively associated with blood as well as urine lead levels. Jain [15] also reported obese to have lower levels of blood lead which is in conformity with what was found for this study. Scinicariello et al. [25] also reported a negative association between body mass index and quartiles of blood lead.

For this study, positive association between hypertension and blood/urine lead levels was observed only among those who were in GF-3B/4 or had moderate to severe loss of glomerular function. There have been many studies that have evaluated the associations between blood lead levels and blood pressure as well as prevalence of hypertension and the results have not necessarily been consistent from one study to another. Park et al. [26] and Lee et al. [27] found systolic and diastolic blood pressure to be positively associated with blood lead levels in a Korean population. In an occupational population, Han et al. [28] reported positive association between blood lead levels and

systolic and diastolic blood pressure and hypertension related morbidity. An et al. [29] did not find elevated blood pressure levels to be associated with blood lead levels among workers of a smelting industry. Low blood lead concentrations were reported to be positively associated with diastolic blood pressure and increased odds of hypertension among ≥ 40 year old Brazilians [30]. In a Swedish follow up study among 46–67 years old, Gambelunghe et al. [31] reported positive associations between blood lead levels in fourth quartile to be associated with higher systolic and diastolic blood pressure as well as increased prevalence of hypertension. Among non-hypertensive Korean adults, Lee et al. [32] reported blood lead levels in the fourth quartile o be associated with prehypertension. Based on a Canadian survey, Bushnik et al. [33] reported a modest association between blood lead levels and systolic blood pressure among 40–54 years old and with diastolic blood pressure among 40–79 years old but no associations were reported with hypertension.

A negative association between blood as well as urine lead with diabetes was observed for this study (Table 5) for those who were in GF-1, GF-2, and GF-3A. We could not find a study that could confirm or deny these findings. More research may be needed to investigate this associations.

For this study, levels of both blood and urine lead increased as glomerular function declined from stage 1 to stage 3A or as eGFR decreased. Thus, a negative associations between blood as well as urine lead levels with eGFR was observed. However, this association did not continue to GF-3B/4. Yu et al. [6] reported an increase of 1 μg/dL in blood lead levels to be associated with a reduction of 4 mL/min in eGFR. Harari et al. [8], for a follow up study, reported higher levels of decrease in eGFR for those who were in third or fourth quartiles of blood lead than those who were in first and second quartiles of blood lead. Trzeciakowski et al. [34] also reported a negative relationship between blood and urine lead and kidney function. Thus, findings of Yu et al. [6], Harari et al. [8], and Trzeciakowski et al. [34] align with what was observed for this study in spite of the differences in study design. Buser et al. [7], however, reported a positive association between urine lead levels and eGFR which is contrary to the findings of this study. The reasons for this contradiction are not known.

### 4.1. Concluding remarks

Concentration levels of both blood and urine lead follow inverted U-shaped distributions across the full spectrum of glomerular function with points of inflections located at GF-3A.

## Conflicts of interests

Ram B Jain declares that he had no financial and/or other conflicts that could have affected the conclusions arrived at in this communication. No human subjects were involved in this research and all data used in this research are available free of cost at www.cdc.gov/nchs/nhanes.htm.

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