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Kidney biomarkers associated with blood lead, mercury, and cadmium in premenopausal women: a prospective cohort study

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Abstract

Certain metals are harmful to the kidney and liver at high levels but associations with functional biomarkers at low exposure levels among premenopausal women has not apparently been evaluated. Healthy, regularly menstruating women (n=259) were followed for up to two menstrual cycles with up to 16 visits. Renal and liver biomarkers were measured in serum at each clinic visit. Cadmium (Cd), lead (Pb), and mercury (Hg) were measured in whole blood at baseline. Linear mixed models were adjusted for age, body mass index (BMI), race, average calories, alcohol intake, smoking, and cycle day. Median levels of Cd, Pb, and Hg were 0.31 μg/l, 0.88 μg/dl, and 1.1 μg/l, respectively. One-third of women had diminished glomerular filtration rate (eGFR) (<90 ml/min/1.73m^2). Each 2-fold increase in Cd was associated with a negative 4.9% change in blood urea nitrogen (BUN) and bilirubin. Each 2-fold rise in Pb was associated with decreased eGFR and increased creatinine. A 2-fold elevation in Hg was associated with higher protein and reduced alkaline phosphatase. In healthy, predominantly nonsmoking women, low levels of Cd, Pb, and Hg were associated with changes in select biomarkers of kidney and liver function.

Keywords

cadmium; lead; mercury; liver; kidney; renal; hepatic; women

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Competing interests
The authors declare no competing financial interest.

Background

Kidney disease is increasing in prevalence and is the ninth leading cause of death in the United States (Coresh et al. 2007) and constitutes a serious public health problem globally. Risk factors for kidney disease include metabolic syndrome, diabetes, and hypertension, but environmental exposures may play a role in the burden of kidney disease, as Cd and Pb exposures at high levels are nephrotoxic (Batuman et al. 1983; Jin et al 1987). However, studies exist among non-occupationally low-level exposed populations with respect to functional kidney and liver biomarkers in healthy populations (Navas-Acien et al. 2009, Ginsberg 2012, Huang et al. 2009, Carneiro et al. 2014).

Non-essential metal exposure is nearly ubiquitous among US women of child-bearing age; sources of Cd include cigarette smoking, consumption of shellfish and organ meats; while Pb sources include inhalation of metal contaminated air and dust and ingestion of Pb contaminated water. Mercury exposure is predominantly from fish consumption (Pirkle et al. 1994; McElroy et al. 2007; Mahaffey et al.2004; Nunes et al. 2014). Metal exposure has been associated with adverse kidney functions (Navas-Acien et al. 2009). In particular, blood Cd and Pb were associated with albuminuria and reduced glomerular filtration rate (eGFR) in a national US sample (Navas-Acien et al. 2009; Ginsberg 2012), as well as with reduced eGFR among a cohort of Korean women (Hwangbo et al. 2011), reduced creatinine clearance and eGFR among older cohorts of women (Satarug et al. 2004; Thomas et al. 2009; Akesson et al. 2005), oxidative stress (Huang et al. 2013), and tubular impairment (Lin et al. 2001; Staessen et al. 1992). Lead was also found to be associated with reduced creatinine clearance (Staessen et al. 1992). To date, few epidemiologic investigations exist on the relationship between nonessential metals and liver function. Increases in liver functional biomarkers were found in an occupational study of metal-exposed paint workers (Orisakwe et al. 2007) and among Pb-exposed mechanical workers (Dioka 2004).

Previous studies have not investigated associations of Pb, Cd, and Hg in relation to markers of liver and renal function in premenopausal, healthy, predominantly nonsmoking women. The comprehensive metabolic panel (CMP) is a group of screening measures that provide clinically relevant information on renal and liver function, electrolyte and acid/base balance, and blood sugar and proteins. These tests are used as a screening tool for diabetes, liver and kidney disease. Normal ranges for specific test components are: eGFR 90 - 120 ml/min/1.73 m^2, albumin 3.9-5 g/dl, blood urea nitrogen (BUN) 7-20 mg/dl, chloride 96-106 mmol/l, CO_2 20-29 mmol/l, creatinine 0.8-1.4 mg/dl, glucose 70-100 mg/dl, potassium 3.7-5.2 mmol/l, total protein 6.3-7.9 g/dl, uric acid 3.8-8.9 mg/dl, alanine aminotransferase (ALT) 8-37 IU/L, alkaline phosphatase (ALP) 44-147 IU/L, aspartate aminotransferase (AST) 10-34 IU/L, and bilirubin 6.3-7.9 mg/dl. The current study evaluated relationships between these markers and levels of Cd, Pb, and Hg.

Methods

Study population

The BioCycle Study was previously explained in detail (Wactawski-Wende et al. 2009). The study goal was to enroll healthy, premenopausal women aged 18-44 from around Buffalo, New York between 2005-2007 to better understand the association between reproductive hormones and biomarkers of oxidative stress. Women were followed for up to 2 menstrual cycles (n=259), with up to 8 clinic visits per cycle. Inclusion criteria comprised self-reported body mass index (BMI) between 18 and 35 at screening, not trying to conceive, not currently taking medication or vitamins, no history of chronic disease such as heart disease, diabetes mellitus, cancer, inflammatory diseases, autoimmune, liver or kidney disease, thyroid disease or any other endocrine dysfunction, no history of liver or kidney disease requiring treatment in the past year, and not following a special diet. The University at Buffalo Health Sciences Institutional Review Board (IRB) approved the study, and served as the IRB designated by the National Institutes of Health for this study under a reliance agreement. All participants provided written informed consent.

The BioCycle Study clinic visits were individually timed using ClearBlue Easy Fertility Monitors to occur on days 2, 7, 12, 13, 14, 18, 22, and 27 of a typical 28-day menstrual cycle. Overall, compliance to the study protocol was high, with 94% of women completing at least 7 clinic visits per cycle and 100% completing 5 visits per cycle.

Metals

Cadmium, Pb, and Hg were measured in whole blood collected at study enrollment in EDTA purple-topped tubes, which were pre-screened for trace metals (Becton, Dickinson and Company, Franklin Lakes, NJ). Samples were analyzed at the Division of Laboratory Sciences, National Center for Environmental Health at the United States Centers for Disease Control and Prevention using inductively coupled plasma mass-spectrometry. The total concentration of Hg in blood characterizes elemental, inorganic, and organic forms of Hg. Lab limits of detection (LOD) for Cd, Pb, and Hg were 0.2 μg/l (25% of samples < LOD), 0.25 μg/dl (0% < LOD), and 0.3 μg/l (12% < LOD). The lab reported all values and did not substitute for levels below the LOD to minimize potential biases and all reported values were used in the analysis (Schisterman et al. 2006).

Kidney and liver biomarkers

The complete metabolic profile (CMP) was measured in fasting samples collected at each clinic visit by the Kaleida Center for Laboratory Medicine, Buffalo, NY using an LX20 automated chemistry analyzer (Beckman, Brea, CA). The CMP measured the following functional biomarkers for kidney (BUN, calcium, chloride, creatinine, CO_2, glucose, eGFR, potassium, protein) and liver (albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin) function in serum. The Modification of Diet in Renal Disease Study equation was used to estimate eGFR in ml/min/1.73 m^2 = 186.3 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ ×0.742 (Levey et al. 2003). The % of measurements with eGFR <60 ml/min/1.73 m^2, the clinical cut-point for chronic kidney disease stages 3-5, was 3.33% (133 measurements below the cut-point out of a total 3833

measurements in this study). An average of 7.67 kidney and liver function measurements were available for each participant per menstrual cycle and 94% of participants had 7 or 8 measures per cycle, with a maximum of 8. Because this proportion was so low, participants were also categorized as having reduced eGFR if levels were <90 ml/min/1.73 m^2, the cutoff for stage 1 risk for chronic kidney disease according to the National Kidney Foundation (National Kidney 2002).

Covariate measurement

Lifestyle (including diet and smoking) and reproductive health history questionnaires were completed by study participants at baseline. A food frequency questionnaire developed by the Nutrition Assessment Shared Resource of the Fred Hutchinson Cancer Research Center (Seattle, WA) was used to assess dietary factors at baseline (6-month recall). Height and weight were measured according to standardized protocols. Alcohol consumption was based upon the average number of drinks recorded each day in the daily diaries. The majority of participants (89%) completed at least 75% of their daily diaries. Reproductive hormones, estradiol, progesterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH), were measured in serum at each visit using solid-phase competitive chemiluminescent enzyme immunoassay (Immulite 2000).

Statistical methods

Descriptive statistics for the whole BioCycle Study population were calculated overall and by category of eGFR. Kidney and liver biomarkers were evaluated for variation outside of normal ranges over the course of the menstrual cycle and for association with reproductive hormones (Prati et al. 2002). Linear mixed models with random intercepts were used to evaluate changes in kidney function in relation to metal exposure levels, as such models account for repeated measures among women. Cadmium, Pb, and Hg were included together in all models. Due to their log normal distribution, metals, liver, and kidney biomarker values were log transformed. Interactions between metals were tested for all kidney and liver biomarkers with metals categorized by tertiles and using continuous levels. Metals were categorized by tertiles to evaluate threshold effects. The risk of reduced eGFR (<60 and <90 ml/min/1.73m^2) associated with increased blood metal levels was evaluated using generalized estimating equations. Confounders were assessed using directed acyclic graphs based upon *a priori* review of the literature and consideration of model convergence. To account for possible differences across the menstrual cycle, we adjusted for cycle day. Linear mixed models were adjusted for age (continuous), race (white, non-Hispanic black, Asian, other), BMI (continuous), alcohol (average number of drinks/day), calories (average/cycle), cycle day, and smoking (current/not current) while generalized estimating equations were adjusted for age, race, and BMI. As exposure and outcome variables were log-transformed, results of these models are presented as a % change in the non-transformed values per 2-fold increase in the non-transformed exposure using the formula: $(2^{\beta-1} \times 100)$, where β is the regression coefficient. Statistical significance level was set at α=0.05 and all statistical tests were two-sided. SAS version 9.3 was used for all statistical analyses (Cary, NC).

Results

Participant characteristics

Overall, BioCycle Study participants were young, 40% were non-white, of normal BMI (mean 24.09), the majority graduated high school, and only 4% reported current smoking (Table 1). Participants with reduced eGFR were slightly older, with higher BMI and creatinine, a greater proportion was white that had lower albumin. Metals levels differed by race, with non-Hispanic blacks displayed the highest levels of Pb and Hg, when compared with those self-identifying as white, Asian, or other. Median (IQR) levels of Cd, Pb, and Hg were 0.3 (0.19-0.43) μg/l, 0.86 (0.68-1.2) μg/dl, and 1.1 (0.58-2.1) μg/l, respectively. Levels of Pb and Cd did not markedly vary by eGFR status, while Hg levels were lower among those with reduced eGFR (Table 2). Overall, mean eGFR was 99.66 (SD 20.63) ml/min/ $1.73m^2$. Biomarker values did not change significantly over the menstrual cycle. eGFR was not significantly associated with reproductive hormones levels (Table 2).

Blood metal levels and kidney and liver functional biomarkers

Estimates were based on models that included all metals in the same analysis. Overall, metals were associated with select significant changes in some of the functional kidney (Table 3) and liver biomarkers (Table 4). Pb was associated significantly with reduced eGFR and with increased serum creatinine. Lead was not associated with BUN, CO_2, chloride, potassium, urate, calcium, protein, albumin, glucose, AST, ALT, ALP, or bilirubin. Cadmium was associated with significantly reduced BUN, bilirubin, but not with other kidney and liver markers. Mercury was associated with significantly increased protein levels and reduced ALP. Mercury was not associated with other kidney or liver markers.

When modeled in tertiles, Pb was associated with significantly decreased eGFR and increased creatinine and AST (Table 5). Cd was associated with significantly elevated potassium and reduced bilirubin when comparing the highest tertile to the lowest while Hg was associated with significantly increased BUN. No statistically significant interactions were observed (results not shown). The odds of low eGFR (<60 and <90 ml/min/$1.73m^2$) were not significantly associated with Cd, Pb, or Hg (Table 6).

Discussion

Low levels of nonessential metal exposure were associated with changes in a few biomarkers of kidney function among a population of healthy, premenopausal women with low smoking prevalence. Further, Cd was associated with decreases in BUN, while Pb was associated with a fall in eGFR and increases in creatinine; three important kidney functional biomarkers. Notably, more than one-third of the eGFR measures indicated elevated risk for kidney disease.

Our finding of an association between Pb and reduced eGFR in healthy, young women with an extremely low smoking prevalence (4% current smokers) is novel. Lead was previously associated with chronic kidney disease (as defined by eGFR <60) among an older, hypertensive population with higher metal exposure levels (Muntner et al. 2003). Lead was associated with reduced creatinine clearance among a Belgian cohort of men and women of

mean age 48 years (Staessen et al. 1992). An association between Cd, Pb, and eGFR both independently and when modeled jointly was reported in a cross-sectional nationally-representative US population (Navas-Acien et al. 2009). In contrast, Cd and Pb were modeled together and it was observed that eGFR was associated with Pb but not Cd. Several studies found an association between Cd and several biomarkers of early kidney damage: eGFR (Akesson et al. 2005), N-acetyl-β-D-glucoamininidase (NAG) (Thomas et al. 2009), and renal tubular damage (Jarup et al. 2000; Jarup and Alfven 2004) and recently urinary Cd was associated with NAG, malondialdehyde, renal and cardiovascular disease and mortality (Tellez-Plaza et al. 2013). Our negative findings with respect to Cd and eGFR may be due to the younger population with lower exposure levels compared with previous investigations. Specifically, the Swedish cohort's median urinary Cd level of 0.6 μg/l and median age of 58 (Akesson et al. 2005) compared with 0.29 μg/l and 27 years among BioCycle Study participants. Further, in Korean adult cohorts an association between Cd and adverse kidney function was observed, although exposure levels there were higher (blood Cd 1.49 μg/l and 1.21 μg/l, respectively), which may partly explain our findings (Hwangbo et al. 2011; Huang et al. 2009). However, recently, Filler et al (2012) noted high Pb levels were among pediatric dialysis patients calling into question the convention that metal exposure and altered renal function solely affects older adults. Lead levels in developing fetuses rose in relation to maternal Pb and this change increased by trimester (Lamadrid-Figueroa et al. 2006). Our findings reinforce the need to examine effects in younger, even presumably healthy, populations.

To our knowledge, there are no prior reports of decreased BUN and Cd among premenopausal women. Previous studies showed that blood Pb was associated with increased BUN at baseline but decreased BUN over time, although this association did not achieve statistical significance among older, occupationally-exposed populations with significantly higher median blood Pb levels, 31.3 μg/dl vs. 0.87 μg/dl in the BioCycle Study (Weaver et al. 2009). A cross-sectional study among adult men did not find that Pb or Cd were associated with BUN (Mortada et al. 2004); however, unlike the BioCycle Study, this study was cross-sectional and included only 68 males. A pilot study among the elderly found no marked association between Cd and BUN (Pennemans et al. 2011). An rise in protein was noted with Hg exposure. One possibility is that our finding of elevated protein levels associated with Hg might be due to confounding by fish consumption, the primary contributor to Hg exposure and a source of protein (Mahaffey et al. 2009; Nunes et al. 2014; Carneiro et al. 2014). To test this, a sensitivity analysis was conducted adjusting for fish consumption (yes/no) reported in the baseline food frequency questionnaire. Fish consumption was strongly associated with Hg exposure when Hg was categorized with those in the lowest category (no detect-0.8 μg/l) averaging 2 servings/month compared with those in the highest Hg category (>1.8 μg/l) reporting 9.8 servings/month. 33% of participants reported no fish consumption. After adjusting for fish consumption, the point estimate elevated from 0.47 to 0.53.

Occupational evidence demonstrated proximal tubular damage and nephrotoxicity (Barregard et al. 1988; Ellingsen et al. 2000; Himeno et al. 1986; Langworth et al. 1992). A small epidemiologic study of 59 women supports Hg possible nephrotoxic effects (Ohno et al. 2007), but others did not (Alinovi et al. 2002; Jarosinska et al. 2008).

Our finding of an elevation in serum creatinine associated with Pb is consistent with the previous observations that indicate that Pb alters renal function (Weaver et al. 2009; Kim et al. 1996; Staessen et al. 1992). However, some occupational studies found that Pb exposure was associated with decreased creatinine (Weaver et al. 2003; Hsiao et al. 2001). As mean Pb levels in the present study were approximately 30-fold lower than occupational exposure levels, these results may not be directly comparable. In cases of Pb toxicity, metal is deposited in the S3 segments of the proximal tubules (Cramer et al. 1974), providing a biological basis for renal effects.

Most liver biomarkers were not associated with metals. However, Cd was associated with a decrease in bilirubin. In animal studies at high exposure levels, Cd exerted adverse hepatic effects (Prabu et al. 2011). One occupational study found that Cd was not markedly associated with alterations in liver biomarkers, including bilirubin (Orisakwe et al. 2007). Levels in this occupational setting were significantly higher and while our finding may be due to chance, low-dose associations may differ from occupational findings. Hg was associated with a decrease in ALP, but in the absence of isoenzyme determination, it was not possible to confirm whether this reflects a liver source of ALP or another, such as bone or intestine. The change in ALP was not clinically significant.

Blood levels of Cd and Pb in the BioCycle Study are similar to those found among nonsmoking women in nationally-representative US population studies and our findings are therefore generalizable to other non-occupationally exposed, premenopausal women with low smoking prevalence (Mijal and Holzman 2010; Jain 2013). BioCycle Study participants had similar levels of Cd and Pb to US women of reproductive age, but higher median Hg levels (1.1 μg/l in BioCycle vs. 0.6 μg/l in US women) (Mahaffey et al. 2004). Study participants displayed blood levels that met HealthyPeople 2020 goal levels, which for Cd, Pb, and Hg are to have 95% of the population below 1.12 μg/L, 2.94 μg/dl, and 3.22 μg/L, respectively.

This study has numerous strengths. The BioCycle Study recruited a healthy population of young women without a history of chronic disease. Further, the population was ethnically diverse, with 40% of participants identifying as non-white. The BioCycle Study measured multiple biomarkers of kidney and liver function as many as 16 times across two months, providing a reliable characterization of these important functional markers. The low smoking levels among study participants was another strength, as smoking is a common source of both Cd and Pb exposure, as well as having been independently associated with adverse kidney outcomes. Due to the low smoking levels, this study was uniquely able to evaluate blood metal exposures largely without the influence of smoking. Finally, the kidney and liver biomarkers were obtained from fasting samples, eliminating some of the inherent variability over the course of the day due to recent dietary intake.

This study was subject to several limitations. Metals were measured only in blood at baseline, while kidney and liver biomarkers were measured multiple times, and it is possible that the variation in timing of measurements might impact our findings. However, assuming the sources of metal exposure are relatively similar over the span of a few months, our baseline blood levels of metals may be thought of as describing a steady-state of exposure.

Further, potentially earlier indicators of heavy metal toxicity, in particular urinary renal biomarkers of intestinal alkaline phosphatase and N-acetyl-b-D-glucosaminidase would be sensitive intermediate biomarkers with utility for future population-based studies, particularly given the signals observed in blood biomarkers in the present study. Such common biomarkers as microalbuminuria, alpha1-microglobulin, or beta2-microglobulin in urine could reflect inter-individual variation in renal uptake of low molecular weight proteins with bound Cd and Pb and may not serve as useful population measures of the effects of non-essential metals. Low levels of Pb were associated with beta2-microglobulin while Cd was associated with retinol binding protein (Chaumont et al. 2011). Further, retention of study participants was excellent, but study follow-up was limited to two menstrual cycles, or approximately two months. This short time period may prevent the observation of chronic changes in blood liver and kidney biomarkers that are associated with metals exposure. Finally, the generalizability of our findings may be limited because of the cohort selection criteria; however, data suggest that more work is needed among presumably healthy populations in particular given the high prevalence of healthy women in our study at risk for kidney disease.

Conclusions

In summary, these results provide preliminary evidence that low blood levels of Pb, Cd, and Hg were associated with select renal and liver functional biomarkers. A signal of low-dose effects of metals was noted. Further research with longer follow-up is needed among women with low-level exposure to metals to better characterize the possible effects on kidney and liver function.

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Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CMP	Complete metabolic profile
CI	Confidence interval
CDC	Centers for Disease Control
eGFR	Estimated glomerular filtration rate

IRB	Institutional Review Board
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
LOD	Limit of detection
NHANES	National Health and Nutrition Examination Survey

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Table 1

BioCycle Study population characteristics by estimated glomerular filtration rate (eGFR) status as measured at the first study visit (2005-2007)

		Reduced eGFR (<90 ml/min/1.73m^2)		
Characteristic	**Total n=257**	**No n=173**	**Yes n=84**	**p value**
Age (years) [1]	27.4 (8.2)	26.7 (7.8)	28.5 (8.9)	0.11
BMI(kg/m^2) [1]	24.1 (3.9)	23.6 (3.7)	24.9 (3.9)	0.01
Race[2]				
White	149 (59.6)	92 (55.1)	57 (68.7)	0.08
Non-Hispanic black	50 (20.0)	34 (20.4)	16 (19.3)	
Asian	36 (14.4)	30 (18.0)	6 (7.3)	
Other	15 (6.0)	11 (6.6)	4 (4.8)	
Education[2]				
<High school	32 (12.45)	18 (10.4)	14 (16.7)	0.15
>High school	225 (87.5)	155 (89.6)	70 (83.3)	
Smoking status[2]				
Never/Former	247 (96.1)	167 (96.5)	80 (95.4)	0.73
Current	10 (3.9)	6 (3.6)	4 (4.8)	
Parity[2]				
Parous	65 (25.9)	40 (23.7)	25 (30.5)	0.25
Nulliparous	186 (74.1)	129 (76.3)	57 (69.5)	
Alcohol(average drinks/day) [1]	0.43 (0.6)	0.46 (0.6)	0.39 (0.6)	0.41

[1] mean (standard deviation)

[2] n (percent)

Table 2

BioCycle Study population mean (standard deviation) biomarker levels by estimated glomerular filtration rate (eGFR) status (2005-2007)

		Reduced eGFR (<90 ml/min/1.73m^2)		
Characteristic	**Total n=257**	**No n=173**	**Yes n=84**	**p value**
Biomarkers				
Metals				
Blood cadmium (μg/l)	0.36 (0.29)	0.36 (0.32)	0.35 (0.23)	0.70
Blood lead (μg/dl)	1.03 (0.63)	1.03 (0.54)	1.02 (0.80)	0.95
Blood mercury (μg/l)	1.50 (1.33)	1.59 (1.41)	1.28 (1.29)	0.06
Cycle 1 Day 2				
Kidney Biomarkers				
Albumin (g/dl)	4.03 (0.25)	4.05 (0.25)	3.98 (0.25)	0.04
BUN (mg/dl)	9.66 (3.31)	9.36 (3.24)	10.26 (3.39)	0.04
Chloride (mmol/l)	105.17 (2.50)	105.1 (2.52)	105.2 (2.48)	0.78
CO_2 (mmol/l)	24.38 (1.61)	24.41 (1.56)	24.31 (1.71)	0.64
Creatinine (mg/dl)	0.76 (0.12)	0.7 (0.09)	0.87 (0.10)	<0.001
Glucose (mg/dl)	87.22 (6.60)	87.47 (6.20)	86.73 (7.35)	0.39
Potassium (mmol/l)	4.04 (0.37)	4.02 (3.7)	4.08 (0.38)	0.17
Protein (g/dl)	6.67 (0.36)	6.69 (0.35)	6.62 (0.36)	0.13
Uric acid (mg/dl)	4.15 (0.77)	4.06 (0.75)	4.34 (0.77)	0.005
Liver Biomarkers				
ALT (U/L)	17.22 (11.37)	16.14 (6.38)	19.43 (17.53)	0.10
ALP (U/L)	51.51 (14.17)	50.48 (14.64)	53.64 (13.00)	0.09
AST (U/L)	19.59 (7.67)	19.03 (5.93)	20.76 (10.33)	0.16
Bilirubin (mg/dl)	0.77 (0.29)	0.76 (0.29)	0.79 (0.29)	0.37
Reproductive hormones				
Estrogen (day 2) (pg/ml)	38.01 (28.18)	35.62 (18.34)	42.91 (41.42)	0.13
FSH (day 2) (mIU/ml)	6.89 (3.45)	6.90 (3.54)	6.85 (0.36)	0.90
Progesterone (day 22) (ng/ml)	8.46 (5.30)	8.68 (5.52)	8.09 (4.92)	0.41
LH (day 14) (ng/ml)	13.74 (14.27)	12.80 (12.70)	15.68 (16.97)	0.13

Table 3

Percent change in kidney biomarkers for a doubling of blood metals levels, BioCycle Study (2005-2007)

Biomarker	Metal	Unadjusted % change[a] (95% CI)	Adjusted % change[a] (95% CI)
BUN (mg/dl)	Cadmium	**−3.41 (−6.57, −0.21)**	**−4.92 (−8.17, −1.55)**
	Lead	**−6.24 (−10.56, −1.79)**	−0.13 (−4.97, 4.96)
	Mercury	2.46 (0.35, 4.68)	0.36 (−1.75, 2.52)
eGFR (ml/min/1.73m^2)	Cadmium	−1.45 (−3.61, 0.77)	−0.87 (−2.92, 1.21)
	Lead	−1.31 (−4.34, 1.89)	**−3.73 (−6.55, −0.83)**
	Mercury	1.19 (−0.28, 2.67)	0.96 (−0.33, 2.27)
Creatinine (mg/dl)	Cadmium	0.28 (−1.51, 2.10)	0.66 (−1.13, 2.48)
	Lead	0.35 (−2.13, 2.95)	3.47 (0.85, 6.16)
	Mercury	**−1.31 (−2.46, −0.21)**	−0.89 (−1.97, 0.20)
CO_2 (mmol/l)	Cadmium	−0.28 (−0.83, 0.28)	0.02 (−0.58, 0.63)
	Lead	−0.35 (−1.17, 0.49)	−0.57 (−1.43, 0.29)
	Mercury	0.07 (−0.28, 0.42)	−0.03 (−0.40, 0.35)
Chloride (mmol/l)	Cadmium	0.14 (−0.07, 0.35)	0.08 (−0.12, 0.28)
	Lead	0.14 (−0.14, 0.35)	0.20 (−0.09, 0.48)
	Mercury	−0.07 (−0.21, 0.07)	−0.07 (−0.19, 0.05)
Potassium (mmol/l)	Cadmium	0.56 (−0.28, 1.40)	0.60 (−0.22, 1.42)
	Lead	0.14 (−0.97, 1.33)	0.01 (−1.15, 1.18)
	Mercury	−0.14 (−0.62, 0.42)	−0.14 (−0.63, 0.36)
Urate mg/dl)	Cadmium	0.21 (−1.99, 2.46)	1.01 (−1.19, 3.25)
	Lead	−0.14 (−3.21, 3.03)	0.90 (−2.22, 4.12)
	Mercury	−0.83 (−2.19, 0.63)	−0.38 (−1.71, 0.97)
Calcium (mg/dl)	Cadmium	−0.35 (−0.62, −0.01)	−0.15 (−0.48, 0.17)
	Lead	−0.42 (−0.83, 0.01)	−0.21 (−0.67, 0.25)
	Mercury	0.01 (−0.21, 0.21)	0.07 (−0.12, 0.27)
Protein (g/dl)	Cadmium	−0.14 (−0.76, 0.42)	−0.19 (−0.79, 0.41)
	Lead	−0.55 (−1.38, 0.28)	−0.76 (−1.61, 0.09)
	Mercury	0.42 (0.07, 0.84)	0.47 (0.10, 0.84)
Albumin (g/dl)	Cadmium	−0.54 (−1.24, 0.17)	−0.27 (−0.90, 0.36)
	Lead	−0.22 (−1.21, 0.79)	−0.38 (−1.28, 0.52)
	Mercury	0.30 (−0.15, 0.77)	0.32 (−0.11, 0.67)
Glucose (mg/dl)	Cadmium	0.21 (−0.55, 0.98)	−0.06 (−0.90, 0.79)
	Lead	1.26 (0.21, 2.38)	0.93 (−0.28, 2.15)
	Mercury	−0.42 (−0.90, 0.07)	−0.50 (−1.01, 0.02)

Adjusted for: age, race, BMI, smoking, average calorie intake, day, and average daily alcohol. Metals and kidney/liver biomarkers were log transformed and metals were modeled together.

[a] Beta coefficients are presented as a percent change in the non-transformed outcome per 2-fold increase in non-transformed exposure using the formula: $(2^{\beta-1} \times 100)$.

Table 4

Percent change in liver biomarkers for a doubling of blood metals levels, BioCycle Study (2005-2007)

Biomarker	Metal	Unadjusted % change[a] (95% CI)	Adjusted % change[a] (95% CI)
AST (U/l)	Cadmium	−0.62 (−3.21, 2.10)	0.95 (−1.91, 3.88)
	Lead	1.54 (−2.19, 5.48)	3.33 (−0.82, 7.65)
	Mercury	−1.65 (−3.34, 0.07)	−1.54 (−3.25, 0.20)
ALT (U/l)	Cadmium	−2.80 (−6.63, 1.12)	−1.44 (−5.54, 10.78)
	Lead	2.60 (−3.07, 8.52)	4.24 (−1.92, 2.49)
	Mercury	−0.42 (−2.94, 2.10)	−0.14 (−2.71, 0.46)
ALP (U/l)	Cadmium	−0.35 (−3.47, 2.95)	0.22 (−3.02, 3.56)
	Lead	−1.58 (−6.05, 3.03)	1.42 (−3.24, 6.30)
	Mercury	**−3.27 (−5.26, −1.24)**	**−2.28 (−4.22, −0.29)**
Bilirubin (mg/dl)	Cadmium	**−3.87 (−7.02, −0.69)**	**−4.92 (−8.17, −1.55)**
	Lead	1.40 (−3.21, 6.22)	−0.13 (−4.97,4.72)
	Mercury	0.70 (−1.38, 2.88)	0.36 (−1.75, 2.46)

Adjusted for: age, race, BMI, smoking, average calorie intake, day, and average daily alcohol. Metals and kidney/liver biomarkers were log transformed and metals were modeled together.

[a]Beta coefficients are presented as a percent change in the non-transformed outcome per 2-fold increase in non-transformed exposure using the formula: $(2^{\beta-1} \times 100)$.

Table 5

Association between kidney and liver biomarkers with tertiles of cadmium, lead and mercury levels, BioCycle Study (2005-2007)

Biomarker	Metal	Cadmium	Lead	Mercury
BUN (mg/dl)	High	−0.13 (−1.01, 0.76)	−0.56 (−1.53, 0.40)	**0.89 (0.01, 1.77)**
	Med	−0.32 (−1.16, 0.53)	0.34 (−0.54, 1.22)	0.43 (−0.48, 1.34)
	Low	Ref	Ref	Ref
eGFR ($ml/min/1.73m^2$)	High	−3.08 (−8.82, 2.67)	**−6.79 (−13.10, −0.49)**	−0.26 (−6.01, 5.49)
	Med	−1.03 (−6.53, 4.48)	**−8.28 (−14.07, −2.50)**	1.07 (−4.89, 7.03)
	Low	Ref	Ref	Ref
Creatinine (mg/dl)	High	0.02 (−0.02, 0.05)	**0.05 (0.006, 0.08)**	0.003 (−0.03, 0.04)
	Med	0.003 (−0.03, 0.04)	**0.05 (0.02, 0.09)**	−0.002 (−0.04, 0.04)
	Low	Ref	Ref	Ref
CO_2 (mmol/l)	High	−0.05 (−0.05, 0.37)	−0.10 (−0.55, 0.35)	−0.12 (−0.53, 0.29)
	Med	0.09 (−0.31, 0.48)	0.05 (−0.36, 0.46)	0.14 (−0.28, 0.57)
	Low	Ref	Ref	Ref
Chloride (mmol/l)	High	0.36 (−0.17, 0.89)	0.09 (−0.48, 0.66)	−0.04 (−0.56, 0.48)
	Med	0.22 (−0.28, 0.73)	0.17 (−0.35, 0.69)	−0.42 (−0.96, 0.12)
	Low	Ref	Ref	Ref
Potassium (mmol/l)	High	**0.10 (0.0003, 0.19)**	0.01 (−0.09, 0.11)	−0.04 (−0.13, 0.06)
	Med	0.004 (−0.09, 0.10)	0.03 (−0.06, 0.13)	−0.04 (−0.14, 0.05)
	Low	Ref	Ref	Ref
Urate (mg/dl)	High	−0.02 (−0.25, 0.22)	0.20 (−0.06, 0.46)	−0.14 (−0.38, 0.09)
	Med	0.18 (−0.04, 0.41)	0.06 (−0.18, 0.29)	−0.03 (−0.27, 0.22)
	Low	Ref	Ref	Ref
Calcium (mg/dl)	High	0.002 (−0.08, 0.08)	0.02 (−0.07, 0.10)	0.02 (−0.06, 0.10)
	Med	**−0.09 (−0.16, −0.01)**	0.04 (−0.04, 0.12)	−0.02 (−0.10, 0.06)
	Low	Ref	Ref	Ref
Protein (g/dl)	High	−0.09 (−0.20, 0.01)	−0.07 (−0.19, 0.05)	0.03 (−0.07, 0.14)
	Med	−0.09 (−0.20, 0.01)	−0.02 (−0.13, 0.08)	0.04 (−0.07, 0.15)
	Low	Ref	Ref	Ref
Albumin (g/dl)	High	−0.03 (−0.10, 0.03)	−0.06 (−0.13, 0.02)	0.04 (−0.03, 0.10)
	Med	−0.04 (−0.10, 0.02)	−0.03 (−0.09, 0.04)	−0.02 (−0.09, 0.04)
	Low	Ref	Ref	Ref
Glucose (mg/dl)	High	−0.63 (−3.03, 2.05)	1.34 (−1.54, 4.20)	0.31 (−2.31, 2.93)
	Med	−0.10 (−2.63, 2.42)	−1.81 (−4.93, 0.81)	0.60 (−2.11, 3.31)
	Low	Ref	Ref	Ref
ALT (IU/L)	High	−2.00 (−6.34, 2.37)	4.35 (−0.39, 9.08)	−0.34 (−4.66, 3.99)
	Med	−2.24 (−6.39, 1.90)	0.44 (−3.88, 4.76)	0.67 (−3.79, 5.14)
	Low	Ref	Ref	Ref
AST (IU/L)	High	0.39 (−1.97, 2.75)	**3.04 (0.49, 5.59)**	−1.69 (−4.02, 0.64)

Biomarker	Metal	Cadmium	Lead	Mercury
	Med	0.02 (−2.22, 2.26)	0.02 (−2.30, 2.34)	−1.26 (−3.67, 1.14)
	Low	Ref	Ref	Ref
ALP (IU/L)	High	0.26 (−4.19, 4.71)	0.07 (−4.78, 4.93)	−2.63 (−7.06, 1.80)
	Med	0.79 (−3.53, 5.04)	−1.94 (−6.36, 2.48)	−2.46 (−7.04, 2.12)
	Low	Ref	Ref	Ref
Bilirubin (mg/dl)	High	**−0.12 (−0.22, −0.02)**	−0.005 (−0.11, 0.10)	−0.002 (−0.10, 0.09)
	Med	−0.04 (−0.14, 0.05)	0.005 (−0.09, 0.10)	0.01 (−0.09, 0.12)
	Low	Ref	Ref	Ref

Adjusted for: age, race, BMI, smoking, average calorie intake, day, and average daily alcohol. Metals and kidney/liver biomarkers were modeled together.

Cadmium tertiles: high >0.36 μg/l, medium 0.36-0.23 μg/l, low <0.23 μg/l. Lead tertiles: high >1.10 μg/dl, medium 1.10-0.72 μg/dl, low <0.72 μg/dl. Mercury tertiles: high >1.6 μg/l, medium 1.6-0.75 μg/l, low <0.75.

Note: $p<0.05$ noted by bold text in table.

Table 6

Association between low eGFR (<60 ml/min/1.73 ^{2}) and metals among reproductive aged-women using generalized estimating equations.

Metal	Unadjusted Coefficient (95% CI)	Adjusted coefficient (95% CI)
eGFR<60 ml/min/1.73 ^{2}		
Cadmium	0.60 (0.33, 1.09)	0.57 (0.26, 1.27)
Lead	0.53 (0.12, 2.31)	0.32 (0.08, 1.21)
Mercury	0.88 (0.47, 1.68)	0.88 (0.50, 1.55)
eGFR<90 ml/min/1.73 ^{2}		
Cadmium	1.19 (0.87, 1.63)	0.57 (0.26, 1.27)
Lead	1.05 (0.61, 1.82)	0.32 (0.08, 1.21)
Mercury	0.80 (0.64, 1.01)	0.88 (0.50, 1.55)

*independent correlation matrix

*adjusted for age, race, BMI