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Bone mineral density and blood metals in premenopausal women

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Abstract

Exposure to metals, specifically cadmium, lead, and mercury, is widespread and is associated with reduced bone mineral density (BMD) in older populations, but the associations among premenopausal women are unclear. Therefore, we evaluated the relationship between these metals in blood and BMD (whole body, total hip, lumbar spine, and non-dominant wrist) quantified by dual energy x-ray absorptiometry in 248 premenopausal women, aged 18–44. Participants were of normal body mass index (mean BMI 24.1), young (mean age 27.4), 60% were white, 20% non-Hispanic black, 15% Asian, and 6% other race group, and were from the Buffalo, New York region. The median (interquartile range) level of cadmium was 0.30 μg/l (0.19–0.43), of lead was 0.86 μg/dl (0.68–1.20), and of mercury was, 1.10 μg/l (0.58–2.00). BMD was treated both as a continuous variable in linear regression and dichotomized at the 10th percentile for logistic regression analyses. Mercury was associated with reduced odds of decreased lumbar spine BMD (0.66, 95% confidence interval: 0.44, 0.99), but overall, metals at environmentally relevant levels of exposure were not associated with reduced BMD in this population of healthy, reproductive-aged women. Further research is needed to determine if the blood levels of cadmium, lead, and mercury in this population are sufficiently low that there is no substantive impact on bone, or if effects on bone can be expected only at older ages.

Keywords

bone mineral density; cadmium; lead; mercury; women

1. Introduction

Osteoporosis is a leading cause of morbidity and mortality in older populations (Rachner et al., 2011) and ensuring sufficient bone mineral density (BMD) throughout the premenopausal years is a primary means to prevent later bone fractures (Seeman et al.,

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1993). Small shifts in attained peak bone mass, which is reached in the majority of women by age 18, may be important on a population scale to avoid injury and increased health care costs from falls and fractures. Many factors influence BMD, including diet, calcium intake, weight bearing physical activity and genetics (Pocock et al., 1987). Widespread exposure to metals may also play a role (Mahaffey et al., 2004;Lee et al., 2005;Mijal et al., 2010), as osteotoxic effects of metals have been reported in several studies of post-menopausal women (Staessen et al., 1999;Korrick et al., 2002;Zhu et al., 2004;Carmouche et al., 2005;Akesson et al., 2006;Campbell et al., 2007), as well as in animal studies (Ronis et al., 2001;Paik et al., 2003). Specifically, lead levels were associated with reduced BMD in postmenopausal women (Korrick et. al., 2002;Potula et al., 2006;Campbell et. al., 2007). Cadmium exposure was first associated with the osteotoxic condition Itai-itai disease in Japan (Tsuchija, 1969), and environmentally relevant levels of cadmium have been associated with reduced BMD in other cohorts (Jarup et al., 1998;Staessen et. al., 1999;Alfven et al., 2000;Akesson et. al., 2006), older populations (Jarup et al., 2004;Zhu et. al., 2004;Gallagher et al., 2008;Chen et al., 2009b;Gallagher et al., 2010), and in experimental studies (Bhattacharyya et al., 1988;Bhattacharyya et al., 1992). Animal studies also support an association between mercury exposure and lower BMD (Jin et al., 2002).

Exposure to metals may affect bone through a variety of potential mechanisms. Lead displaces calcium in bone and exposure has been shown to decrease osteoblast expression, thus decreasing collagen synthesis and bone generation (Klein et al., 1993;Ronis et. al., 2001). Cadmium may affect BMD via bone resorption at low exposure levels (Schutte et al., 2008;Chen et al., 2009a). Mercury has been found to influence calcium metabolism and affects bone (Suzuki et al., 2004).

Though these relationships have been well studied in postmenopausal women (Staessen et. al., 1999;Korrick et. al., 2002;Zhu et. al., 2004;Carmouche et. al., 2005;Akesson et. al., 2006;Campbell et. al., 2007), the association between metals exposure and BMD at multiple sites in otherwise healthy, premenopausal women has not yet been assessed. Given the widespread exposure to metals among US women (Mahaffey et. al., 2004;Lee et. al., 2005;Mijal et. al., 2010) and the evidence suggesting exposure is associated with lower BMD in postmenopausal women, our goal was to examine the effects of environmentally relevant levels of cadmium, lead, and mercury, on BMD in a cohort of healthy premenopausal women.

2. Materials and Methods

2.1 BioCycle Study

The BioCycle Study has been described elsewhere in detail (Wactawski-Wende et al., 2009). Briefly, the study goal was to enroll healthy, premenopausal women aged 18–44 from western New York State to elucidate the relationship between reproductive hormones and biomarkers of oxidative stress (Schisterman et al., 2010). Women were followed for up to 2 menstrual cycles (n=259, 250 followed for 2 cycles, 9 followed for 1 cycle), with up to 8 clinic visits per cycle (median=8) and >94% had 7 or 8 visits per cycle. Fasting blood and urine specimens were obtained at each clinic visit. Inclusion criteria included self-reported regular menstrual cycle length between 21 and 35 days for the past 6 months, self-reported body mass index (BMI) between 18 and 35 at screening, no use of hormonal contraception in the past 3 months, not pregnant or breast feeding in the past 6 months, not currently taking medication or vitamins, and not following a special diet. Recruitment and data collection occurred from 2005–2007. 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.

2.2 Metal Assessment

Metals were measured in whole blood collected at the enrollment visit. Samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes, prescreened for trace metals using inductively-coupled plasma mass spectrometry (ICP-MS) to ensure no contamination and were kept whole and refrigerated until shipment. Clinic staff followed protocols developed jointly by the Centers for Disease Control and Prevention (CDC) for sample collection, storage, and transport. ICP-MS was performed at the Division of Laboratory Sciences, National Center for Environmental Health at the CDC, to detect cadmium, lead, and mercury in whole blood. The limits of detection (LOD) for cadmium, lead, and mercury were 0.20 μg/dl (25% of samples < LOD), 0.25 μg/dl (0% < LOD), and 0.30 μg/dl (12% < LOD), respectively. Values below the LOD were reported by the lab and used in analysis to minimize potential bias (Schisterman et al., 2006).

2.3 Bone Mineral Density Measurement

BMD was measured at the final clinic visit (mean time from baseline: 73 days) among 248 participants, by dual energy X-ray absorptiometry (DXA) and is presented as grams per square centimeter. Whole body, lumbar spine, total non-dominant hip, and non-dominant wrist BMD were assessed (Hologic Discovery Elite, Waltham, MA). Licensed and certified technicians performed all DXA scans. Machine drift was monitored daily and the coefficient of variation was <1%. As women in this cohort were premenopausal, clinical cutoffs for osteoporosis were not appropriate. Therefore, we dichotomized BMD into less than the 10^{th} percentile for whole body, total hip, lumbar spine, and wrist BMD sites compared to greater than or equal to the 10^{th} percentile and also examined BMD as a continuous variable.

2.4 Covariate Assessment

Health and reproductive history, lifestyle information, and anthropometric measurements including height and weight, were collected at the baseline visit. Potential confounders assessed for their association with metals and BMD included age, average calorie intake, age at menarche, race, BMI, physical activity, parity, alcohol consumption, dietary calcium, vitamins D and K, magnesium, phosphorous, omega-3 fatty acids, polyunsaturated fatty acid 18:2, dark fish consumption, exposure to environmental tobacco smoke, parity, and current smoking status. Typical physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) and categorized using standard IPAQ cut-points (Craig et al., 2003).

Typical alcohol intake, vitamins consumed through diet (calcium, vitamin D, magnesium, phosphorous and vitamin K), fatty acids, and fish were characterized by food frequency questionnaire (FFQ) at baseline (Nutrition Assessment Shared Resource of the Fred Hutchinson Cancer Research Center). Total calorie intake was averaged for each cycle based on four 24-hour dietary recalls completed during menses, follicular phase, ovulation, and the luteal phase (NDSR, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, 2005). The final sample size used in the analysis was 248 participants with information on both BMD and metals.

2.5 Statistical Methods

Descriptive statistics were assessed for the total cohort and for groups above and below the 10^{th} percentile for whole body BMD. Continuous covariates were compared between BMD groups using ANOVA and categorical covariates using chi square or Fisher's exact tests where appropriate. Metals were log transformed for regression analyses. The appropriateness of the natural log transformation was determined by checking the distribution of the residuals from the final linear models. BMD was normally distributed and

was not log transformed. Correlations between variables were evaluated using Pearson correlation coefficients. Logistic regression was used to determine the odds of low BMD ($<10^{th}$ percentile) per log unit change in metal levels compared to those $\geq 10^{th}$ percentile. Linear regression was also used to determine continuous associations between metals and BMD. Linear spline models were explored to account for possible nonlinear relationships but spline terms were not statistically significant and were therefore not included in final models. Similarly, we tested for effect modification between metals both as continuous variables and dichotomized at the median. Potential confounders were selected based on a hybrid approach incorporating covariates strongly associated within the data and *a priori* by literature review. Models were adjusted for age, race, parity, BMI, age at menarche, and average number of calories consumed. Adjustment for vitamin and mineral consumption, alcohol, environmental tobacco smoke, and physical activity did not appreciably alter the estimates. As there were no currently smoking individuals with low whole body BMD, smoking was not included as a confounder, though sensitivity analyses were conducted while restricting to nonsmokers. Each metal (cadmium, lead, mercury) and bone site (whole body, total hip, lumbar spine, wrist) was evaluated in a separate model given the different sources of exposure and hypothesized mechanisms of action. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

3. Results

Women in the BioCycle Study had a mean (standard deviation (SD)) age of 27.4 (8.2) years and mean BMI of 24.1 (SD 3.9) kg/m^2. Fifty-nine percent of the women identified themselves as white, 20% as non-Hispanic black, 15% as Asian and 6% as other. Mean (SD) whole body, total hip, lumbar spine, and wrist, BMDs were measured in 248 women and were 1.13 (0.08), 0.99 (0.11), 1.08 (0.12), and 0.59 (0.04) g/cm^2, respectively. Geometric mean metal levels for cadmium, lead, and mercury were 0.29 (95% confidence interval (CI): 0.26, 0.31) μg/l, 0.91 (95% CI: 0.86, 0.96) μg/dl, and 1.05 (95% CI: 0.93, 1.19) μg/l. Low BMD was associated with younger age, lower average daily calories, and nulliparity but was not significantly associated with race, BMI, physical activity, education, or alcohol consumption (Table 1). Although calcium and vitamin D intakes were slightly higher among those with whole body BMD above the 10^{th} percentile, these differences were not significant (p=0.3). Similarly, there were no differences in consumption of magnesium, phosphorous, vitamin K, omega-3 fatty acid, polyunsaturated fatty acid 18:2, or dark fish consumption by BMD category. Blood mercury was positively correlated with fish consumption (rho=0.76 p <0.001), dark fish consumption (rho=0.35 p <0.001), omega-3 fatty acids (rho=0.19 p=0.003), but not with polyunsaturated fatty acid 18:2 (rho=0.05 p=0.3).

Overall, whole body, lumbar spine, total hip, and wrist BMD were not associated with blood cadmium, lead, or mercury levels (Table 2). Mercury was associated with a decreased odds of lumbar spine BMD $<10^{th}$ percentile compared to $\geq 10^{th}$ percentile (OR=0.65, 95% CI: 0.43, 0.97), but no associations were observed for other BMD sites and mercury was not associated with lumbar spine BMD in continuous models (Table 3). Similarly, linear regression models did not support an association between metals and BMD (Table 3). There was no evidence of effect modification using either continuous measures of metals or values dichotomized at the median and reproductive hormone levels were not associated with BMD (data not shown).

4. Discussion

Overall, our results do not provide support for the hypothesis that background levels of cadmium, lead, or mercury are associated with decreased BMD in healthy, premenopausal

women. While we did observe a decreased risk for decreased lumbar spine BMD in association with mercury exposure, there was no significant linear relation and no relation between mercury and other BMD sites.

Exposures to cadmium, lead, and mercury stem from a variety of sources among individuals who are not occupationally exposed. Smoking is the primary source of cadmium exposure among smokers, while among nonsmokers; those who reside near nickel-cadmium industrial sites or eat food grown near such areas receive exposure either from the air or via ingestion of food. Foods that are high in cadmium content include shellfish, organ meats, leafy vegetables, and grains (Groten et al., 1994). Lead exposure stems primarily from inhalation and ingestion, although it has declined in recent decades (Pirkle et al., 1994). Mercury is released into the atmosphere via industrial emissions. Elemental mercury is transformed to methylmercury by bacteria in water and methylmercury subsequently concentrates in fish. Therefore, the primary source of mercury exposure in the population is fish consumption (ATSDR, 1999a). While our isolated finding for mercury may be due to chance or may result from residual confounding, one other study that evaluated the role of total blood mercury on BMD in Korean women found that mercury (mean level 4.5 μg/l) was associated with decreased osteoporosis risk (Cho et al., 2011). These results could be driven by the fact that the primary source of mercury in Korea was fish consumption (Jo et al., 2010), which is also true among individuals in the US (Mahaffey et al., 2009). Fish consumption provides essential n-3 and n-6 fatty acids (Philibert et al., 2006), which are protective against osteoporosis (Farina et al., 2011). We observed that adjusting for dark fish consumption strengthened the association between mercury and lumbar spine BMD seen in our study (OR=0.65 (95% CI: 0.43, 0.97)). Though fish consumption was measured imperfectly via food frequency questionnaire it may still represent a plausible pathway by which mercury is protective against low BMD. Further, BioCycle Study participants had generally similar levels of cadmium and lead to US reproductive-aged females, but had higher median mercury levels (1.10 in BioCycle vs. 0.60 μg/l in US women) (Mahaffey et. al., 2004).

Ours is the first study to our knowledge to evaluate the association between metals exposure and multiple BMD sites in premenopausal women. A cohort study evaluating cadmium and forearm BMD also found no association but their population of premenopausal women was older than in the current study (mean age 39.7 years vs. 27.4 years) (Trzcinka-Ochocka et al., 2010). In other populations, and at higher exposure levels, metals have been associated with decreased BMD. Specifically, among a population of men and women of all ages (6 to 85) living near an industrial complex, cadmium was associated with low BMD, though the levels of cadmium exposure were much higher than in our study (mean urinary cadmium 0.63 μg/g) (Shin et al., 2011). Further, cadmium has consistently been associated with diminished BMD in postmenopausal women at median urinary cadmium levels per g creatinine (cr) ranging from 0.34 to 2.87 μg/g cr (Alfven et. al., 2000;Honda et al., 2003;Akesson et. al., 2006;Engstrom et al., 2010). Lead exposure has also been associated with reduced BMD in postmenopausal women (Nash et al., 2004), but not in other study populations in Sweden and Baltimore, Maryland (Alfven et al., 2002;Theppeang et al., 2008). As lead, which is primarily stored in bone, is mobilized at menopause, (Latorre et al., 2002) studies of lead exposure between pre- and post-menopausal women are not directly comparable. To that end, Jackson et al. found that markers of bone resorption and formation among pre- and post-menopausal women were associated with higher blood lead levels in the National Health and Nutrition Examination Survey with geometric mean blood lead of 1.44 μg/dL (Jackson et al., 2010). Mercury has been associated with harmful effects on bone in experimental studies (Jin et. al., 2002), and as previously discussed, one study among postmenopausal Korean women found a decreased risk of osteoporosis among women with higher mercury levels (≥2.67 μg/l) (Cho et. al., 2011).

Over time, metal exposure can impair calcium absorption, displacing calcium with metals and decreasing bone mineralization. Lead and calcium also compete for binding and transport sites (Pounds et al., 1991;Berglund et al., 2000) leading to uptake of lead in bone. Experimental evidence supports associations between lead and bone formation, as growth plate chondrocyte expression works via changes in alkaline phosphatase, collagen, proteoglycan and thymidine levels, leads to inhibited bone formation (Hicks et al., 1996). Further, while lead levels observed *in vitro* are greater than those observed in blood, lead concentrates in bone, which could drive localized levels upward, making *in vitro* findings more directly applicable in terms of dose. Effects on BMD by lead and cadmium may occur via increased bone turnover, either through their direct action on the kidney which may increase renal tubular calcium resorption, or through bone resorption from increased parathyroid hormone and a decrease in active vitamin D ($1,25\text{-}(OH)_2\text{-}D_3$) (Berglund et. al., 2000). Alternatively, cadmium may directly affect bone cells (Bhattacharyya et. al., 1988). The lack of association observed in this study may be due to the nature of our healthy population with participants who are premenopausal, have yet to experience bone loss, and have very low blood levels of lead and cadmium.

A limitation of this study is the single measurement of metals in blood given that blood levels reflect exposure on the order of several months. Urinary levels of metals, or hair levels of mercury or bone lead would have provided a longer-term biomarker of exposure. Specifically, cadmium in urine has a half-life between 15–30 years while it is on the order of months in blood (ATSDR, 1999b). Bone is the primary storage site for lead, where it remains for up to decades compared with 1–2 months in blood. However, blood can be thought of as representative of a steady state of lead burden (Rabinowitz, 1991;Hu et al., 2007). Inorganic mercury is stored in the kidney but methylmercury can pass through the blood brain barrier and its half life is 1–2 months (ATSDR, 1999a). We were also limited in our measurement of bone loss as there was no specific cutpoint to define low BMD among this healthy population. The World Health Organization guidelines for t-scores to diagnose low BMD were only intended for postmenopausal women (World Health Organization., 1994;Siris et al., 2001). Osteopenia is not meant to be applied to premenopausal, healthy women and thus, standard cutoffs were not appropriate in our study. The 10^{th} percentile cutpoint used in this study may be sufficiently high such that no adverse effects were detectable. In light of this, we performed sensitivity analyses wherein we categorized BMD in quartiles and as a continuous variable and similarly found no associations between cadmium, lead, mercury and four BMD sites. Research indicates that low BMD in the first year or two after menopause is strongly predictive of 10-year BMD (Abrahamsen et al., 2006). While 32 (13%) women in the BioCycle Study were older than 39 years of age, their BMDs were not lower than younger study participants. In fact, BMD increased slightly with age in the BioCycle Study. Participants in this study were regularly menstruating and had not yet experienced BMD decreases concomitant to the peri- and post-menopausal transition. It is also unlikely that parous women had increased circulating blood lead levels as a result of pregnancy and lactation because of the study exclusion criteria. A comparison of mean blood lead levels between parous (0.99 μg/dl) and nulliparous (1.04 μg/dl) suggests that this was not the case.

Strengths of this study included the comprehensive assessment of BMD, which included multiple sites. Selection of the study population is another strength. Study participants were healthy and regularly menstruating, decreasing the likelihood that BMD alterations were attributable to changes in estrogen. Further, this study extended evaluation of BMD to premenopausal women, while most previous literature on metals and BMD has focused on post- and peri-menopausal women. Consideration of multiple confounding factors associated with metals exposure and BMI, such as, age at menarche, nutrient intakes, fatty acid intake, and fish consumption represent improvements from previous studies.

In summary, our findings indicate that environmentally-relevant blood levels of cadmium, lead, and mercury were not associated with decreases of whole body, total hip, lumbar spine or wrist BMD in premenopausal women. We found some indication that blood mercury may be associated with increased BMD, however this finding did not remain significant when BMD was treated as a continuous variable and further research is needed. Given the widespread exposure to metals, it is important to investigate further whether osteotoxic effects are only present at higher levels of exposure or if effects on bone can be expected only at older ages.

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Abbreviations

BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
Cd	Cadmium
CR	Creatinine
Hg	Mercury
OR	Odds ratio
Pb	Lead

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Highlights

- Low levels of metals were not associated with reduced bone mineral density in premenopausal women
- Mercury associated with reduced odds of low lumbar spine BMD
- Extends evaluation of BMD and metals to premenopausal women
- Consideration of many confounders: age at menarche, nutrient, fatty acid & fish intake

Table 1

Characteristics of women aged 18–44 years in the BioCycle Study, Buffalo, NY, 2005–2007.

Characteristic Mean (SD) or n (%)	Total Population N=248	≥10th percentile (1.04–1.41 g/cm^2) Whole body BMD N=223	<10th percentile (0.86–1.03 g/cm^2) Whole body BMD N=25	P value*
Metals				
Cadmium μg/l	0.36 (0.29)	0.36 (0.29)	0.33 (0.29)	0.92
Lead μg/dl	1.03 (0.64)	1.02 (0.64)	1.09 (0.66)	0.76
Mercury μg/l	1.51 (1.34)	1.55 (1.36)	1.91 (1.08)	0.19
Demographics				
Age (years)	27.4 (8.2)	27.9 (8.3)	23.4 (5.3)	0.009
Age at Menarche (years)	12.6 (1.24)	12.6 (1.24)	12.9 (1.01)	0.19
BMI (kg/m^2)	24.1 (3.9)	24.3 (3.9)	22.5 (3.4)	0.39
Height (cm)	164.06 (6.21)	164.40 (6.19)	161.90 (6.26)	0.06
Race				0.18
White	147 (59)	133 (60)	14 (56)	
Non-Hispanic Black	50 (20)	46 (20)	4 (16)	
Asian	36 (15)	29 (13)	7 (28)	
Other	15 (6)	15 (7)	0 (0)	
Smoker				0.60
No/Former	238 (96)	213 (96)	25 (100)	
Environmental Tobacco Smoke				0.20
Yes	149 (60)	131 (59)	18 (72)	
Physical Activity				0.63
Low	22 (9)	19 (9)	3 (12)	
Med	90 (36)	80 (36)	10 (40)	
High	136 (55)	124 (56)	12 (48)	
Parity				0.004
Nulliparous	179 (73)	155 (71)	24 (96)	
Ever consume alcohol				0.48
Yes	163 (66)	148 (67)	15 (60)	
Education				0.41
>High School	216 (87)	195 (87)	4 (16)	
Diet				
Calories (kcal/day)	1608.9 (392.1)	1611.2 (404.0)	1588.6 (268.6)	0.02
Calcium (mg/day)	918.2 (604.3)	924.4 (625.0)	900.0 (443.7)	0.80
Vitamin D (mcg/day)	4.7 (3.7)	4.8 (3.8)	4.0 (2.9)	0.31
Magnesium (mg/day)	272.7 (149.5)	272.9 (152.7)	287.2 (130.6)	0.66
Phosphorous (mg/day)	1158.0 (606.9)	1163.7 (623.2)	1151.8 (493.4)	0.93
Vitamin K (μg/day)	125.0 (126.3)	118.0 (106.2)	166.6 (222.5)	0.30
Omega-3 (g/day)	1.42 (0.83)	1.40 (0.79)	1.59 (1.18)	0.43
PUFA 18:2 (g/day)	10.85 (5.85)	10.81 (5.70)	11.60 (6.86)	0.52

Characteristic Mean (SD) or n (%)	Total Population N=248	≥10th percentile (1.04–1.41 g/cm2) Whole body BMD N=223	<10th percentile (0.86–1.03 g/cm2) Whole body BMD N=25	P value*
Dark fish (servings/3 months)	10.13 (25.34)	10.54 (26.65)	7.36 (13.35)	0.32

*Fisher's exact test, chi-square or t-test

PUFA: Polyunsaturated fatty acid

Table 2

Odds of low bone mineral density (<10th percentile) by log-transformed metal exposure in the BioCycle Study, Buffalo, NY, 2005–2007.

BMD Site	n <10%/total	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Whole Body (g/cm^2)			
Cadmium (μg/l)	25/248	0.75 (0.39, 1.46)	0.76 (0.36, 1.61)
Lead (μg/dl)	25/248	1.28 (0.53, 3.11)	0.97 (0.88, 1.07)
Mercury (μg/l)	25/248	0.84 (0.54, 1.28)	0.85 (0.56, 1.29)
Total Hip (g/cm^2)			
Cadmium (μg/l)	24/245	1.49 (0.78, 2.85)	0.98 (0.89, 1.07)
Lead (μg/dl)	24/245	0.92 (0.36, 2.33)	1.00 (0.91, 1.09)
Mercury (μg/l)	24/245	0.91 (0.58, 1.41)	0.88 (0.56, 1.38)
Lumbar Spine (g/cm^2)			
Cadmium (μg/l)	25/248	1.08 (0.57, 2.07)	1.17 (0.56, 2.46)
Lead (μg/dl)	25/248	1.51 (0.64, 3.55)	1.63 (0.58, 4.53)
Mercury (μg/l)	25/248	0.66 (0.44, 0.98)	0.65 (0.43, 0.97)
Wrist (g/cm^2)			
Cadmium (μg/l)	24/243	0.75 (0.39, 1.45)	0. 91 (0.43, 1.94)
Lead (μg/dl)	24/243	0.80 (0.31, 2.08)	0.87 (0.30, 2.54)
Mercury (μg/l)	24/243	0.74 (0.49, 1.12)	0.80 (0.53, 1.21)

Adjusted for age (continuous), race (white, black, Asian, other), parity, average caloric intake (continuous), age at menarche (continuous)

Table 3

Association between bone mineral density site and log-transformed metal exposure per log-unit increase in metals among women in the BioCycle Study, Buffalo, NY, 2005–2007.

BMD Site	Unadjusted β (95% CI)	Adjusted β (95% CI)
Whole Body (g/cm^2)		
Cadmium (μg/l)	0.006 (−0.010, 0.022)	0.004 (−.014, 0.022)
Lead (μg/dl)	−0.0004 (−0.023, 0.022)	−0.004 (−0.029, 0.020)
Mercury (μg/l)	0.002 (−0.008, 0.013)	0.002 (−0.009, 0.013)
Total Hip (g/cm^2)		
Cadmium (μg/l)	0.011 (−0.033, 0.012)	0.003 (−0.020, 0.026)
Lead (μg/dl)	−0.013 (−0.045, 0.018)	−0.002 (−0.034, 0.029)
Mercury (μg/l)	−0.005 (−0.020, 0.010)	−0.0004 (−0.014, 0.015)
Lumbar Spine (g/cm^2)		
Cadmium (μg/l)	−0.001 (−0.019, 0.017)	0.018 (−0.004, 0.040)
Lead (μg/dl)	−0.028 (−0.053, −0.003)	−0.015 (−0.045, 0.016)
Mercury (μg/l)	0.0005 (−0.011, 0.012)	−0.001 (−0.015, 0.012)
Wrist (g/cm^2)		
Cadmium (μg/l)	0.007 (−0.001, 0.015)	0.003 (−0.006, 0.011)
Lead (μg/dl)	0.006 (−0.005, 0.018)	0.001 (−0.011, 0.013)
Mercury (μg/l)	0.007 (0.001, 0.012)	0.005 (−0.0004, 0.010)

Adjusted for age (continuous), BMI (continuous), race (white, black, Asian, other), parity, average caloric intake (continuous), age at menarche (continuous)