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Blood Cadmium Levels in Women of Childbearing Age Vary by Race/Ethnicity

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Abstract

The heavy metal cadmium (Cd) is long-lived in the body and low-level cumulative exposure, even among non-smokers, has been associated with changes in renal function and bone metabolism. Women are more susceptible to the adverse effects of Cd and have higher body burdens. Due to increased dietary absorption of Cd in menstruating women and the long half-life of the metal, reproductive age-exposures are likely important contributors to overall body burden and disease risk. We examined blood Cd levels in women of reproductive age in the US and assessed variation by race/ethnicity. Blood Cd concentrations were compared among female NHANES participants aged 20–44 who were neither pregnant nor breastfeeding. Sample size varied primarily based on inclusion/exclusion of smokers (n = 1734–3121). Mean Cd concentrations, distributions and odds ratios were calculated using SUDAAN. For logistic regression Cd was modeled as high (the upper 10% of the distribution) vs. the remainder. Overall, Mexican Americans had lower Cd levels than other groups due to a lower smoking prevalence, smoking being an important source of exposure. Among never-smokers, Mexican Americans had 1.77 (95% CI: 1.06–2.96) times the odds of high Cd as compared to non-Hispanic Whites after controlling for age and low iron (ferritin). For non-Hispanic Blacks the odds were 2.96 (CI: 1.96–4.47) times those of non-Hispanic Whites in adjusted models. Adjustment for relevant reproductive factors or exposure to environmental tobacco smoke had no effect. In this nationally representative sample, non-smoking Mexican American and non-Hispanic Black women were more likely to have high Cd than non-Hispanic White women. Additional research is required to determine the underlying causes of these differences.

Keywords

Cadmium; race; lead; NHANES; women

Introduction

Cadmium (Cd) is a ubiquitous, long-lived, toxic heavy metal to which most individuals are exposed. Cd is widely used in the manufacture of batteries and paints, as well as in metal plating, and is commonly found in fertilizers. Contamination of soil and air has resulted from mining of the metal, the use of Cd-containing products and, often, the failure to recycle

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Human Subjects Review: The study was approved by CDC's Ethics Review Board (CDC, 2001–2006a).

them. Exposure occurs occupationally, through use of tobacco products, via the diet, and from the local environment (Jarup, 2003). Among non-occupationally exposed individuals, tobacco is the most important source of exposure due to high Cd concentrations in the plant. Inhalational absorption is efficient and smokers have higher blood Cd levels than non-smokers (Jarup, 2003; Satarug and Moore, 2004). For non-smokers, diet is the most important source of Cd (Satarug and Moore, 2004). While intestinal absorption in adults averages ~ 5% of the ingested dose (Satarug and Moore, 2004), women of childbearing age absorb 2–4 times this amount (Choudhury et al., 2001) and as a result have higher blood Cd levels than men or post-menopausal women. Cd is absorbed from the intestine via iron transporters, the expression of which is induced by low iron levels more frequently found in menstruating or pregnant/lactating women (Vahter et al., 2007). Additionally, low calcium intake may facilitate increased intestinal absorption of Cd (Kippler et al., 2009; Min et al., 2008). In the blood Cd has a half-life of ~3–4 months and is later transported to other parts of the body, chiefly the kidney where its half-life is 10–30 years. Cd in blood largely reflects recent exposure, with a small component reflecting levels stored in the body, while urinary excretion estimates body burden (Järup and Åkesson, 2009). In both compartments women tend to have higher Cd concentrations (Vahter et al., 2007).

While high-level Cd exposure has long been associated with kidney damage and lung cancer risk, a number of recent reports suggest that low, non-occupational exposures have adverse effects on bone, kidney and, perhaps, the cardiovascular system. Decreased forearm bone density, increased bone turnover and elevated risk of osteoporosis have been associated with urinary Cd levels in post-menopausal women (reviewed in (Järup and Åkesson, 2009)); increased bone turnover appears independent of the kidney and is consistent with Cd-mediated increases in osteoclast differentiation and subsequent changes in bone tissue including demineralization and calcium release (Engström et al., 2009; Schutte et al., 2008). Effects have been observed in populations residing in areas with and without significant environmental pollution and in groups of non-smokers. Additionally, low levels of Cd exposure previously thought to be without adverse renal effects have recently been associated with increased markers of renal tubular damage (Vahter et al., 2007). Furthermore, some studies have found low-level blood Cd concentrations are associated with elevations in blood pressure (~1–3 mm Hg) (Staessen 1991, Tellez-Plaza 2008); with potentially stronger effects among never-smokers. The effects of Cd on other health endpoints have been studied less extensively, however increased risk of insulin resistance and diabetes, endometrial and breast cancers and higher miscarriage rates have been found (Gerhard et al., 1998; Järup and Åkesson, 2009). Finally, animal and some human studies suggest prenatal exposures may also change endocrine and behavioral (potentially neurodevelopmental) function in offspring (Apinan et al., 2009; Hanson et al., 2010; Tian et al., 2009; Windham et al., 2006).

The purpose of this work is to describe blood Cd levels in women of childbearing age in the United States and, specifically, to compare levels found in different racial/ethnic groups. Most research characterizing exposures in women of reproductive age has been performed in Western European nations, Japan and China and little is known about potential racial/ethnic variation in blood Cd levels in US women. A recent study of New York City adults suggests that blood Cd levels vary between racial/ethnic groups (McKelvey et al., 2007). Using a nationally representative sample of women in their reproductive years (ages 20–44 years) from the National Health and Nutrition Examination Survey (NHANES) 1999–2006, we compare blood Cd concentrations among women of different race/ethnicities stratifying on smoking behavior. Among never-smokers we examine the odds of having high Cd levels (≥ 0.50 $\mu\text{g/L}$) by race/ethnicity after adjusting for demographic, reproductive and biologic factors.

Material and Methods

Study population

NHANES is an annual survey of the health status of the non-institutionalized civilian US population which includes an in-person interview, health questionnaires and a detailed medical examination component (MEC) during which blood and urine samples are collected. Annually ~ 5,000 individuals selected based on US census data are invited to participate in the study. Minority groups are oversampled to obtain more stable estimates of health status (CDC, 1999–2006a).

Between 1999–2006, 50,939 people were invited to participate, of whom 81% were interviewed ($n = 41,474$) and 39,352 participated in the MEC (CDC, 1999–2006a). Our study population is comprised of women aged 20–44 years who were MEC examined, were not pregnant or breastfeeding at the time of interview and had blood Cd measures available. Of the 4970 women 20–44 years old who were interviewed, 4729 were MEC examined and 3121 met inclusion criteria. Most exclusions were due to women being pregnant/breastfeeding at the time of the interview ($n = 1243$); others resulted from missing Cd measures ($n = 205$) or uncertain pregnancy status ($n = 160$) (CDC, 1999–2000a, CDC, 2001–2002b, CDC 2003–2004a, CDC 2005–2006a).

Demographic and reproductive history variables

All demographic and reproductive variables were based on self-report. Variables were grouped multiple ways for preliminary analyses. Ultimately, age was evaluated as < 35 years old and ≥ 35 years old. Race/ethnicity was categorized as non-Hispanic White (NHW), non-Hispanic black (NHB), Mexican American (MA) and 'Other'. Educational attainment was described as less than high school or completion of high school. Income was dichotomized as family income above or at/below 1.5 times the federal poverty limit. Parity was assessed as 0–1 or 2+ births. Breastfeeding was categorized as yes/no if a woman had ever nursed a child. Two variables for birth control were used: "ever use" and "current use" among women with an intact uterus and at least one ovary. Finally, the association between Cd levels and having ever been diagnosed with fibroids or endometriosis was examined.

Measures of tobacco exposure

Unless specified, smoking status was defined based on self-reported cigarette use: never smokers smoked <100 cigarettes in their lifetime and women who smoked 100 or more cigarettes were classified as former or current smokers based on current usage. An alternative definition of smoking status was created taking into account self-reported use of cigarettes and use of pipes, cigars, snuff and chew within the last 5 days (a proxy for regular use which was missing for 2005–2006 participants). Using this information an additional 27 women were defined as current smokers; analyses using this more comprehensive definition did not change results.

Serum cotinine levels measured via gas chromatography coupled mass spectrometry were used to confirm self-reported smoking status and to measure intensity of tobacco exposure. The assay limit of detection (LOD) improved slightly over time, therefore to standardize measures, the highest detection limit (0.05 ng/mL) for all 8 years was used as the limit of detection for all data. All values below 0.05 ng/mL ($n = 1247$) were retained in the analysis and the $\text{LOD}/\sqrt{2}$ was imputed (CDC, 1999–2000b; CDC, 2001–2002b). Four former smokers who used nicotine replacement therapy were removed from analyses using cotinine values, leaving measurements available for 98% of individuals. To classify individuals as smokers two different serum cotinine cut-off values were used: ≥ 14 ng/mL as proposed by Jarvis et al. and race-specific values (range: ≥ 1 to ≥ 6 ng/mL) that account for variation in

intensity of smoking and metabolism (Benowitz et al., 2009; Jarvis et al., 1987). While cotinine levels were utilized in sensitivity analyses to determine the effect of misreported non-smoking status on effect estimates, concordance between self-reported smoking status and cotinine levels were checked through all analyses. The highest degree of misclassification was found among former smokers with 10–11% having cotinine levels consistent with active smoking. For this reason and for ease of comparison, only mean Cd levels grouped by study year include former smokers; all other analyses are stratified and limited to current and never-smokers.

Exposure to environmental tobacco smoke (ETS) was defined multiple ways. First, ETS exposure was determined based on self-reported exposure (yes/no) at home and/or at work. Second, variables took into account the level of exposure among the ETS exposed (i.e. no exposure was compared to low exposure (<10 cigarettes/day smoked in the home) vs. high (10 or more cigarettes/day smoked in home); similar categories were created based on the number of smokers living in the home). Third, cotinine levels were used to define ETS exposure, with women having > 0.05 ng/mL cotinine defined as exposed and those with lower levels classified as unexposed. Further classification of exposed into high/low groups was also conducted.

Blood Lead and Cadmium measures

Blood metal measurements were performed by the NHANES laboratory at the National Center for Environmental Health (CDC) under conditions that minimize external contamination (CDC, 2001). Blood Cd measurements $\geq 0.50 \mu\text{g/L}$ are considered unlikely to be affected by contamination and more reliable, whereas lower concentrations are more susceptible to bias by contamination. Furthermore, these values are in the range of values reported to be associated with changes in blood pressure (Tellez-Plaza et al., 2008). From 1999–2002 Cd was measured via atomic absorption spectroscopy, which had a LOD of $0.3 \mu\text{g/L}$; 28% of samples were < LOD (CDC, 2001–2002c). From 2003–2006 Cd was measured by inductively-coupled plasma mass spectroscopy lowering the LOD to $0.2 \mu\text{g/L}$; only 19% of samples were < LOD (CDC, 2005–2006b). For calculation of mean Cd levels the $\text{LOD}/\sqrt{2}$ was imputed for samples below the LOD. If all 8 years of data were used in calculations, the highest LOD for the study period was used; otherwise the LOD specific to the analytical method was utilized. For 8 year analyses Cd concentrations measured to one decimal point were used in calculations. Data were handled similarly for lead, for which the LOD varied between $0.6 \mu\text{g/dL}$ for 1999–2002 and $0.3 \mu\text{g/dL}$ for 2003–2006. Blood Cd and lead measures were log-transformed to calculate geometric means (GM) and were back-transformed for presentation with their corresponding 95% confidence intervals.

GM and distributions for Cd and lead levels were calculated in two ways: separately for data obtained using the same laboratory technique (1999–2002 and 2003–2006) and for the entire period. For lead this was especially critical, given the decline in ambient exposure and lead levels in the US since the 1970s (Muntner et al., 2005). For logistic regression analyses in non-smokers a dichotomized Cd variable was created based on the distribution of blood Cd levels for each analytical year among women included in the regression model. High Cd exposures (> 90th percentile) were > $0.49 \mu\text{g/L}$ (2003–2006) and > $0.50 \mu\text{g/L}$ (1999–2002) and were contrasted with all lesser values. The 90th percentile did not change significantly if the distribution for all never-smokers was used. Neither did estimates change if > $0.50 \mu\text{g/L}$ was used as the high cut off for all years in regression models. To test if the observed relations were also observed at lower Cd levels, we also ran models using blood Cd levels above the 75th percentile as the outcome of interest. Lead was dichotomized in a similar fashion with high lead defined as > $1.9 \mu\text{g/dL}$ for 1999–2002 and > $1.53 \mu\text{g/dL}$ for 2003–2006.

Ferritin

Ferritin was measured using two different assays during the study; therefore, regression equations were utilized to convert older measures to the scale of the newer method (CDC, 2003–2004c). Ferritin status was dichotomized as adequate (≥ 20 ng/mL) or low (< 20 ng/mL-units) based on previous use as an indicator of body iron stores (Milman, 2006; Satarug et al., 2004; Tsukahara et al., 2003).

Statistical Analysis

Statistical analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC) and SAS-callable SUDAAN 10.1 (RTI, Research Triangle Park, NC) using appropriate statistical weights to account for the multistage sampling design. Weights were recalculated for 8 years of data and Taylor-Series Linearization was used to estimate variances. Frequencies of demographic characteristics were compared between women included in analyses and all women aged 20–44 enrolled in NHANES. Weighted frequencies were compared using Student-t test. Confidence intervals for frequencies of categorical variables were calculated using standard formulas unless the number of observations was ≤ 10 or the column percent was $\leq 2\%$, in which case small percentage confidence intervals were determined. GM and distributions for Cd levels were calculated for the entire sample, for groups defined by race/ethnicity, and for those defined by smoking status and were compared using the Wald F statistic. GM among never smokers (and cotinine-confirmed never-smokers) Cd levels were also examined by level of ETS exposure reported.

Logistic regression was used to test associations between high Cd levels and race/ethnicity after adjusting for other covariates. All models included a term adjusting for the time period when Cd was measured (1999–2002 vs. 2003–2006) to account for variability in the laboratory method percentage of individuals classified as having high Cd. Initially, covariate-Cd associations were evaluated individually and described by odds ratios (OR), 95% confidence intervals (CI) and Wald Chi-Square Tests. Associations were examined in the whole sample and within strata of race/ethnicity. Multivariable models of the relationship between race/ethnicity (excluding other) and elevated Cd were constructed as follows. In addition to measurement period, all models included age and ferritin, previously shown to be associated with elevated Cd levels (Berglund et al., 1994; Olsson et al., 2002; Tsukahara et al., 2002) and associated with race/ethnicity in these data. All additional covariates individually associated ($p < 0.05$) with Cd were tested in the multivariable model as well as those identified as potential confounders using directed acyclic graphs. Covariates that changed the point estimate of the OR for race/ethnicity by 10% were included in final models. ORs and 95% confidence intervals are reported. The robustness of the results was tested by: 1) varying the women included in analyses (ie. former and never-smokers, cotinine-confirmed never-smokers), 2) examining sub-groups of women who might be more homogeneous (ie. all women who reported not being menopausal or who had serum cotinine levels ≤ 0.05 ng/mL consistent with low/no ETS exposure), and 3) standardizing the outcome variable Cd to % hematocrit, which may correlate with the Cd binding capacity of the blood (Aitio et al., 2007).

Results

Women included in this analysis ($n = 3121$) were MEC examined, were neither pregnant nor currently breastfeeding and had blood Cd measures available. Table 1 compares these women to all 20–44 year old female NHANES participants ($n = 4970$). The sample was slightly older (33.0 ± 0.2 years) than the survey as a whole (32.4 ± 0.1 years), due to the exclusion of younger women who were pregnant and/or breastfeeding (average age 28.4 ± 0.3 years). Otherwise, groups were not significantly different.

Mean Cd levels in all women by smoking status

GM blood Cd levels in women of childbearing age were 0.40 µg/L (95% CI:0.39–0.42) (Table 2). Significant differences were noted when stratified by smoking status as smokers had blood Cd levels ~ 3–4 times higher than never-smokers (GM = 0.88 µg/L vs. 0.29 µg/L, $p < 0.0001$) (Tables 3a and 3b). Former smokers appeared to have slightly higher Cd concentrations than never-smokers ($p = 0.002$) when all 8 years of data were examined; Among never-smokers, GM Cd concentrations were compared between women with varying levels of ETS exposure; we were unable to detect any differences in GM Cd concentrations between groups even when analyses were restricted to never-smokers who had cotinine levels consistent with not smoking.

Mean Cd levels by race/ethnicity

Cd levels were compared between Mexican American (MA), non-Hispanic Black (NHB), non-Hispanic White (NHW, referent group) and Other women. Overall, Cd levels by race/ethnicity only differed significantly between MA (GM = 0.34 µg/L (95% CI: 0.33–0.37)) and NHW (GM = 0.41 µg/L (95% CI: 0.38–0.43)). This is consistent with the lower prevalence of smoking among MA as compared to NHW women (14.4% for MA, 22.1% in NHB and 31.7% for NHW).

Mean Cd levels by race/ethnicity stratified on self-reported smoking

When data were stratified by smoking behavior, current smokers who were either MA or 'Other' race/ethnicity had lower Cd levels than NHW (Table 3a), in agreement with lower GM cotinine measures in these groups as compared to NHW (MA: 21.8 ng/mL (95% CI: 13.5–34.8, different from NHW $p < 0.001$); Other: 82.3 ng/mL (95% CI: 51.4–131.6); NHW: 117.9 ng/mL (95% CI: 99.5–139.8)). Among non-smokers, all groups had higher mean Cd concentrations than NHW, particularly women belonging to the 'Other' race/ethnicity groups (GM = 0.35 µg/L vs. 0.27 µg/L for NHW ($P < 0.0001$)); also for minority women, the blood Cd distribution appeared right shifted relative to NHW (Table 3b).

Logistic regression modeling the race/ethnicity-Cd association

Concerned that demographic or reproductive characteristics might explain differences in blood Cd levels by race/ethnicity, we developed multivariable models to adjust for potential confounding. Analyses were restricted to never-smokers since 1) the numbers of smokers are small, 2) smoking intensity was poorly reported, varies by race-ethnicity (Benowitz et al., 2009; Camilli et al., 1994) and is difficult to control adequately, 3) current/prior smoking may affect micronutrient levels and subsequently handling of Cd (Northrop-Clewes and Thurnham, 2007) and 4) recent reports underscore the importance of low-level Cd exposure and health effects in never-smokers (Akesson et al., 2008; Gallagher et al., 2008). In logistic regression models, Cd was modeled as high (values ≥ 0.50 µg/L) vs. not high, with high representing exposure at or above the 90th percentile of the distribution among never-smokers (corresponding to the 20–25th percentile among smokers).

Individual covariate-Cd associations adjusted for measurement period ($n = 1761$ for MA, NHB and NHW), showed the following demographic/laboratory variables to be positively associated with high Cd ($p < 0.05$): race/ethnicity other than NHW, age 35 or older, less than a high school education, having been born outside of the US, high blood lead levels, and low ferritin (< 20 ng/mL) as a marker of low body iron stores. All of these variables were also associated with race/ethnicity. No association was found for ETS exposure or occupation. To examine the influence of reproductive characteristics, analyses were restricted to women for whom complete data was available. These women were not different from the whole of NHANES participants except for age, as reported for the larger sample. Previously

described associations were unchanged in this sample. Only multiparity was associated with high Cd levels, with increased odds for women who had 3 or more births.

Multivariable models considered demographic, laboratory and reproductive characteristics in modeling the race/ethnicity-Cd association, but found that reproductive characteristics had no influence on the point estimates of the race/ethnicity-Cd association after adjustment for other covariates. After adjustment for age and low ferritin, MA had 1.77 times the odds of high blood Cd levels (95% CI: 1.06–2.96), where as NHB had 2.75 times (95% CI: 1.79–4.22) the odds of NHW women (Table 4, Model 1). Adjustment for education, the socioeconomic status (SES) marker for which data was most complete, attenuated associations especially for MA (OR = 1.45) (Table 4, Model 2). Similar findings were observed when exposures above the upper 75% percentile were modeled as the outcome; the OR for MA strengthened (OR = 1.91 (95%CI: 1.26–2.90) and those for age, ferritin and education and lead weakened. In these models high blood lead levels (above the 75th percentile) tracked with Cd >90th percentile (OR = 2.17 (1.31–3.59)), even after adjustment for race/ethnicity, age, ferritin and education. The association between high Cd (above the 90th percentile) and high blood lead levels (90th percentile) could not be examined due to the small numbers of individuals who had high levels of both metals; in other words, the power was limited.

Sensitivity Analyses

To test the robustness of the race/ethnicity-Cd association, we re-ran models including different sets of women of reproductive age in the analysis (a crude sensitivity analysis). ORs for race/ethnicity were attenuated 10–20% when examined among never and former smokers combined (the ferritin OR was attenuated substantially). Limited to never smokers for whom cotinine levels confirmed self-reported behavior, the ORs for MA increased (~20%) and NHW decreased slightly. No significant changes were observed in analyses restricted to non-menopausal women. Also exclusion of women likely to have chronic inflammation or infection (defined by (Blanck et al., 2005)) that would impair the ability of ferritin to accurately indicate iron reserves attenuated results slightly, but did not change the interpretation (See Table 4, Model 2b). Finally, analyses were repeated with blood Cd concentrations standardized to percent hematocrit (an indicator of Cd binding capacity in the blood and results changed little.

Discussion

We used the NHANES data and found that among never-smokers Mexican Americans and non-Hispanic Black women of childbearing age had higher blood Cd levels as compared to NHW women. Women of 'Other' racial/ethnic groups also have elevated blood Cd concentrations, but small numbers precluded more than a crude analysis. These results were bolstered by the following: 1) use of reliable Cd measurements ≥ 0.50 $\mu\text{g/L}$ as measures of elevated internal dose (blood Cd), 2) the robustness of the results to inclusion/removal of women based on influential characteristics (eg. accuracy of smoking behavior) and 3) the similar findings between models describing associations with Cd levels using either the upper quartile or upper decile cut-off.

Our results are consistent with other reports examining the contributions of tobacco exposure and health/reproductive status to blood Cd levels. We found Cd levels were 3 times higher in smokers, similar to the 3–4 fold higher concentrations in smokers vs. non-smokers previously reported (NCEH, 2005; Satarug and Moore, 2004). We also observed differences in blood Cd concentration among smokers that tracked with variation in smoking intensity by race (Camilli et al., 1994). Levels found in never-smokers were similar to those reported among (largely non-smoking) European women, but are lower than those of

Japanese women (Batárióvá et al., 2006; Berglund et al., 1994; Olsson et al., 2002; Reis et al., 2007; Yamagami et al., 2008). Similar to others, we failed to detect a difference in Cd levels among adult never-smokers who reported ETS exposure (Copes et al., 2008; McElroy et al., 2007). This may be due to either 1) limited sensitivity to detect small changes in Cd concentration since there is some, albeit inconsistent, evidence for higher blood Cd levels in children exposed to ETS (Arora et al., 2008; Friedman et al., 2006; Link et al., 2007), or 2) difficulty accurately measuring average ETS exposure as reflected in the weak correlation between self-reported ETS exposure and serum cotinine levels (Delorenze et al., 2002). Additionally, we found age and ferritin to be strongly associated with blood Cd levels, consistent with previous work showing these variables can explain much (up to 60%) of the variation in blood Cd levels (Berglund et al., 1994; Olsson et al., 2002).

We found little influence of parity or breastfeeding on Cd levels in this sample of women. Inclusion of ferritin in the model may already account for the effect of pregnancy/lactation on iron status, however, we found little association between reproductive variables and ferritin. The studies which have most clearly shown an effect of parity on blood Cd levels have measured Cd levels in pregnant women, a time in which iron stores are significantly stressed and differences in iron status related to reproductive history may be more easily detected (Akesson et al., 2002). The inclusion of time between last pregnancy and measurement of blood Cd in models evaluating the relationship between parity and blood Cd level did not alter parity-Cd associations.

To the best of our knowledge, this is the first report to specifically examine racial/ethnic differences in blood Cd levels among women of childbearing age, a group that has elevated blood levels which are likely to significantly contribute to body burden (Satarug et al., 2004; Vahter et al., 2007). One recent study of New York City adults aged 20 and older found statistically significantly higher blood Cd concentrations in Asians and non-Hispanic Blacks when compared to non-Hispanic Whites and Hispanic individuals (McKelvey et al., 2007). Results were not stratified by gender or age making a direct comparison with our data difficult, but these results are consistent with our observation of higher blood Cd levels among women of 'Other' race/ethnicity, a group that would include women of Asian ancestry. In addition, the New York-based study identified immigrants as having higher Cd levels than native-born Americans; in our data this was observed in crude analyses for NHB and 'Other' and among NHB in adjusted analyses using the lower blood Cd threshold of the 75% percentile. There was insufficient power to model these relations at higher Cd thresholds.

It is unclear why minority never-smoking women of childbearing age might have higher blood Cd levels, but several explanations are possible. First, dietary differences may result in higher Cd exposures. This has been demonstrated for fish consumption and mercury (Hightower et al., 2006; McKelvey et al., 2007), and Cd levels are reportedly high in shellfish, as well as offal, cereals and some vegetables (Satarug and Moore, 2004; Vahter et al., 2007); additionally, dietary intake of minerals like iron and calcium, likely associated with Cd and Pb uptake, can vary by race/ethnicity and result in differences in internal dose (Miranda et al., 2009). Second, cultural practices may result in elevated exposures. This has been demonstrated for lead through use of traditional lead-glazed pottery among Mexican Americans (Brown and Longoria, 2009) and use of traditional medicinals in several immigrant populations (Brown and Longoria, 2009; Saper et al., 2008). Third, environmental and occupational exposure to Cd may be unequally distributed across the population. Occupational exposures vary by race/ethnicity (Brown and Longoria, 2009). Geographical differences in soil content of Cd have been reported (US Department of Health and Human Services, 2008) and as demonstrated by lead, residential exposure can vary by location and neighborhood SES (Brown and Longoria, 2009; Sexton and Hattis, 2007).

Finally, genetic differences could contribute, particularly in the case of genes that may control iron levels and hence metal absorption (Bjorkman et al., 2000; Vahter et al., 2007). Interestingly, we did observe increased odds of Pb among women who had high levels of Cd (above the 75th percentile) ; higher levels of Pb would also be likely if these explanations for increased levels of Cd were valid.

The strengths of this study include the use of NHANES data which permits characterization of blood levels of environmental contaminants in a nationally representative sample and comparisons between persons belonging to different race/ethnicity groups. Stratification on race/ethnicity and tobacco exposure reduced confounding by smoking prevalence and intensity. Additionally, examination of non-smokers permitted a clearer estimation of blood Cd levels not attributable to tobacco exposure. Finally, multiple sensitivity tests were performed to test the robustness of the reported associations.

Limitations include limited power to study smaller race/ethnic groups and more thorough modeling of the relation between Cd and other covariates including lead. Use of a single measure of cotinine to estimate exposure to ETS and confirm smoking status likely resulted in some misclassification due to differences in half-life between biomarkers; serum cotinine with a half-life of less than 1 day reflects exposure within the last couple of days (NCHS., 1999–2000), whereas blood Cd with (the predominant) half -life of ~ 30 days, likely represents exposures occurring over a much longer period of time. Also, we lacked information regarding geographic location of participants, which may be associated with levels of Cd exposure. Finally, residual confounding by SES is likely; however it is important to note that SES may be a mediator of the race/ethnicity-Cd association such that the unadjusted estimate appropriately captures the extent of inter-racial/ethnic differences.

In summary, two important conclusions can be drawn from this analysis of blood Cd concentrations among US women of childbearing age. First, to accurately evaluate differences in blood Cd concentrations by race/ethnicity analyses must take account of smoking. Two, even after adjustment for important potential confounders, non-smoking minority women of childbearing age appear to have higher blood Cd levels than non - Hispanic whites; this is especially true for non-Hispanic Blacks and potentially for other minority groups. These women are also more likely to have higher blood lead levels. Additional studies are required to confirm these findings and to explore dietary, occupational, environmental, lifestyle, and host factors that might account for these differences. The reported variation in Cd levels by race/ethnicity may 1) inform population-based risk assessment and 2) may suggest novel hypotheses regarding the burden of chronic diseases like kidney disease, high blood pressure and osteoporosis in the population.

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Table 1
Demographic Characteristics in Women Included in NHANES and Women Included in Analysis

Characteristic	NHANES Source Population			Study Sample			P-value*
	N (4970)	Percent $\pm$ SE#	95% CI	N (3121)	Percent $\pm$ SE#	95% CI	
<i>Age</i>							
20–24 years	1142	19.6 $\pm$ 0.8	18.1–21.2	620	18.6 $\pm$ 0.9	16.9–20.4	
25–29 years	1084	17.6 $\pm$ 0.7	16.3–19.1	521	15.0 $\pm$ 0.7	13.6–16.5	<0.01
30–34 years	1008	20.1 $\pm$ 0.9	18.4–21.9	581	19.6 $\pm$ 0.9	17.7–21.5	
35–39 years	885	20.6 $\pm$ 1.1	18.5–22.8	634	22.0 $\pm$ 1.2	19.8–24.5	
40–44 years	881	22.1 $\pm$ 0.7	20.7–23.6	765	24.8 $\pm$ 1.0	22.9–26.9	0.02
<i>Race/Ethnicity</i>							
Mexican American	1242	9.7 $\pm$ 0.8	8.2–11.4	758	9.0 $\pm$ 0.8	7.6–10.8	
NH White	2195	64.6 $\pm$ 1.6	61.4–67.7	1360	66.4 $\pm$ 1.7	62.9–69.8	
NH Black	1034	13.5 $\pm$ 1.1	11.5–15.8	714	12.8 $\pm$ 1.1	10.8–15.1	
Other	499	12.2 $\pm$ 1.2	10.0–14.8	289	11.7 $\pm$ 1.2	9.5–14.5	
<i>Nativity</i>							
US	3682	82.8 $\pm$ 1.4	79.9–85.3	2372	84.0 $\pm$ 1.4	81.0–86.5	
Outside of US	1287	17.2 $\pm$ 1.4	14.7–20.1	749	16.0 $\pm$ 1.4	13.5–19.0	
Missing	1	0.0 $\pm$ 0.0	0.00–0.08				
<i>Years in US if born outside US</i>							
< 5 years	361	27.0 $\pm$ 1.6	23.9–30.4	168	24.3 $\pm$ 2.0	20.3–28.9	
5 or more years	908	71.7 $\pm$ 1.6	68.5–74.8	568	74.1 $\pm$ 2.0	69.6–78.2	
Missing	18	1.3 $\pm$ 0.5	0.5–2.5	13	1.5 $\pm$ 0.6	0.6–3.3	
<i>Education</i>							
< High school	1226	16.4 $\pm$ 0.8	15.0–18.1	740	15.8 $\pm$ 0.9	14.1–17.5	
HS graduate	1124	23.4 $\pm$ 1.0	21.6–25.3	721	23.7 $\pm$ 1.0	21.7–25.8	
Some college	1538	33.7 $\pm$ 1.0	31.6–35.7	1031	34.8 $\pm$ 1.2	32.5–37.2	
College graduate	1077	26.4 $\pm$ 1.3	24.0–29.0	626	25.6 $\pm$ 1.3	23.0–28.4	
Missing	5	0.1 $\pm$ 0.06	0.02–0.31	3	0.1 $\pm$ 0.1	0.02–0.4	
<i>Smoking status</i>							

Characteristic	NHANES Source Population			Study Sample			P-value *
	N (4970)	Percent ±SE#	95% CI	N (3121)	Percent ±SE#	95% CI	
Never	3226	59.1 ± 1.2	56.6–61.4	1954	58.4 ± 1.4	55.6–61.1	
Former	696	14.7 ± 0.9	13.1–16.5	373	13.9 ± 0.8	12.4–15.7	
Current	1042	26.1 ± 1.0	24.2–28.2	790	27.6 ± 1.1	25.4–29.9	
Missing	6	0.10 ± 0.05	0.03–0.26	4	0.08 ± 0.05	0.01–0.3	
<i>Ferritin+</i>							
< 20 µg/mL	1172	17.7 ± 0.5	16.6–18.8	659	18.3 ± 0.7	17.0–19.7	
≥ 20 µg/mL	3240	71.5 ± 0.8	69.9–73.1	2430	80.8 ± 0.7	79.3–82.2	
Missing	558	10.8 ± 0.7	9.6–12.2	32	0.97 ± 0.2	0.5–1.6	
<i>Currently Pregnant+</i>							
Yes	1165	7.6 ± 0.4	6.9–8.4				
No	3400	82.8 ± 0.8	81.3–84.3		100 ± 0.0		
Unknown	405	9.6 ± 0.7	8.3–11.0				

* All p-values > 0.05 unless reported.

+ High proportion of missing values in the NHANES source population stems from ferritin only being measured among MEC examined women (n = 4792).

Note that all percentages are weighted according to sampling fractions so that estimates are generalizable to the entire population.

Overall Distribution of Cadmium Levels for Women of Childbearing Age in the US (NHANES 1999–2006) Grouped by Analytical Method

Table 2

Year	N	Geo. Mean Cd $\mu\text{g/L}$ (95% CI)	Percentile Cut-Off (95% CI)			
			50 th	75 th	90 th	95 th Max ⁺
1999–2002 [*]	1569	0.42 (0.39–0.45)	0.34 (0.31–0.36)	0.58 (0.52–0.63)	1.09 (1.00–1.21)	1.51 (1.35–1.77) 8.5
2003–2006 [*]	1552	0.34 (0.32–0.36)	0.27 (0.26–0.29)	0.54 (0.48–0.63)	1.15 (1.02–1.25)	1.68 (1.48–1.93) 7.40
1999–2006 [†]	3121	0.40 (0.39–0.42)	0.31 (0.28–0.33)	0.57 (0.52–0.61)	1.13 (1.04–1.20)	1.60 (1.45–1.77) 8.5

^{*} For values less than LOD the $\text{LOD}/\sqrt{2}$ was imputed. LOD = 0.3 $\mu\text{g/L}$ (1999–2002), LOD = 0.2 $\mu\text{g/L}$ (2003–2006).

[†] These results were obtained by using the highest limit of detection (LOD = 0.3 $\mu\text{g/L}$) for the two analytical methods and imputing the (LOD/ $\mu 2$) for each value below the LOD.

⁺ Number of significant figures differ due to the precision of the reported blood cadmium levels.

[#] Note that all percentages are weighted according to sampling fractions so that estimates are generalizable to the entire population.

Table 3a
Blood Cadmium Levels in Female Smokers of Childbearing Age by Race/Ethnicity

Year	Race or Ethnicity	N [#]	Geo. Mean Cd $\mu\text{g/L}$ (95% CI)	p-value	Percentile Cut-Off (95% CI)				
					50 th	75 th	90 th	95 th	Max ⁺
1999–2006 ^L	All Women	790	0.88 (0.83–0.93)		0.84 (0.77–0.90)	1.31 (1.21–1.39)	2.03 (1.80–2.18)	2.64 (2.32–2.86)	8.5
1999–2006 ^L	Non-Hispanic White	465	0.91 (0.85–0.97)	Referent	0.86 (0.79–0.94)	1.35 (1.23–1.48)	2.10 (1.86–2.34)	2.75 (2.34–3.06)	3.5
1999–2006 ^L	Mexican American	110	0.63 (0.55–0.70)	<0.0001	0.55 (0.49–0.64)	0.90 (0.72–1.19)	1.55 (1.31–2.01)	2.03 (1.48–2.29)	8.5
1999–2006 ^L	Non-Hispanic Black	163	0.90 (0.82–1.01)	0.93	0.89 (0.79–1.00)	1.34 (1.16–1.45)	1.90 (1.57–2.14)	2.34 (1.97–2.83)	4.8
1999–2006 ^L	'Other'	61	0.76 (0.65–0.90)	0.03	0.73 (0.62–0.92)	1.11 (0.94–1.32)	1.45 (1.16–1.77)	1.68 (1.28–NC)	3.1

^LThese results were obtained by using the highest limit of detection ($\text{LOD} = 0.3 \mu\text{g/L}$) for the two analytical methods and imputing the ($\text{LOD}/\sqrt{2}$) for each value below the LOD.

⁺ Number of significant figures differ due to the precision of the reported blood cadmium levels.

[#] Note that all percentages are weighted according to sampling fractions so that estimates are generalizable to the entire population.

Table 3b
Blood Cadmium Levels in Female Never-Smokers of Childbearing Age By Race/Ethnicity

Year	Race or Ethnicity	N	GM blood Cd $\mu\text{g/L}$ (95% CI)	p-value	Percentile Cut-Off (95% CI)					Max ⁺	Weighted% < 0.50 $\mu\text{g/L}$
					50 th	75 th	90 th	95 th			
1999–2006 ^Δ	All Women	1954	0.29 (0.28–0.30)		0.21 ^Δ (–, 0.23)	0.35 (0.33–0.36)	0.49 (0.47–0.51)	0.59 (0.57–0.63)	2.8	9.3%	
1999–2006 ^Δ	Non-Hispanic White	681	0.27 (0.26–0.28)	Referent	<LOD (0,0.21)	0.31 (0.28–0.34)	0.43 (0.39–0.46)	0.51 (0.47–0.54)	1.1	5.4%	
1999–2006 ^Δ	Mexican American	568	0.31 (0.30–0.33)	0.0003	0.25 ⁺ (0.22–0.29)	0.38 (0.35–0.40)	0.50(0.46–0.55)	0.60 (0.54–0.69)	2.0	9.5%	
1999–2006 ^Δ	Non-Hispanic Black	502	0.31 (0.30–0.33)	<0.0001	0.23 ⁺ (0.21–0.25)	0.39 (0.35–0.42)	0.59 (0.53–0.64)	0.70 (0.65–0.78)	2.8	14.3%	
1999–2006 ^Δ	‘Other’	203	0.35 (0.32–0.39)	<0.0001	0.30 ⁺ (0.25–0.33)	0.44 (0.38–0.51)	0.70 (0.55–0.82)	0.85 (0.72–1.54)	2.2	19.9%	

^ΔThese results were obtained by using the highest limit of detection (LOD = 0.3 $\mu\text{g/L}$) for the two analytical methods and imputing the (LOD/ $\sqrt{2}$) for each value below the LOD.

⁺Number of significant figures differ due to the precision of the reported blood cadmium levels

^ΔValues are imprecise due to the influence of many imputed values on the estimate.

[#]Note that all percentages are weighted according to sampling fractions so that estimates are generalizable to the entire population.

Table 4

Odds of High Blood Cd Levels (upper 10% of the distribution) Varies by Race/Ethnicity Among Never-Smoking Women of Childbearing Age (20–44 years)

Model [†]	N	Mexican American	Non-Hispanic Black	Non-Hispanic Whites	Age > 35 years	Low ferritin (< 20 µg/L)	< high school education
Unadjusted	1734	1.89 (1.17–3.06)	3.05 (1.97–4.70)	1 (referent)			
Model 1	1734	1.77 (1.06–2.96)	2.96 (1.96–4.47)	1 (referent)	2.37 (1.57–3.58)	5.71 (3.43–9.51)	
Model 2	1734	1.45 (0.78–2.69)	2.75 (1.79–4.22)	1 (referent)	2.36 (1.56–3.56)	5.70 (3.42–9.48)	1.51 (0.91–2.52)
Model 1b [*]	1450	1.76 (1.01–3.08)	2.66 (1.75–4.04)	1 (referent)	2.38 (1.58–3.60)	5.61 (3.23–9.77)	
Model 2b [*]	1450	1.31 (0.67–2.58)	2.39 (1.56–3.66)	1 (referent)	2.39 (1.59–3.61)	5.62 (3.23–9.77)	1.83 (1.06–3.15)

[†] All models exclude observations for which ferritin measures were unavailable (n = 17) and do not include women of 'other' race/ethnicity as the numbers of women are too small.

^{*} Models re-run excluding women who had elevated liver enzymes and/or C-reactive protein which may indicate recent infection or chronic inflammation, conditions which impair the ability of ferritin to accurately indicate iron stores.

[#] Note that all percentages are weighted according to sampling fractions so that estimates are generalizable to the entire population.