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Characterization of trace elements exposure in pregnant women in the United States, NHANES 1999–2016.

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Abstract

Objective: The objective of the current study is to report on urine, blood and serum metal concentrations to characterize exposures to trace elements and micronutrient levels in both pregnant women and women of child-bearing age in the U.S. National Health and Nutrition Examination Survey (NHANES) years 1999–2016.

Methods: Urine and blood samples taken from NHANES participants were analyzed for thirteen urine metals, three blood metals, three serum metals, speciated mercury in blood and speciated arsenic in urine. Adjusted and unadjusted least squares geometric means and 95% confidence intervals were calculated for all participants among women aged 15–44 years. Changes in exposure levels over time were also examined. Serum cotinine levels were used to adjust for smoke exposure, as smoking is a source of metal exposure.

Results: Detection rates for four urine metals from the ATSDR Substance Priority List: arsenic, lead, mercury and cadmium were ~83–99% for both pregnant and nonpregnant women of child bearing age. A majority of metal concentrations were higher in pregnant women compared to non-pregnant women. Pregnant women had higher mean urine total arsenic, urine mercury, and urine lead; however, blood lead and mercury were higher in non-pregnant women. Blood lead, cadmium, mercury, as well as urine antimony, cadmium and lead in women of childbearing age decreased over time, while urine cobalt increased over time.

Conclusions: Pregnant women in the US have been exposed to several trace metals, with observed concentrations for some trace elements decreasing since 1999.

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Declaration of competing interest

The authors have no competing financial interests in relation to the work described.

1. Introduction

The Agency for Toxic Substance and Disease Registry (ATSDR) includes trace metals on the Substance Priority List based on frequency of occurrence at National Priorities List (NPL) sites, toxicity, and potential for human exposure (ATSDR, 2019). Metals such as lead, mercury, cadmium and arsenic are on the list. Trace elements from anthropogenic sources, such as manufacturing and mining, have been shown to accumulate in the environment (Wu et al., 2016). People can be exposed to these and other metals through soil, water, diet, air, commercial products and occupational sources. Exposure sources for individual metals may differ by geographical location and lifestyle characteristics (King et al., 2015; Callan et al., 2013). For example, the primary routes of arsenic exposure in the United States are drinking water and breathing airborne particles (ATSDR, 2007; Bloom et al., 2014), while exposure to methylmercury is the result of dietary intake (Hong et al., 2012).

Pregnant women are particularly vulnerable to metal accumulation due to changing body chemistry. For example, blood iron concentration can decrease during pregnancy, resulting in an accumulation of blood cadmium (Lee and Kim, 2012). Additionally, metals, such as arsenic and lead, can cross the placenta during pregnancy (Zhou et al., 2017). Maternal exposure to heavy metals has been linked to adverse birth outcomes including low birth weight, small head circumference, and developmental delays (Kumar et al., 2017; Shirai et al., 2010). Even low dose exposure to cadmium, lead, mercury and arsenic has been linked to low birth weight (King et al., 2015). Cadmium, in particular, has been linked to both low birth weight and decreased head circumference (Cheng et al., 2017). Smoking remains a non-occupational source of cadmium exposure (Ikeh-Tawari et al., 2013), and an estimated 13.8% of expectant mothers in the U.S. smoked while pregnant in 2005 (Centers for Disease Control and Prevention, 2017). Some metals, e.g. mercury and arsenic, exist in both organic and inorganic species and have different exposure routes and health effects depending on the chemical characteristics of the specific species (Park and Zheng, 2012). For example, there is little evidence linking elemental mercury exposure to adverse maternal health outcomes, while mercury metabolites like methylmercury are highly teratogenic and have been linked to developmental delays (Hinwood et al., 2013).

Other elements, such as iodine, copper, selenium, zinc, cobalt, and molybdenum are essential micronutrients and are particularly important during pregnancy, provided exposure does not exceed recommended levels. Micronutrient deficiencies have a range of negative health implications and can lead to low birth weight, preterm birth, fetal malformations, developmental delays, and miscarriage (Cetin et al., 2010; Gernand et al., 2016). Iodine is necessary for thyroid hormone synthesis; maternal iodine deficiency can lead to neurological complications and mental retardation in the developing fetus (Bailey et al., 2015). Zinc is a component of over 300 enzymes and is involved in DNA/RNA transcription (Zimmermann and Andersson, 2012; Andersson et al., 2010; Hu et al., 2014). Zinc deficiency in the maternal diet has been linked to intrauterine growth retardation and teratogenesis (Uriu-Adams and Keen, 2010). Copper helps ensure normal fetal hematopoiesis, and low copper levels have been linked to low birth weight (Bermudez et al., 2015). However, high levels of maternal copper have been linked to congenital heart defects (Hu et al., 2014). Selenium

helps prevent free radical accumulation, and cobalt is used in the formation of vitamin B12 and red cell production (Fort et al., 2015; Mistry et al., 2014).

The objective of the current study is to report on trace element concentrations in urine, blood and serum in pregnant women of childbearing age (here defined as age 15–44 years) in the U.S compared to non-pregnant women of childbearing age. The National Health and Nutrition Examination Survey (NHANES) screens for chemicals and trace elements in the U.S. general population and the data is publicly available (National Center for Health Statistics, 2008). While the aim of NHANES is to collect data from 5000 participants annually and report the data biannually (also referred to as a "cycle"), the urine metal analyses are conducted on subsamples of this population, while the blood metals analysis captures the entire population. To increase sample sizes, multiple NHANES cycles from 1999 to 2016 were used in this analysis. This paper reports on trace metal exposure in pregnant women, compares the concentrations to non-pregnant women, and includes an analysis of geometric means by NHANES cycle for maternal exposure to metals since 1999.

2. Methods

2.1. Study populations

NHANES is administered by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC) and combines questionnaires, medical examinations, and laboratory biomonitoring methods to determine the prevalence of diseases and environmental exposures in the civilian, non-institutionalized general U.S. population. Participants receive a health examination at mobile examination centers (MECs). At the time of the exam, pregnancy status is ascertained by urine pregnancy tests and self-reported pregnancy status for women aged 8–44. Though NHANES documentation notes that pregnancy status is publicly released only for women aged 20–44 (National Center for Health Statistics, 2009-2010), data is in fact available for women outside of that range in some public release datasets as well as from the Research data Center upon request. NHANES cycles typically capture small numbers of pregnant women; though in the 1999–2006 cycles, pregnant women were sampled at a higher rate than usual.

To increase samples sizes of pregnant women for this analysis, groupings of NHANES cycles spanning the years 1999–2016 (referred to here as "multicycles") were combined for analysis. The number of cycles available for inclusion in any multicycle was analyte-dependent, reflecting whether NHANES collected data on the analyte in a particular year. For this analysis, eight multicycle groups were formed (Table 1). Non-pregnant women of childbearing age, defined as women aged 15–44, were included as a comparison population. The study population for geometric means plots included all women aged 15–44. In order to assess the effect of covariates, the analysis population was further restricted to those women who had non-missing values of age, race/ethnicity, household poverty-to-income ratio, body mass index (BMI), and serum ln-cotinine.

2.2. Analytical measures

Urine and blood samples obtained from NHANES participants were analyzed by the Division of Laboratory Sciences in the National Center for Environmental Health at the CDC. Elemental analysis was performed using either graphite furnace atomic absorption spectroscopy (GFAAS), flow injection cold vapor atomic absorption spectroscopy (FICVAA), inductively coupled plasma mass spectrometry (ICP-MS), high pressure liquid chromatography ICP-MS (HPLC-ICP-MS), or isotope dilution solid-phase microextraction ICP-MS (ID-SPME-ICP-MS) (Stoeppler M, 1980; Guo and Baasner, 1993; Caldwell et al., 2003; Caldwell et al., 2005; Jarrett et al., 2008; Jarrett et al., 2007; Jones et al., 2017; Verdon et al., 2009; Sommer et al., 2014; Miller et al., 1987). The complete analytical methods for each panel can be found on the NHANES website (National Center for Health Statistics, 2011). The urine total element analytes include arsenic, barium, cadmium, cobalt, cesium, mercury, iodine, molybdenum, lead, antimony, thallium, tungsten and uranium. Urine beryllium and platinum were part of NHANES from 1999 to 2010 but were dropped from later cycles due to low detection rates. Cadmium, lead, and mercury were evaluated from the whole blood metals panel. Zinc, copper and selenium are analyzed in the serum metals panel. Speciated arsenic and mercury are also measured in urine and blood, respectively. Creatinine was analyzed for all urine samples; the analytical method can also be found on the NHANES website (National Center for Health Statistics, 2011). Urine samples were ratio adjusted for creatinine to account for urinary dilution (National Center for Health Statistics, 2011). Serum cotinine was included in the analysis as smoking is a source of exposure to metals; the analytical method is published elsewhere (Bernert et al., 2009).

2.3. Statistical methods

We used linear regression on ln-transformed analytes to estimate adjusted and unadjusted least squares geometric means of analyte concentration by pregnancy status. For each analyte, the percent of respondents with concentrations above the LOD was calculated. When the concentration of an analyte was below the LOD, NHANES substitutes the value of the LOD divided by the square root of 2 for that concentration (National Center for Health Statistics, 2011). For analytes with less than 40% detection rate, GMs were not calculated, per NHANES guidelines (National Center for Health Statistics, 2011). All statistical analyses were conducted using SAS Version 9.4 survey procedures (SAS Institute Inc., Cary, NC, 2012). NHANES-assigned weights were modified for combined cycles as described on the NHANES website (National Center for Health Statistics, 2011). Weights and design variables were used to account for NHANES's complex sample design and make results generalizable to the respective groups in the U.S. civilian, non-institutionalized population. Adjusted least squares geometric means were adjusted for age, race/ethnicity, household poverty-to-income ratio, body mass index (BMI), and serum ln-cotinine. The household poverty-to-income ratio is calculated by dividing family income by the poverty guidelines set forth by the Department of Health and Human Services specific to family size, as well as the appropriate year and state. BMI is calculated as weight (kg) divided by height in meters squared (National Center for Healt, 2009-2010). For urinary analytes, both ratio creatine-adjusted and non-creatinine-adjusted estimates were calculated. Wald's F tests were calculated to test for the effect of pregnancy status on analyte least squares geometric means.

Additionally, plots of geometric means of analyte levels among women of childbearing age were plotted by NHANES cycle to assess changes over time for select analytes.

3. Results

Covariate sample sizes, means (continuous variables) and percent estimates (classification variables) are reported in Table 2. Estimates of least squares regression covariates in Table 2 from combined years represent the average over the time period covered by a particular multicycle, and thus these estimates vary somewhat across multicycles. Nevertheless, Table 2 shows a general pattern in which pregnant women tended to be younger, to be non-White, and to have lower cotinine levels across the various multicycles when compared to their non-pregnant counterparts. Cotinine levels were analyzed for all women included in this study. For the multicycle spanning 1999–2016, the GM (and 95% confidence interval) for cotinine for pregnant women was 0.112 (0.082, 0.153) ng/ml compared to 0.338 (0.292, 0.392) ng/ml for non-pregnant women. The 90th percentile (and 95% confidence interval) for cotinine in pregnant women was 48.2 (14.4, 81.9) ng/ml compared to 203 (189,217) ng/ml for non-pregnant women. Among pregnant women, 12.9% (9.30%, 15.7%) had a cotinine level greater than 10 ng/ml (an indicator of smoke exposure), compared to 24.8% (23.3%, 26.3%) among non-pregnant women.

Detection rates for urine total metals ranged from 79 to 100% in pregnant women and 78–100% in non-pregnant women (Table 3). The creatinine and covariate-adjusted least squares GMs for antimony in pregnant women versus non-pregnant women were 0.078 (0.069, 0.087) vs. 0.068 (0.066, 0.071) μg/g creatinine, 1.86 (1.37, 2.19J) vs. 1.23 (1.17, 1.29) μg/g creatinine for barium, 0.183 (0.165, 0.203) vs. 0.181 (0.174, 0.189) μg/g creatinine for cadmium, 4.84 (4.55, 5.14) vs. 4.20 (4.11, 4.30) μg/g creatinine for cesium and 0.627 (0.573, 0.685) vs. 0.447 (0.433, 0.461) μg/g creatinine for cobalt. The creatinine and covariate adjusted least squares GMs for urine lead in pregnant women versus non-pregnant women was 0.582 (0.519, 0.651) vs 0.397 (0.381, 0.413) μg/g creatinine, 49.0 (44.6, 53.9) vs. 39.5 (38.2, 40.8) μg/g creatinine for molybdenum, 0.171 (0.161, 0.1810) vs. 0.166 (0.162, 0.171) μg/g creatinine for thallium, 0.085 (0.076, 0.096) vs 0.074 (0.070, 0.077) μg/g creatinine for tungsten and 0.007 (0.006, 0.009) vs. 0.007 (0.006, 0.007) μg/g creatinine for uranium.

Detection rates for elemental species ranged widely. Urine speciated arsenic levels had a broad range of detection rates in pregnant women, with arsenocholine at only 2.7% and dimethylarsenic acid at 87%. The creatinine and covariate adjusted least squares GMs in pregnant women versus non-pregnant women were 1.94 vs. 2.06 μg/g creatinine for arsenobetaine, 5.04 vs. 4.09 μg/g creatinine for dimethylarsenic acid, and 10.3 vs. 9.11 μg/g creatinine for total urine arsenic. Blood speciated mercury included in the NHANES analysis also had variable detection rates with ethyl mercury at 1.0% and methyl mercury at 76%. The creatinine and covariate adjusted least squares GM in pregnant women versus non-pregnant women for methyl mercury was 0.408 vs. 0.510 μg/L and 0.787 vs. 0.863 μg/L for total mercury. Detection rates, 90th percentiles and both adjusted and unadjusted GMs with confidence intervals for all analytes are reported in Table 3.

Detection rates for blood metals ranged from 66 to 94% in pregnant women and 70–99% in non-pregnant women (Table 3). The covariate-adjusted least square GM for blood cadmium in pregnant women vs non-pregnant women was 0.332 vs. 0.335 μg/L and 0.717 vs. 0.797 μg/dL for blood lead (Table 3). The serum metals, derived from participant bloods specimens included copper, selenium and zinc and were only measured in the 2011–2012, 2013–2014 and 2015–2016 cycles. Because there were only 3 cycles included in the analysis, there were smaller sample sizes for pregnant women. Detection rates for all three serum metals were 100%, with covariate-adjusted least squares GMs between pregnant and non-pregnant women of 191 vs. 127 μg/dL for serum copper, 113 vs 123 μg/L for serum selenium, and 70.2 vs. 76.6 μg/dL for serum zinc (Table 3).

To evaluate changes in exposures over time, we examined geometric means across NHANES cycles for urine and blood metals among all women of childbearing age (defined here as 15–14 years of age, regardless of pregnancy status). GMs and 95% confidence intervals of select urine heavy metals across all NHANES cycles included in this analysis are presented in Figs. 1 and 2. Urine cadmium, arsenic and antimony have decreased from 1999 to 2016 (Figs. 1 and 2). Cobalt concentrations have increased since 1999, with the exception of the 2003–2004 NHANES cycle data, which is lower than all other cycles (Fig. 3). There is no apparent change in concentrations of other urine metals from 1999 to 2016. GMs and 95% confidence intervals of blood cadmium, lead, and mercury across all NHANES cycles included in this analysis are presented in Figs. 1 and 2. Blood lead, cadmium and mercury have decreased from 1999 to 2016 (Figs. 1 and 2). We did not analyze time trends for the serum micronutrients due to limited cycle availability.

4. Discussion

Characterization of trace elements in urine, blood and serum in pregnant women living in the U.S. (NHANES, 1999–2016) is presented here. Pregnant women and non-pregnant women of childbearing age had 14 metals (antimony, barium, cadmium, cesium, cobalt, dimethylarsinic acid, iodine, lead, inorganic mercury, molybdenum, thallium, arsenic, tungsten and uranium) measured in urine with a detection rate greater than 75% in NHANES 1999–2016. Meanwhile, six metals (copper, lead, mercury, methyl mercury, selenium, zinc, and mercury) were measured in blood and/or serum with a detection rate of greater than 75% in NHANES 2011–2016. Some metabolites of arsenic and mercury had lower detection rates. Of the metals analyzed in this study, four are included on the ATSDR priority list: arsenic, lead, mercury and cadmium. Both pregnant and non-pregnant women of child bearing age had ~83–99% detection rates for these urine metals. It should be noted that rates of detection are not a measure of risk, we report detection rates here to characterize the prevalence of exposure in the study sample, noting that some analytes with high detection rates are essential micronutrients. Also, while some urine measurements reflect recent exposures, that is not the case for every analyte included here. In the case of cadmium, the blood measurement can reflect both recent and cumulative exposures (Fourth National Report on, 2009).

Trace metal concentrations were generally higher for pregnant versus non-pregnant women, with some exceptions. Pregnant women had higher mean urine barium, cesium, lead, and

tungsten. Lower mean urine cadmium concentrations, however, were observed in pregnant women, as were blood lead, cadmium, and mercury. Concentrations of other analytes were similar among pregnant and non-pregnant women; especially once creatinine adjustment was taken into account. We expected to see higher blood lead levels in pregnant women, as lead is known to mobilize out of the bones during pregnancy (Rabito et al., 2014), but that was not the finding. Pregnant women had significantly lower blood lead than non-pregnant women yet significantly higher urine lead. This finding could provide evidence for bone resorption of lead during pregnancy (Wang et al., 2019). However, without information on gestational age for study participants, we cannot analyze blood lead changes throughout the course of pregnancy as others have done (Tellez-Rojo et al., 2004).

There was a decrease in urine and blood lead in all women of childbearing age from 1999 to 2016, which is expected due to the removal of lead from gasoline and other restrictions on lead use (Muntner et al., 2005). Additionally, there was a decrease from 1999 to 2016 in blood cadmium. Tellaz-Plaza et al. attribute a reduction in blood cadmium levels in the general population to a reduction in smoking, resulting in less cadmium exposures in both smokers and non-smokers (Tellez-Plaza et al., 2012). There was also a decrease in urine antimony over the time of these NHANES cycles, which is not as well documented due to a lack of research on antimony exposure. Decreases in urine antimony, as well as other elements reported here, could be due to decreases in occupational exposures or environmental regulations setting exposure limits similar to those placed on cadmium (Agency for Toxic Substances and Disease Registry, 2015). The only metal we observed increasing over time was cobalt (Fig. 3). Cobalt is a component of vitamin B12, which is included in multivitamins and supplements but is primarily found in animal-based foods (Simpson et al., 2010). This increase could be explained by increasing multivitamin supplementation, or dietary changes, but there is no current trend data to support these hypotheses (Simpson et al., 2010).

The elements categorized as micronutrients included in this analysis serve essential functions in the body, especially during pregnancy. Deficiencies in copper, selenium, iodine and zinc can lead to adverse birth outcomes (Bailey et al., 2015). Selenium has been shown to mitigate cadmium accumulation and damage, and low selenium has been associated with low birth weight, likely due to effects of increased cadmium (Shen et al., 2015). Published reference ranges (lowest to highest across all three trimesters) for copper, selenium and zinc are 112–240 μg/dL, 71–146 μg/L, and 51–88 μg/dL, respectively. GMs for these micronutrients fit within these ranges, though it should be noted NHANES samples are collected at a single time point and not across three trimesters for pregnant women (Abbassi-Ghanavati et al., 2009). The findings of this study suggest that pregnant women in the U.S. have adequate levels of copper, selenium, and zinc, essential micronutrients based on published reference ranges, and there were no significant differences in GM between the two groups in this analysis.

Iodine is needed for thyroid function, and maternal iodine intake is the only source of iodine to the developing fetus. Previous data suggests that only 6.9% of pregnant women have adequate iodine (Simpson et al., 2011). However, WHO states that during pregnancy, median urinary iodine concentrations in a range of 150–249 μg/L define a population which

has no urinary iodine deficiency (World Health Organization, 2008). The GM for pregnant women from this study (138 [119,160] μg/L) is below that range, as was previously described, indicating that there is evidence of iodine deficiency in pregnant women in the U.S. (Pan et al., 2013; Caldwell et al., 2013).

Finding comparative studies with pregnant women that utilized the same urine and blood metals panels was challenging; however, there were some comparable cross-sectional studies in the literature, but these studies do not report multiple values over time. GMs for antimony, cadmium, cesium and total arsenic were comparable to those published in a French study (Dereumeaux et al., 2016). However, the GM for cobalt was twice as high in France and three times as high in Australia (Callan et al., 2013). Additionally, Australia reported much higher GM total arsenic (38.3 μg/L). A study published in Myanmar reported much higher cadmium and lead (Wai et al., 2017). For blood metals, there was greater availability for comparable studies. Values reported here were very similar to those reported in Canada (Thomas et al., 2015); however, Saudi Arabia, Korea and China reported much higher blood lead, cadmium and mercury (Al-Saleh et al., 2014; Jin et al., 2014; Jeong et al., 2017).

The current study is not without limitations. Due to changes between NHANES cycles, some metals, such as urine tin, manganese, and strontium as well as blood manganese and selenium were excluded from the analysis as they were only recently added to NHANES analytical panels. Manganese is required for essential functions, including amino acid and protein metabolism and normal immune function, and should be included in future studies when more data is available (Tsai et al., 2015). Other metals like copper, selenium and zinc are also relatively new additions, so sample sizes of pregnant women were very small compared to other analytes. NHANES pregnancy data is only released for a certain age range, which makes comparing to other studies challenging as they likely have a wider age range for pregnant women. While we did correct for urine dilution using the creatinine measurement, we did not consider the increased blood volume of pregnant women. Pregnant woman have an increased blood volume, which could dilute exposures, resulting in lower blood metals values (Woodruff et al., 2011). Metals in cord blood were not measured, as other studies have, which limits the ability to comment on fetal exposures.

Differences between pregnant and non-pregnant women could be attributed to pregnant women altering health behaviors due to pregnancy. Fewer women smoke during pregnancy, as our own data indicates, and smoking is a source of exposure to metals (Lange, n.d.). This could be a cause for lower GM of metals such as cadmium. In the U.S., women are advised to avoid high mercury fish during pregnancy (Oken et al., 2003), which could lower methylmercury levels in this population. Results were not compared to self-reported health behaviors, which could further account for exposure differences between pregnant and non-pregnant women. Covariates such as supplement use, geography and occupational exposures were either not available across all NHANES cycles or are not publicly available and were therefore excluded from this analysis. Dietary intake is also an important covariate but was not included in this analysis.

The findings of this study indicate that pregnant women in the U.S. are exposed to several trace elements simultaneously. These results are intended to provide background levels of

metals in pregnant women and women of childbearing age in the U.S. This study does not make any direct comparisons to adverse birth outcomes or attempt to identify sources of exposure. NHANES is intended to be representative of the general U.S. population, and special subpopulations in the U.S. likely have higher or lower exposures, depending on the element. The estimates presented here can be used as a reference for future epidemiological studies focused on special populations of pregnant women.

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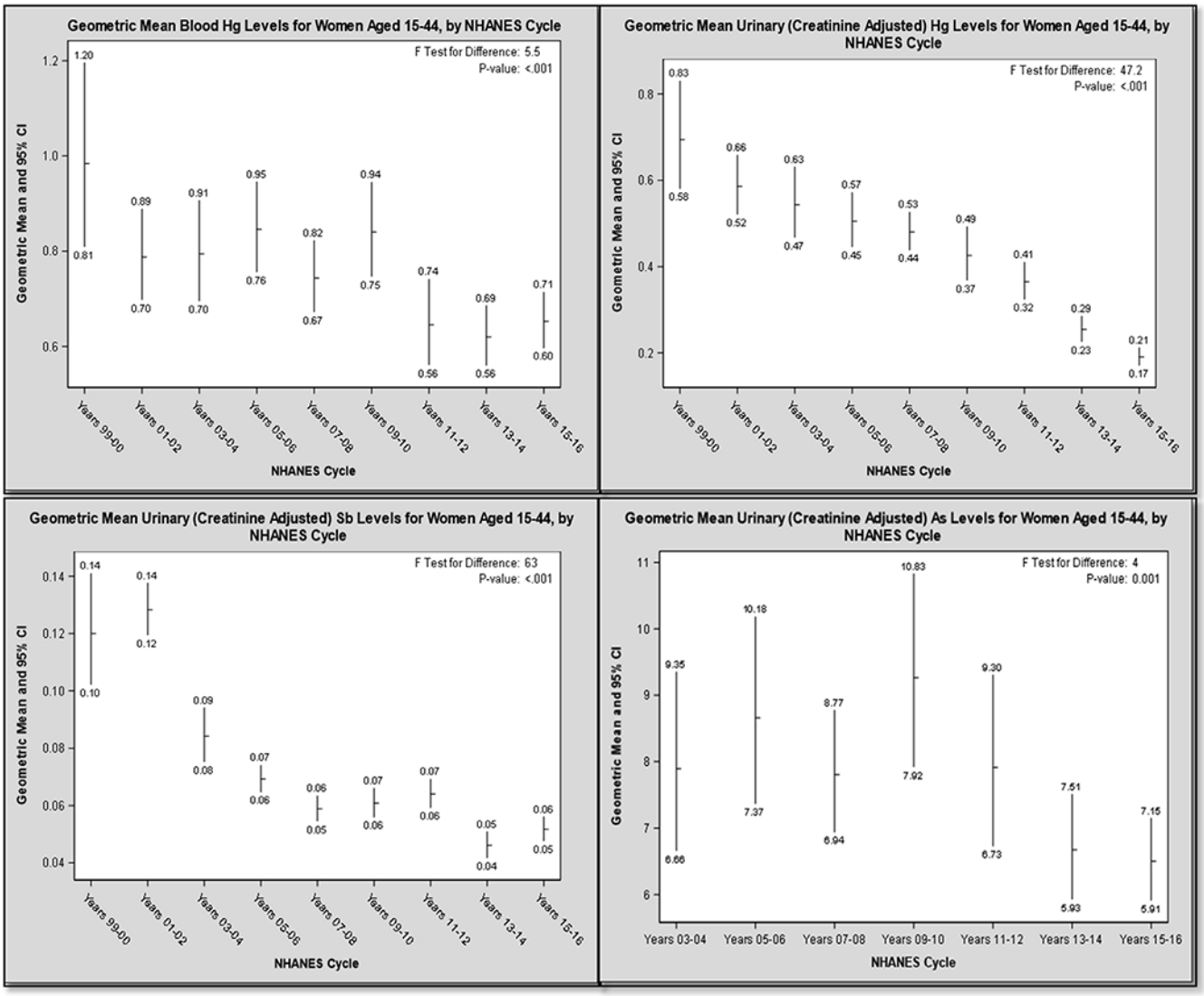

Fig. 1.

GMs (95% CIs) for blood mercury, urine mercury, urine antimony, urine total arsenic by NHANES cycle (1999–2016), among women aged 15–44, regardless of pregnancy status.

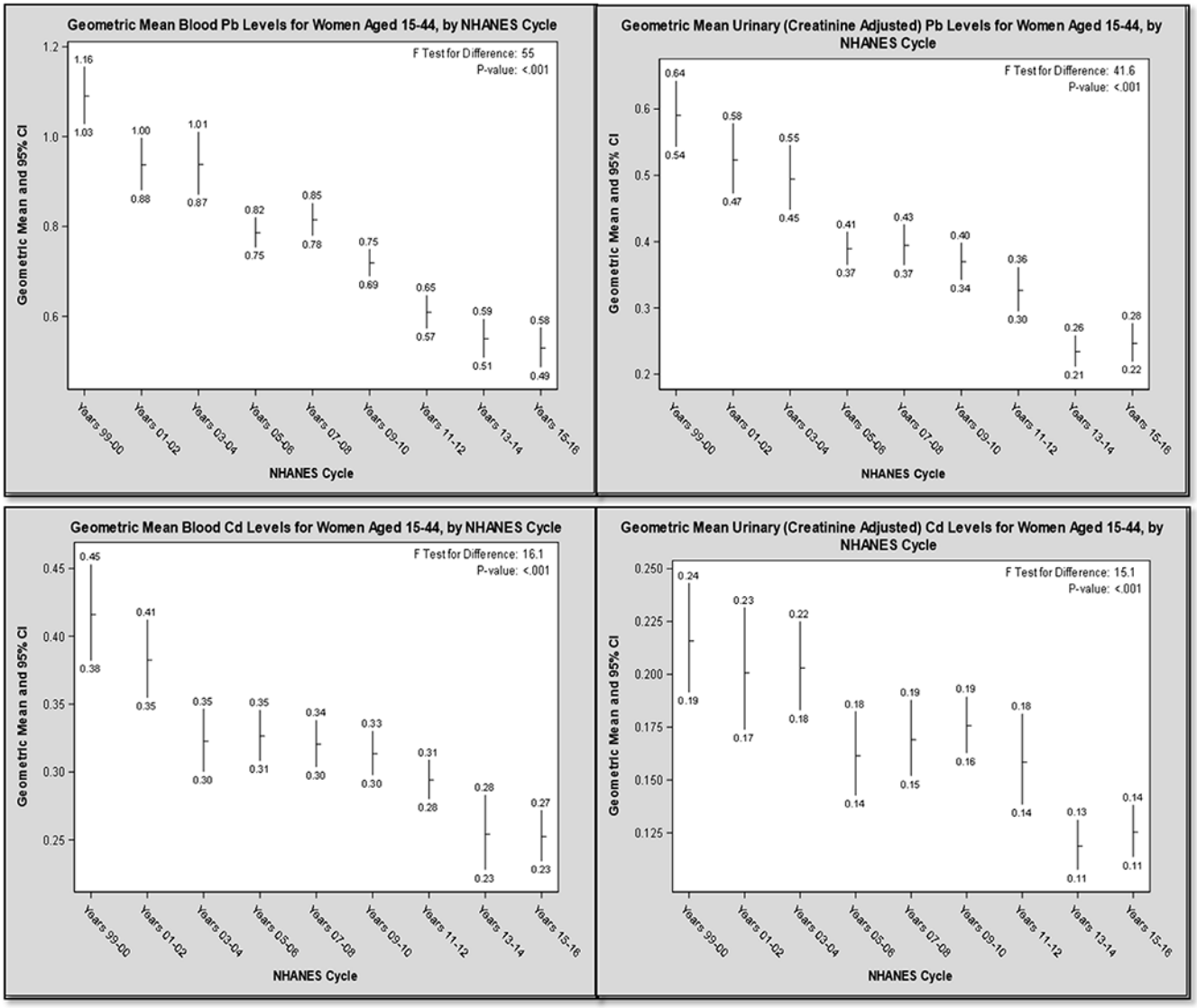

Fig. 2.

GMs (95% CIs) for blood lead, urine lead, blood cadmium and urine cadmium by NHANES cycle (1999–2016), among women aged 15–44, regardless of pregnancy status.

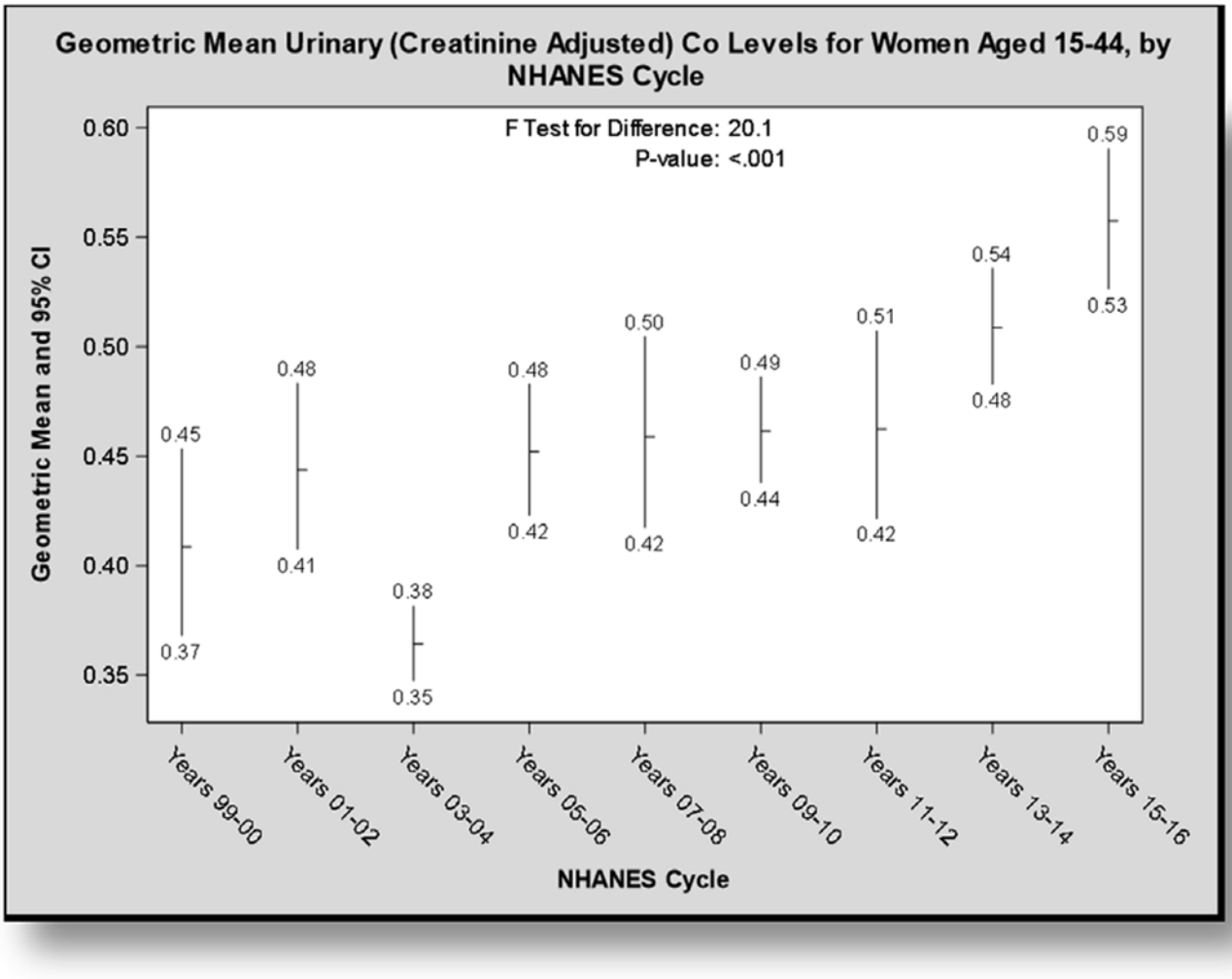

Fig. 3.

GMs (95% CIs) for urinary cobalt by NHANES cycle (1999–2016), among women aged 15–44, regardless of pregnancy status.

Table 1

Analyte availability by NHANES Cycle.

Analytes Examined	NHANES Cycle Availability								
	1999–2000	2001–2002	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016
Antimony in urine, μg/L	x	x	x	x	x	x	x	x	x
Arsenic, Total in urine, μg/L			x	x	x	x	x	x	x
Arsenic (V) Acid in urine, μg As/L			x	x	x	x	x	x	x
Arsenobetaine in urine, μg As/L			x	x	x	x	x	x	x
Arsenocholine in urine, μg As/L			x	x	x	x	x	x	x
Arsenous (III) Acid in urine, μg As/L			x	x	x	x	x	x	x
Dimethylarsinic Acid in urine, μg As/L			x	x	x	x	x	x	x
Monomethylarsonic Acid in urine, μg As/L			x	x	x	x	x	x	x
Inorganic-related Arsenic Species, in urine, μg As/g									
Trimethylarsine oxide in urine, μg As/L			x	x	x	x	x		
Barium in urine, μg/L	x	x	x	x	x	x	x	x	x
Cadmium in blood, μg/L	x	x	x	x	x	x	x	x	x
Cadmium in urine, μg/L	x	x	x	x	x	x	x	x	x
Cesium in urine, μg/L	x	x	x	x	x	x	x	x	x
Cobalt in urine, μg/L	x	x	x	x	x	x	x	x	x
Copper in serum, μg/dL							x	x	x
Iodine in urine, μg/L		x	x	x	x	x	x	x	x
Lead in blood, μg/dL	x	x	x	x	x	x	x	x	x
Lead in urine, μg/L	x	x	x	x	x	x	x	x	x
Mercury, Total in blood, μg/L			x	x	x	x	x	x	x
Mercury, Inorganic in blood, μg/L			x	x	x	x	x	x	x
Mercury, Ethyl in blood, μg/L							x	x	x
Mercury, Methyl in blood, μg/L							x	x	x
Mercury, Inorganic in urine, μg/L			x	x	x	x	x	x	x
Molybdenum in urine, μg/L	x	x	x	x	x	x	x	x	x
Selenium in serum, μg/L							x	x	x
Thallium in urine, μg/L	x	x	x	x	x	x	x	x	x

Analytes Examined	NHANES Cycle Availability								
	1999–2000	2001–2002	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016
Tungsten in urine, μg/L	x	x	x	x	x	x	x	x	x
Uranium in urine, μg/L	x	x	x	x	x	x	x	x	x
Zinc in serum, μg/dL							x	x	x

Table 2

Sample sizes, means, and percentile for least squares regression covariates, by NHANES multicycle.

Variable Name		Blood Metals 1999–2016		Urine I and Hg Mercury 1999–2016		Urine Metals 1999–2016		Urine Uranium 2001–2016		Urine Iodine 2001–2016		Urine Arsenic Species 2003–2016		Serum Metals 2011–2016		Blood Hg Species 2011–2016	
		Pregnant	Not Pregnant	Pregnant	Not Pregnant	Pregnant	Not Pregnant	Pregnant	Not Pregnant	Pregnant	Not Pregnant	Pregnant	Not Pregnant	Pregnant	Not Pregnant	Pregnant	Not Pregnant
Continuous																	
Age	N	1283	8783	775	4736	413	3228	353	2976	419	3680	264	2536	52	978	98	1941
	Mean	**27.9**	**31.5**	**28.1**	**31.4**	**27.9**	**31.4**	**27.8**	**31.3**	**28.1**	**31.4**	**28.3**	**31.6**	**28.7**	**32.0**	**28.3**	**32.1**
Income to Poverty Ratio	N	1283	8783	775	4736	413	3228	353	2976	419	3680	264	2536	52	978	98	1941
	Mean	**2.7**	**2.7**	**2.8**	**2.7**	**2.8**	**2.6**	**2.8**	**2.6**	**2.6**	**2.7**	**2.9**	**2.6**	**2.8**	**2.6**	**2.7**	**2.6**
BMI	N	1283	8783	775	4736	413	3228	353	2976	419	3680	264	2536	52	978	98	1941
	Mean	**29.3**	**27.9**	**28.9**	**27.8**	**28.8**	**27.9**	**29.1**	**27.9**	**29.5**	**27.7**	**29.0**	**28.0**	**29.7**	**28.5**	**29.9**	**28.9**
Ln Cotinine	N	1283	8783	775	4736	413	3228	353	2976	419	3680	264	2536	52	978	98	1941
	Mean	**−2.2**	**−1.1**	**−2.1**	**−1.0**	**−1.9**	**−1.0**	**−2.0**	**−1.1**	**−2.1**	**−1.1**	**−2.3**	**−1.2**	**−2.2**	**−1.5**	**−2.3**	**−1.6**
Categorical																	
Mexican American	N	363	2008	211	1192	106	726	88	642	116	805	63	516	5	157	11	280
	%	**15.2**	**9.9**	**14.5**	**10.2**	**14.8**	**10.1**	**15.2**	**10.5**	**14.1**	**10.5**	**14.5**	**10.7**	**9.0**	**11.7**	**9.8**	**11.1**
Non-Hispanic Black	N	213	2023	113	1056	66	723	61	674	77	806	46	571	15	190	30	437
	%	**16.7**	**12.9**	**14.7**	**12.8**	**14.5**	**12.8**	**14.7**	**13.0**	**18.2**	**12.8**	**14.6**	**13.1**	**21.2**	**12.7**	**21.9**	**13.7**
Non-Hispanic White	N	544	3438	350	1815	181	1240	153	1145	161	1449	115	965	13	348	27	681
	%	**52.1**	**63.3**	**54.3**	**63.1**	**53.8**	**63.4**	**51.9**	**62.6**	**49.7**	**62.7**	**54.4**	**62.0**	**46.1**	**57.6**	**46.7**	**57.8**
Other Hispanic	N	73	654	45	339	26	254	22	239	31	309	17	218	7	104	12	195
	%	**5.9**	**6.6**	**5.4**	**6.7**	**4.7**	**6.7**	**4.9**	**6.5**	**6.8**	**6.0**	**5.5**	**6.3**	**10.1**	**8.0**	**9.5**	**7.5**
Other Race	N	90	660	56	334	34	285	29	276	34	311	23	266	12	179	18	348
	%	**10.1**	**7.2**	**11.2**	**7.1**	**12.1**	**7.0**	**13.2**	**7.4**	**11.3**	**8.0**	**11.0**	**8.0**	**13.6**	**10.0**	**12.0**	**9.9**
Total	N	1283	8783	775	4736	413	3228	353	2976	419	3680	264	2536	52	978	98	1941
	%	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 3

Ln-transformed urine and blood concentrations of trace elements in NHANES pregnant and non-pregnant women, aged 15–44 years.

Analyte	Pregnancy Status	N	NHANES Years	% At/ Above LOD	P90	Geometric Mean (95% CI)	Pr > F	Geometric Mean (95% CI) Adjusted	Pr > F Adjusted
Antimony, urine (ug/L)	**Pregnant**	**404**	**1999–2016**	**82.4**	**.230**	**.079 (.070–.089)**	**.009**	**.081 (.072–.090)**	**.012**
	Not Pregnant	3174	1999–2016	77.1	.199	.067 (.063–070)		.069 (.065–.073)	
Antimony, urine (ug/g creatinine)	**Pregnant**	**404**	**1999–2016**	**82.4**	**.179**	**.078 (.069–.087)**	**.183**	**.078 (.069–.087)**	**.033**
	Not Pregnant	3173	1999–2016	77.1	.187	.072 (.069–075)		.068 (.066–.071)	
Total Arsenic, urine (ug/L)	**Pregnant**	**259**	**2003–2016**	**99.0**	**40.3**	**8.77 (7.14–10.8)**	**.066**	**10.1 (8.24–12.4)**	**.179**
	Not Pregnant	2502	2003–2016	98.6	32.3	7.21 (6.69–7.78)		8.78 (8.10–9.51)	
Total Arsenic, urine (ug/g creatinine)	**Pregnant**	**259**	**2003–2016**	**99.0**	**39.6**	**9.10 (7.43–11.1)**	**.226**	**10.3 (8.47–12.4)**	**.229**
	Not Pregnant	2501	2003–2016	98.6	30.9	7.98 (7.51–8.48)		9.11 (8.59–9.67)	
Arsenic (V) acid, urine (ug/L)	**Pregnant**	**260**	**2003–2016**	**3.7**	*	*	*	*	*
	Not Pregnant	2518	2003–2016	3.1	*	*	*	*	*
Arsenic (V) acid, urine (ug/g creatinine)	**Pregnant**	**260**	**2003–2016**	**3.7**	*	*	*	*	*
	Not Pregnant	2517	2003–2016	3.1	*	*	*	*	*
Arsenobetaine, urine (ug/L)	**Pregnant**	**260**	**2003–2016**	**58.8**	**17.2**	**1.68 (1.23–2.28)**	**.985**	**1.94 (1.45–2.59)**	**.869**
	Not Pregnant	2521	2003–2016	57.0	18.1	1.67 (1.52–1.84)		1.99 (1.79–2.22)	
Arsenobetaine, urine (ug/g creatinine)	**Pregnant**	**260**	**2003–2016**	**58.8**	**23.0**	**1.71 (1.22–2.40)**	**.703**	**1.94 (1.42–2.64)**	**.714**
	Not Pregnant	2520	2003–2016	57.0	15.8	1.84 (1.66–2.03)		2.06 (1.86–2.28)	
Arsenocholine, urine (ug/L)	**Pregnant**	**260**	**2003–2016**	**2.7**	*	*	*	*	*
	Not Pregnant	2521	2003–2016	6.6	*	*	*	*	*
Arsenocholine, urine (ug/g creatinine)	**Pregnant**	**260**	**2003–2016**	**2.7**	*	*	*	*	*
	Not Pregnant	2520	2003–2016	6.6	*	*	*	*	*
Arsenous (III) acid, urine (ug/L)	**Pregnant**	**260**	**2003–2016**	**13.9**	*	*	*	*	*
	Not Pregnant	2521	2003–2016	22.3	*	*	*	*	*
Arsenous (III) acid, urine (ug/g creatinine)	**Pregnant**	**260**	**2003–2016**	**13.9**	*	*	*	*	*

Analyte	Pregnancy Status	N	NHANES Years	% At/ Above LOD	P90	Geometric Mean (95% CI)	Pr > F	Geometric Mean (95% CI) Adjusted	Pr > F Adjusted
	Not Pregnant	2520	2003–2016	22.3	*	*	*	*	*
Dimethylarsinic acid, urine (ug/L)	**Pregnant**	**260**	**2003–2016**	**87.4**	**11.8**	**4.45 (3.8–5.21)**	**< .001**	**5.05 (4.29–5.95)**	**.005**
	Not Pregnant	2521	2003–2016	79.8	9.56	3.35 (3.19–3.52)		3.95 (3.73–4.19)	
Dimethylarsinic acid, urine (ug/g creatinine)	**Pregnant**	**260**	**2003–2016**	**87.4**	**11.3**	**4.55 (3.90–5.31)**	**.010**	**5.04 (4.35–5.84)**	**.008**
	Not Pregnant	2520	2003–2016	79.8	8.92	3.69 (3.55–3.84)		4.09 (3.92–4.26)	
Inorganic-related Arsenic Species, urine (ug/L)	**Pregnant**	**260**	2003–2016	**n/a**	**14.5**	**6.89 (6.10–7.79)**	**.001**	**7.52 (6.63–8.53)**	**.007**
	Not Pregnant	2518	2003–2016	**n/a**	12.6	5.63 (5.42–5.85)		6.30 (6.01–6.59)	
Inorganic-related Arsenic Species, urine (ug/g creatinine)	**Pregnant**	**260**	2003–2016	**n/a**	**16.3**	**7.05 (6.12–8.12)**	**.083**	**7.51 (6.56–8.59)**	**.047**
	Not Pregnant	**2517**	2003–2016	**n/a**	**14.8**	**6.20 (5.99–6.42)**		**6.51 (6.28–6.75)**	
Monomethylarsonic acid, urine (ug/L)	**Pregnant**	**260**	**2003–2016**	**26.5**	*	*	*	*	*
	Not Pregnant	2521	2003–2016	40.5	1.42	.649 (.627–672)		.660 (.630–.691)	
Monomethylarsonic acid, urine (ug/g creatinine	**Pregnant**	**260**	**2003–2016**	**26.5**	*	*	*	*	*
	Not Pregnant	2520	2003–2016	40.5	1.94	.715 (.685–.746)		.683 (.653–.715)	
Trimethylarsine Oxide, urine (ug/L)	**Pregnant**	**224**	**2003–2016**	**14.6**	*	*	*	*	*
	Not Pregnant	1855	2003–2016	26.9	*	*	*	*	*
Trimethylarsine Oxide, urine (ug/g creatinine)	**Pregnant**	**224**	**2003–2016**	**14.6**	*	*	*	*	*
	Not Pregnant	1855	2003–2016	26.9	*	*	*	*	*
Barium, urine (ug/L)	**Pregnant**	**402**	**1999–2016**	**98.1**	**7.35**	**2.01 (1.71–2.36)**	**< .001**	**1.90 (1.61–2.26)**	**< .001**
	Not Pregnant	3170	1999–2016	98.3	4.53	1.27 (1.21–1.34)		1.24 (1.18–1.30)	
Barium, urine (ug/g creatinine)	**Pregnant**	**402**	**1999–2016**	**98.1**	**7.43**	**2.00 (1.69–2.36)**	**< .001**	**1.86 (1.57–2.19)**	**< .001**
	Not Pregnant	3169	1999–2016	98.3	4.09	1.37 (1.31–1.44)		1.23 (1.17–1.29)	
Cadmium, blood (mg/L)	**Pregnant**	**1282**	**1999–2016**	**66.1**	**.602**	**.265 (.247–.284)**	**< .001**	**.332 (.314–.351)**	**.765**
	Not Pregnant	8778	1999–2016	75.9	1.07	.334 (.325–343)		.335 (.328–.343)	
Cadmium, urine (ug/L)	**Pregnant**	**403**	**1999–2016**	**83.4**	**.511**	**.151 (.130–.174)**	**.138**	**.188 (.162–.218)**	**.728**
	Not Pregnant	3169	1999–2016	83.8	.627	.169 (.159–.180)		.183 (.173–.193)	
Cadmium, urine (ug/g creatinine)	**Pregnant**	**403**	**1999–2016**	**83.4**	**.323**	**.150 (.135–.167)**	**< .001**	**.183 (.165–.203)**	**.857**
	Not Pregnant	3168	1999–2016	83.8	.495	.182 (.174–.191)		.181 (.174–.189)	

Analyte	Pregnancy Status	N	NHANES Years	% At/ Above LOD	P90	Geometric Mean (95% CI)	Pr > F	Geometric Mean (95% CI) Adjusted	Pr > F Adjusted
Cesium, urine (ug/L)	**Pregnant**	**408**	**1999–2016**	**99.8**	**10.2**	**4.79 (4.27–5.37)**	**.003**	**4.99 (4.45–5.60)**	**.009**
	Not Pregnant	3195	1999–2016	99.9	9.71	4.01 (3.84–4.20)		4.24 (4.06–4.42)	
Cesium, urine (ug/g creatinine)	**Pregnant**	**408**	**1999–2016**	**99.8**	**7.79**	**4.75 (4.44–5.07)**	**.007**	**4.84 (4.55–5.14)**	**< .001**
	Not Pregnant	3194	1999–2016	99.9	7.65	4.32 (4.23–4.42)		4.20 (4.11–4.30)	
Cobalt, urine (ug/L)	**Pregnant**	**408**	**1999–2016**	**99.4**	**1.77**	**.600 (.529–.681)**	**< .001**	**.647 (.569–.735)**	**< .001**
	Not Pregnant	3195	1999–2016	98.9	1.19	.407 (0.39–.424)		.451 (.433–0.47)	
Cobalt, urine (ug/g creatinine)	**Pregnant**	**408**	**1999–2016**	**99.4**	**1.52**	**.595 (.542–.654)**	**< .001**	**.627 (.573–.685)**	**< .001**
	Not Pregnant	3194	1999–2016	98.9	1.03	.438 (.425–.451)		.447 (.433–.461)	
Copper, Serum (ug/dL)	**Pregnant**	**52**	**2011–2016**	**100.0**	**270**	**198 (184–213)**	**< .001**	**191 (178–205)**	**< .001**
	Not Pregnant	971	2011–2016	100.0	179	128 (125–132)		127 (124–130)	
Iodine, urine (ug/L)	**Pregnant**	**413**	**2001–2016**	**100.0**	**360**	**137 (118–159)**	**.033**	**138 (119–160)**	**.127**
	Not Pregnant	3622	2001–2016	100.0	374	115 (110–121)		121 (116–127)	
Iodine, urine (ug/g creatinine)	**Pregnant**	**413**	**2001–2016**	**100.0**	**438**	**152 (134–172)**	**.019**	**154 (137–173)**	**.003**
	Not Pregnant	3621	2001–2016	100.0	328	131 (126–135)		127 (122–132)	
Lead, blood (ug/dL)	**Pregnant**	**1282**	**1999–2016**	**96.2**	**1.30**	**.624 (.576–.676)**	**< .001**	**.717 (.666–.771)**	**.007**
	Not Pregnant	8778	1999–2016	98.8	1.61	.781 (.762–.800)		.797 (.777–.818)	
Lead, urine (ug/L)	**Pregnant**	**408**	**1999–2016**	**94.9**	**1.27**	**.517 (.443–.604)**	**< .001**	**.600 (.518–.695)**	**< .001**
	Not Pregnant	3195	1999–2016	93.6	1.14	.357 (0.34–.376)		.400 (.380–.422)	
Lead, urine (ug/g creatinine)	**Pregnant**	**408**	**1999–2016**	**94.9**	**1.32**	**.512 (.452–.581)**	**< .001**	**.582 (.519–.651)**	**< .001**
	Not Pregnant	3194	1999–2016	93.6	.930	.385 (.372–.398)		.397 (.381–.413)	
Mercury (total), blood (ug/L)	**Pregnant**	**1280**	**1999–2016**	**86.4**	**2.2**	**.704 (.638–.776)**	**.007**	**.787 (.716–.866)**	**.048**
	Not Pregnant	8638	1999–2016	88.5	3.09	.804 (.769–0.84)		.863 (.829–.899)	
Mercury (inorganic), Blood (ug/L)	**Pregnant**	**98**	**2011–2016**	**31.1**	*	*	*	*	*
	Not Pregnant	1940	2011–2016	23.5	*	*	*	*	*
Mercury (ethyl), Blood (ug/L)	**Pregnant**	**98**	**2011–2016**	**1.0**	*	*	*	*	*
	Not Pregnant	1940	2011–2016	2.0	*	*	*	*	*
Mercury (methyl), Blood (ug/L)	**Pregnant**	**98**	**2011–2016**	**75.7**	**2.03**	**.365 (0.26–.511)**	**.310**	**.408 C.286–.582)**	**.226**
	Not Pregnant	1940	2011–2016	85.8	2.58	.440 C396–.489)		.510 (.473–.549)	

Analyte	Pregnancy Status	N	NHANES Years	% At/ Above LOD	P90	Geometric Mean (95% CI)	Pr > F	Geometric Mean (95% CI) Adjusted	Pr > F Adjusted
Mercury (inorganic), urine (ug/L)	**Pregnant**	**764**	**1999–2016**	**88.1**	**2.44**	**.491 (.414–.582)**	**.043**	**.534 (.450–.634)**	**.013**
	Not Pregnant	4557	1999–2016	86.4	2.08	.411 (.387–.437)		.425 (.402–.449)	
Mercury (inorganic), urine (ug/g creatinine)	**Pregnant**	**511**	**1999–2016**	**88.1**	**1.85**	**.459 (.380–.555)**	**.396**	**.485 (.402–.586)**	**.068**
	Not Pregnant	3583	1999–2016	86.4	1.72	.422 (.401–.445)		.403 (.384–.424)	
Molybdenum, urine (ug/L)	**Pregnant**	**405**	**1999–2016**	**100.0**	**125**	**49.3 (43.1–56.3)**	**< .001**	**50.3 (43.6–58.0)**	**.003**
	Not Pregnant	3176	1999–2016	100.0	104	36.1 (34.4–37.9)		39.8 (37.8–41.9)	
Molybdenum, urine (ug/g creatinine)	**Pregnant**	**405**	**1999–2016**	**100.0**	**95.6**	**49.0 (44.5–54.0)**	**< .001**	**49.0 (44.6–53.9)**	**< .001**
	Not Pregnant	3175	1999–2016	100.0	80.1	38.9 (37.8–40.0)		39.5 (38.2–40.8)	
Selenium, Serum (ug/L)	**Pregnant**	**52**	**2011–2016**	**100.0**	**135**	**114 (109–119)**	**< .001**	**113 (108–118)**	**< .001**
	Not Pregnant	970	2011–2016	100.0	146	124 (123–126)		123 (121–125)	
Thallium, urine (ug/L)	**Pregnant**	**408**	**1999–2016**	**99.6**	**.340**	**.168 (.152–.186)**	**.073**	**.176 (.159–.196)**	**.352**
	Not Pregnant	3189	1999–2016	99.6	.386	.153 (.147–0.16)		.167 (.161–.174)	
Thallium, urine (ug/g creatinine)	**Pregnant**	**408**	**1999–2016**	**99.6**	**.314**	**.167 (.157–.178)**	**.748**	**.171 (.161–.181)**	**.367**
	Not Pregnant	3188	1999–2016	99.6	.304	.165 (.161–.169)		.166 (.162–.171)	
Tungsten, urine (ug/L)	**Pregnant**	**405**	**1999–2016**	**83.2**	**.300**	**.087 (.075–.100)**	**.004**	**.088 (.076–.101)**	**.031**
	Not Pregnant	3179	1999–2016	82.0	.247	.070 (.066–.074)		.074 (.070–.079)	
Tungsten, urine (ug/g creatinine)	**Pregnant**	**405**	**1999–2016**	**83.2**	**.255**	**.086 (.076–.097)**	**.027**	**.085 (.076–.096)**	**.018**
	Not Pregnant	3178	1999–2016	82.0	.215	.075 (.072–.078)		.074 (.070–.077)	
Uranium, urine (ug/L)	**Pregnant**	**348**	**2001–2016**	**79.0**	**.030**	**.007 (.006–.008)**	**.118**	**.007 (.006–.009)**	**.244**
	Not Pregnant	2943	2001–2016	80.6	.020	.006 (.006–.006)		.007 (.006–.007)	
Uranium, urine (ug/g creatinine)	**Pregnant**	**348**	**2001–2016**	**79.0**	**.026**	**.007 (.006–.008)**	**.448**	**.007 (.006–.009)**	**.277**
	Not Pregnant	2942	2001–2016	80.6	.020	.006 (.006–.007)		.007 (.006–.007)	
Zinc, Serum (ug/dL)	**Pregnant**	**52**	**2011–2016**	**100.0**	**89.3**	**69.4 (66.1–72.8)**	**< .001**	**70.2 (66.8–73.8)**	**.001**
	Not Pregnant	971	2011–2016	100.0	95.4	76.8 (75.5–78.1)		76.6 (75.4–77.9)	

Abbreviations: LOD, limit of detection; GM, geometric mean; LCL & UCL, lower and upper confidence limits of geometric mean; P90, 90th percentile; Pr, probability.

(*) < 40% above LOD.

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Regression calculations are based on ln-transformed analytes. Adjusted least squares geometric means were adjusted for age, race/ethnicity, household poverty-to-income ratio, BMI, and serum ln-cotinine. For urinary analytes, both ratio creatine-adjusted and non-creatinine-adjusted estimates were calculated. Ratio adjustments were calculated as analyte concentration/creatinine concentration.

F-tests test for difference in least squares geometric means by pregnancy status, adjusted for all covariates in the model.

All analytical results were weighted and design-adjusted according to NHANES analytic guidelines.

Inorganic-related Arsenic Species is the sum of arsenic acid, arsenous acid, dimethylarsinic acid, and monomethylarsonic acid as reported in (41). Imputed values were used when observed values in the sum were below LOD.