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Exposure To Atmospheric Metals Using Moss Bio-Indicators And Neonatal Health Outcomes In Portland, Oregon

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ABSTRACT
***Background**:* Exposures to certain metals are associated with adverse birth outcomes, including inhibited fetal growth and congenital defects. Previous studies focused on metals such as lead and arsenic, and primarily assessed exposure using biological monitoring, which does not provide insights into sources. Examining exposure to metals via atmospheric pathways is challenging due to a lack of high-resolution air-pollution data. We applied a unique map of atmospheric metal pollution, derived from bio-indicator moss samples, as a screening tool to study neonatal health risks of atmospheric metal pollution in Portland, Oregon, a city of 640,000 people with several metal-emitting industrial sources.

Methods: We used previously collected data of metal concentrations measured in 346 moss samples in December 2013, to which an inverse-distance weighting scheme was applied to map ambient/environmental metal concentrations. Birth records for Portland live births (2008-2014) were obtained from the Oregon Health Authority. Exposure to atmospheric metals was assigned based on mother's residential address. Metal exposure was evaluated continuously and by quartile. Associations were evaluated for six metals previously identified as metalloestrogens toxic to plant and animal life (arsenic, cadmium, chromium, cobalt, nickel, lead) and two birth outcomes (preterm (<37 weeks), very preterm (<32 weeks)) using logistic regression models with adjustment for birth characteristics and demographic variables.

Results: Results indicate statistically significant associations between chromium exposure and preterm birth (OR=1.10, 95% CI: 1.02, 1.19) and very preterm birth (OR=1.10, 95% CI: 1.01, 1.19). Stratifying metal exposure by quartiles found some evidence of a dose-response effect for arsenic, cobalt and lead, but not for other metals. Stratified analysis by mother's race (white / non-white) finds that cadmium, chromium and lead are significant risk factors for very preterm birth among non-white women, but not among white women.

Conclusions: Results suggest that atmospheric metal exposure to chromium, measured via bio-indicator moss samples, is associated with an increased risk of preterm and very preterm birth. Exposure to cadmium, chromium and lead is a significant risk factor for very preterm birth among non-white women, indicating an effect due to race; this is an important result that requires further investigation. This novel exposure metric may be useful when bio-monitoring and more invasive/expensive exposure metrics are not feasible.

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CONTENTS

1. INTRODUCTION

Adverse birth outcomes are a significant public health concern. Preterm birth, defined as live birth prior to 37 completed weeks of gestation, is a leading cause of death in children under five years of age globally, is associated with lifelong disability, and is a significant financial burden to families and the healthcare system (Blencowe et al., 2012, Mwaniki, et al., 2012; Twilhaar, et al., 2017; Frey & Klebanoff, 2016).

Metal exposure is associated with several adverse birth outcomes, including inhibited fetal growth (Rahman, Kumarathasan, & Gomes, 2016), preterm birth, congenital defects (Jin et al., 2016) and impaired development later in life (Tian et al., 2009). Arsenic, cadmium, chromium, cobalt, nickel and lead are metals of particular concern because they are metalloestrogens, meaning they can mimic estrogen, bind to oestrogen receptors and thereby have an endocrine disrupting effect (Darbre 2006). Metalloestrogens are considered harmful and potentially linked to breast cancer (Wallace, 2015). Acute *in vivo* administration of metalloestrogens elicits estrogenic responses, including increased uterine weight, hyperplasia, hypertrophy of the endometrial lining, expression and density of progesterone receptors, and mammary tissue density; these endpoints were examined primarily with regard to breast cancer, and not neonatal outcomes (Wallace, 2015). Current literature focuses on cadmium as a representative metalloestrogen and primarily addresses breast cancer as the outcome of interest; other metallogrestrogen exposures and reproductive endpoints require further research. In addition to their estrogen-mimicking effects, arsenic, cadmium, chromium and lead may cause toxicity via production of reactive oxygen species and oxidative stress (Tchounwou, Yedjou, Patlolla, & Sutton, 2012).

Exposure to poor air quality is a major environmental threat to public health and is a known risk factor for adverse birth outcomes (Bobak, 2000; Friedrich, 2018; Ritz, Wilhelm, Hoggatt, & Ghosh, 2007; Slama et al., 2008; Šrám, Binková, Dejmek, & Bobak, 2005). Exposure to metals, specifically, can occur via several different pathways, however research on exposure to metals from atmospheric sources and neonatal health outcomes is limited. Several studies have found that exposure to metals in airborne particulate matter (PM) is associated with lower birth weight (for nickel, titanium, vanadium, silicon, aluminum, zinc, arsenic and cadmium) (Bell et al., 2010; Ebisu, Belanger, & Bell, 2014; Zhang et al., 2016), stillbirth due to inhibited fetal growth (for copper, iron, potassium and potassium ion, titanium, vanadium, and zinc) and stillbirth due to congenital malformation (for aluminum and silicon) (Ebisu, Malig, Hasheminassab, Sioutas, & Basu, 2018). Proximity to significant industrial or other defined point sources of atmospheric metal pollution is also associated with preterm birth and impaired fetal development (Y. Guo et al., 2010; Porter, Kent, Su, Beck, & Gohlke, 2014; Xu et al., 2012)

Previous studies examining the health impacts of metal exposure have predominantly used biological monitoring of urinary, blood and placental metal concentrations (Al-Saleh, Shinwari, Mashhour, & Rabah, 2014; Cheng, Zhang, Huo, et al., 2017; Govarts et al., 2016). While biomonitoring is a strong method for etiological investigation, it provides little indication of the source of exposure and is expensive/resource-intensive. Few studies have focused on atmospheric measurements of metals, which would advance understanding about the potential sources of metal exposures. This is likely due to a lack of high-resolution air-pollution data, as many major cities in the United States (U.S.) have only one permanent instrumental air-quality monitor (EPA AirData).

Bio-indicators (animal or plant species used to assess the quality of the environment and how it changes over time) are one low-cost complement to traditional instrumental monitoring (Holt & Miller, 2010). Moss have been used as bio-indicators of atmospheric metal concentrations for decades (Smodiš & Parr, 1999). Mosses lack roots, so they obtain all of their nutrients from precipitation and deposition of airborne particles. Therefore, metal concentrations solely reflect atmospheric sources (Smodiš & Parr, 1999). Several validation studies have shown that metal concentrations in moss tissue correlate well with instrumental measures of atmospheric metals, although the strength of relationship varies by element (Aboal, Fernández, Boquete, & Carballeira, 2010; Ares, Ángel Fernández, Ramón Aboal, & Carballeira, 2011; Fernández, Boquete, Carballeira, & Aboal, 2015; Gerdol, Marchesini, Iacumin, & Brancaleoni, 2014; Vuković et al., 2015).

Therefore, we conducted a study of metal exposure and adverse birth outcomes using a unique map of atmospheric metal pollution, derived from from bio-indicator moss samples (Donovan et al., 2016), as a screening tool to study the health risks of atmospheric pollution. Of the 22 elements measured in the Portland moss sample by Donovan, et al. in December 2013, six (arsenic, cadmium, chromium (except Cr(III)), cobalt, nickel and lead) were included for analysis in this study because they are considered generally toxic to plant and/or animal life (Gatziolis, Jovan, Donovan, & Amacher, 2016). Donovan, et al. (2016) found that moss concentrations of cadmium were highly correlated with contemporaneous instrumental readings of atmospheric concentrations; they did not examine correlations for other metals (Donovan et al., 2016).

2. METHODS

2.1 Population and Study Area

This retrospective cohort study was conducted in Multnomah County, which is located in northwest Oregon and includes Portland, a city with a population of 639,863 (U.S. Census Bureau 2016). Study subjects included all live births in in Multnomah County from 2008 to 2014 for whom state birth records were available (n=66,942). IRB approval for this study was obtained from the Yale University Human Subjects Committee and the Oregon Health Authority (OHA) (protocol ID number: 2000023085). The OHA Center for Health Statistics database provided birth-certificate data for live births occurring in Oregon from 2008 to 2014 under a data-use agreement.

2.2 Exposure Assessment

Maternal exposure to metals was assigned using continuous surface maps of metals and geocoded maternal residential address at the time of delivery (provided by the State of Oregon). Maps of atmospheric metal concentrations were obtained from the U.S. Forest Service, Pacific Northwest Research Station using research performed by Donovan et al., 2016. Donovan, et al. collected and measured metal concentrations in 346 moss samples in December 2013. An inverse-distance weighting scheme, in which estimated values at a point are a function of the inverse distance to a point with an actual measurement, was applied to metals data to produce continuous surface maps. A complete description of the methodology involved in collecting samples and modeling exposures has previously been published in (Donovan et al., 2016). Of the 66,942 subjects, 483 maternal residential addresses could not be matched to a metal value and therefore were excluded from further analysis. For ease of interpretation and to allow for comparison of values within an exposure, we standardized all distance-weighted variables by subtracting the mean and dividing by the standard deviation. Exposure variables were analyzed as continuous and categorical (quartiles of exposure) variables.

2.3 Outcome Assessment

Analysis was restricted to singleton births in Multnomah County for which birth weight was greater than 250g (n=10 excluded) and gestational age was between 20 and 44 weeks (n=5 excluded). Under these criteria and after excluding individuals lacking metal values, 63,986 births qualified for inclusion. We considered preterm birth (gestational age less than 37 weeks) and very preterm birth (gestational age less than 32 weeks).

2.4 Covariates

Birth records from the OHA also provided information on maternal demographic and health characteristics. An *a priori* set of covariates previously and consistently associated with fetal growth parameters in the literature (Claus Henn et al., 2016) were considered for inclusion in this study: maternal age (years, continuous) at child's birth, infant sex, mother race/ethnicity (categorical), primiparity (yes/no), and maternal smoking during pregnancy (yes/no). Race/ethnicity was categorized based on which race/ethnicity self-identification patterns were most common in the population. Race was categorized as non-Hispanic white, Hispanic white, Black (individuals who selected only Black or Black and any other combination of races), Asian (individuals who selected only Asian or Asian and white), other and non-report.

Additional maternal characteristics considered as potential confounders were: mother's pre-pregnancy body mass index (BMI; kg/m^2; categorized into underweight, normal, overweight, and obese), education level (less than high school, high school graduate, some college, bachelor's degree or greater), use of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) benefits (yes/no), use of alcohol during pregnancy (ever/never), payment method for delivery (private, public, self, other), prenatal care (none/one or more visits), previous preterm birth (yes/no), and baby's sex.

2.5 Statistical Analysis

Associations were tested in separate logistic regression models for six metals (arsenic, cadmium, chromium, cobalt, nickel and lead) as both continuous and categorical (quartiles) variables and two birth outcomes (preterm birth, very preterm birth). All models included the *a priori* set of covariates previously identified in the literature (see section 2.4). For additional covariates, two criteria were applied to assess whether covariates were confounders in this data: a) covariate associations with metal exposure and birth outcomes in bivariate models ($\alpha = 0.1$), and b) change in metal exposure effect estimates (> 10%). By these criteria, all final preterm and very preterm multivariable models were adjusted for mother's age, race, tobacco use, education, BMI, baby sex, primiparity, payment method, no prenatal care, and previous preterm birth. Models were performed using both standardized (for metals exposure values and outcomes) and unstandardized data; no changes in significance in the results were observed, therefore standardized values are reported.

Mother's pre-pregnancy BMI met the criteria for inclusion as a confounder, but was unknown for n=1,117 mothers. Due to the substantial proportion missing, Chi-square tests were performed to compare demographic characteristics of individuals with and without BMI data and models were run in two ways: (1) individuals with missing BMI data excluded (complete BMI cases only) and (2) missing BMI data coded as a separate category in the multilevel BMI variable. Results from method (1) are presented as the primary analysis and results from method (2) are in the appendix.

We also conducted several sub-analyses. Because exposure to multiple metals may occur concurrently, we tried running the models with all metals included simultaneously as independent variables (results presented in appendix). Additionally, stratified analysis was performed to examine differences in associations by race (white vs. non-white). All statistical analysis was performed in the SAS statistical software package (SAS Institute, Inc., Cary, North Carolina) and p-values < 0.05 were considered statistically significant.

3. RESULTS

Chi-square tests comparing demographic characteristics of individuals with and without BMI data revealed some differences (Table A, appendix). The group missing BMI data was significantly different in terms of mother's age, race, education, method of payment, primiparity, and number of prenatal care visits (Table A, appendix). However, models were run (1) excluding the subjects with missing data, and (2) with missing BMI data coded as a separate category, and checked for changes in associations greater than 10% between the outputs of (1) and (2). The odds ratios for the association between arsenic and very preterm birth and lead and very preterm birth did change by greater than 10%, however remained not significantly associated with the outcome regardless of how the missing BMI data were treated. Therefore, based on the recommendations of (Groenwold et al., 2012), individuals with missing BMI data (n=1,117) were excluded from all further analysis (final sample size n=62,869).

After all applied exclusions, a total sample size of 62,869 was included for analysis. Maternal sociodemographic and birth characteristics for the sample (excluding individuals with missing BMI data) are summarized in Table 1. The majority of mothers were non-Hispanic white, did not use WIC benefits, did not use alcohol or tobacco, paid for delivery privately, had previously given birth, had prenatal care, did not have pre pregnancy or gestational diabetes or hypertension or previous preterm birth.

Unadjusted and adjusted associations between the birth outcomes and individual metals are presented in Table 2. Exposure to chromium significantly increased the odds of very preterm birth in both unadjusted (OR=1.103, 95% CI: 1.019, 1.194) and adjusted (OR=1.097, 95% CI: 1.013, 1.189) models. No other metals were significantly associated with odds of preterm or very preterm birth in these models. Examining metals by quartiles of exposure (Table 3), a significant association between cobalt and very preterm birth emerges in the highest quartile of exposure (relative to the lowest quartile) (adjusted model; OR=1.344, 95% CI: 1.038, 1.741). The association between lead and preterm birth is significant in the second quartile relative to the first (OR=1.100, 95% CI: 1.100, 1.209); however the third and fourth quartiles do not have significantly higher odds of preterm birth relative to the first quartile of lead exposure. No other metals display differences in odds relative to the lowest quartile of exposure for preterm and very preterm birth (Table 3).

When associations were stratified by race (white versus non-white), cadmium, chromium, and lead were all significant risk factors for very preterm birth in both unadjusted and adjusted models among non-white mothers, but not among white mothers (Table 4). Cadmium exposure was associated with 1.149 greater odds of very preterm birth (adjusted model; 95% CI: 1.023, 1.291), chromium was associated with 1.182 greater odds of very preterm birth (adjusted model; 95% CI: 1.065, 1.313), and lead was associated with 1.223 greater odds of very preterm birth (adjusted model; 95% CI: 1.086, 1.378) among non-white mothers (Table 4). Among white mothers, in unadjusted models lead displayed a protective effective for preterm birth (OR=0.940, 95% CI: 0.899, 0.984), which attenuated and was not significant in the adjusted model (Table 4).

4. DISCUSSION

These results suggest that chromium may be a risk factor for very preterm birth in the overall population. No significant dose-response trend is observed for chromium. High levels of cobalt exposure (fourth quartile relative to first quartile) appear to be significant risk factors for very preterm birth. Results for lead are inconclusive, as overall exposure does not appear to be a significant risk factor, while association by quartile is not consistent with the trend for a dose-response effect. Other metals- arsenic, cadmium, and nickel- do not appear to be risk factors for preterm and very preterm birth in the full sample. Race appears to be a significant effect modifier in these data, since cadmium, chromium and lead are significant risk factors for very preterm birth among non-white mothers, but not among white mothers.

4.1 Arsenic (As)

Previous research on the association between arsenic and birth outcomes is inconclusive (Zheng et al., 2016). A number of studies have found that arsenic exposure is associated with reduced birth weight (Claus Henn et al., 2016; Govarts et al., 2016), impaired fetal growth (Claus Henn et al., 2016; Rahman, Kumarathasan, & Gomes, 2016), reduced length of gestation (Claus Henn et al., 2016), neonatal death (Rahman et al., 2016) and increased risk of congenital heart defects (Jin et al., 2016). However, others have found no associations between arsenic levels and fetal birth weight (Sabra, Malmqvist, Saborit, Gratacós, & Gomez Roig, 2017; Shirai, Suzuki, Yoshinaga, & Mizumoto, 2010) or small for gestational age (SGA) (Thomas et al., 2015). Our results do not find associations between arsenic exposure and preterm birth.

4.2 Cadmium (Cd)

Cadmium is the most extensively studied of the metalloestrogens (Wallace, 2015). Estrogen-dependent tissues are highly sensitive to cadmium in females, and cadmium exposure can induce changes that lead to the overdevelopment of breast tissues, and potentially the development of breast cancers (Wallace, 2015). Prenatal exposure to cadmium is associated with preterm birth (Yang et al., 2016), decreased birth weight (Al-Saleh et al., 2014; Cheng, Zhang, Zheng, et al., 2017; Rahman et al., 2016; Sabra et al., 2017; Shirai et al., 2010; Vidal et al., 2015), and increased incidence of SGA (Al-Saleh et al., 2014; Cheng, Zhang, Zheng, et al., 2017; Rahman et al., 2016; Sabra et al., 2017), as well as other developmental outcomes later in life, including lower IQ scores (Tian et al., 2009). Not all studies have found a significant association between maternal cadmium concentrations and birth outcomes, including for birth length, head circumference, birth weight (J. Guo et al., 2017; Yang et al., 2016), and SGA (Thomas et al., 2015; Yang et al., 2016). (Bloom et al., 2015) found that women exposed to cadmium delivered heavier babies than those with less exposure. A small pilot study in China found no significant associations between any metals examined (lead, thallium, cadmium, selenium, arsenic, nickel, vanadium, cobalt, and mercury) and birth weight (Hu et al., 2016). Our results do not find significant associations between cadmium and preterm birth in the general population. However, when stratified by race, non-white mothers did have increased odds of very preterm birth with cadmium exposure, while white mothers did not.

The effects of cadmium may depend on a range of other factors. Several studies have found sex-specific effects, including significant associations between cadmium and birth size in female infants, but no such associations for male infants (Cheng, Zhang, Zheng, et al., 2017; Kippler et al., 2012; Röllin, Kootbodien, Channa, & Odland, 2015; Taylor, Golding, & Emond, 2016). Timing of exposure may be critical, as maternal cadmium exposure during earlier periods of pregnancy appears to have a larger impact on delayed fetal growth (Cheng, Zhang, Zheng, et al., 2017). Unfortunately, in this study we cannot assess timing of exposure during the pregnancy, due to limitations of the exposure metric. Other health behaviors may mediate the cadmium and birth outcomes relationship. Smoking is itself a major source of cadmium exposure and some studies have found a significant negative correlation between maternal blood cadmium and birth weight among mothers who smoke, but no such correlation among non-smoking mothers (Menai et al., 2012).

4.3 Chromium (Cr)

Hexavalent chromium (Cr(VI)) is a well-known endocrine disrupter (Remy, Byers, & Clay, 2017). A study of reproductive outcomes in an area heavily polluted by toxic Cr(VI) from industrial sources found those infants had significantly higher rates of preterm birth, low birth weight, SGA, macrosomia (large for gestational age), perinatal jaundice, and conditions affecting the nervous/sense system when compared to infants from a less polluted area (Remy et al., 2017). Other research on the reproductive and neonatal health effects of chromium has been limited. Our results support previous findings that exposure to chromium is associated with increased odds of preterm birth, although we only observed this association using the more stringent very preterm (less than 32 week) definition and do not observe a dose-response effect when examining chromium exposure by quartile. In addition, when stratified by race, non-white mothers have increased odds of very preterm birth with cadmium exposure, while white mothers do not.

4.4 Cobalt (Co)

Cobalt is a biologically necessary constituent of vitamin B12; however, excessive exposure is associated with neurological, cardiovascular and endocrine dysfunction (Leyssens, Vinck, Van Der Straeten, Wuyts, & Maes, 2017). Few studies, to our knowledge, have examined the association between neonatal cobalt exposure and birth outcomes. One study that examined cobalt exposure, among other metals, did not find significant associations with birth weight or gestational age (Bloom et al., 2015). Although we did not observe significant associations between cobalt and preterm birth in the overall model, after stratifying by quartile of cobalt exposure, it appears that the highest level of cobalt exposure does increase the odds of very preterm birth.

4.5 Lead (Pb)

In vivo measurements of prenatal lead exposure have found significant associations with preterm birth (Cheng, Zhang, Huo, et al., 2017), impaired fetal growth (Rahman et al., 2016), decreased birth weight (Xie et al., 2013; Xu et al., 2012) and neonatal death (Rahman et al., 2016). Other studies contradict these results and have found that lead is not significantly associated with SGA (Al-Saleh et al., 2014; Thomas et al., 2015) and birth weight (Shirai et al., 2010). Our results are inconsistent for lead, as a significant increase in odds of preterm birth are observed in the second quartile of lead exposure, but not the third or fourth. In addition, stratified analysis suggests that lead is a risk factor for preterm and very preterm birth among non-white women. However, in unadjusted models among white women, lead appears to have a protective effect. After adjusting for other relevant covariates, this protective effect is attenuated and no longer significant, suggesting the presence of negative confounding in the data.

4.6 Nickel (Ni)

Previous research suggests that the developing fetus is particularly vulnerable to nickel. Nickel can easily cross the placenta and concentrate in fetal organs and tissues (Hou et al., 2011). Studies in rats found that lack of efficient clearance by fetal kidneys and the fetus' confined environment lead to accumulation of nickel in fetal blood, heart, liver, and brain (Hou et al., 2011). Studies examining nickel and birth outcomes have had mixed results (Zheng et al., 2016). Exposure to nickel decreased rat fertility and increased mortality of pups (Käkelä, Käkelä, & Hyvärinen, 1999). Epidemiologic evidence from China suggests that maternal urinary nickel is associated with increased odds of preterm delivery in a dose-response relationship (Chen et al., 2018) and prenatal exposure to informal e-waste recycling (including elevated nickel, lead, cadmium, chromium, arsenic, and cobalt) is related to higher rates of adverse birth outcomes (Xu et al., 2012). A case-control study of nickel exposed refinery workers found no statistical association between maternal exposure in early pregnancy and the risk of self-reported spontaneous abortion (Vaktskjold, Talykova, Chashchin, Odland, & Nieboer, 2008). A separate study performed in a similar occupationally exposed population found no association with malformations of genital organs in offspring (Vaktskjold et al., 2006). Maternal nickel exposure has also been found to not be associated with increased risk of an SGA birth (Vaktskjold, Talykova, Chashchin, Odland, & Nieboer, 2007). In our data, no significant associations between nickel and preterm birth were observed.

4.7 Strengths and Limitations

Although moss have been used as bio-indicators of atmospheric metal concentrations for decades (Smodiš & Parr, 1999), this is the first study, to our knowledge, that uses moss bio-indicators as an exposure metric for health outcomes in an epidemiologic context. Further research is needed to validate the relevance of moss bioindicators as a health-exposure metric.

Using registry-based data for demographic, health and outcome information also has some limitations. Although the OHA Center for Health Statistics collects information on a large number of mother demographic, mother health, and birth outcome variables, mis-coding and missing/unknown values are a persistent problem. In our study, the BMI variable had a significant number of missing values due to missing/unknown mother height and weight data in the set provided by OHA. Based on our analysis, women missing BMI data did appear to be significantly different from women not missing data on a number of characteristics. Future work should address missing data using multiple imputation rather than excluding incomplete cases. In addition, we were limited by the variables provided by OHA in our ability to adjust for possible confounding; it is possible that there is residual confounding that we have not accounted for in this study.

Due to the timing of exposure data collection relative to health outcomes, exposure misclassification is possible. Moss samples were collected in December 2013 and birth records from 2008 through 2014 were used. Additional research is needed to ascertain the relevant time window of exposure that a single moss measurement can represent. Furthermore, a single moss measurement relative to maternal residential address cannot account for movement of people or the other ways in which women may experience exposure to atmospheric pollution. Previous research has found air pollution exposure can be underestimated when ignoring occupational mobility and commuting mode of pregnant women (Blanchard, Deguen, Kihal-Talantikite, François, & Zmirou-Navier, 2018); our exposure metric is limited due to lack of information on the mobility of pregnant women and their non-residential exposures.

5. CONCLUSIONS

Moss samples appear to be a useful preliminary screening tool for studying neonatal health risks of atmospheric metal pollution. We found that chromium exposure is a risk factor preterm birth and very preterm birth. Mother's race may be an important effect modifier in these data, since significant associations between cadmium, chromium and lead and very preterm birth emerged only among non-white women. This is particularly important since the majority of the study population was white, suggesting that different demographic groups may be at higher risk, and these associations may be masked in the general birth cohort. Further research is needed to clarify the associations (and lack thereof) observed in these data. Specifically, future research should focus on improving the temporal relationship between exposure data and pregnancy and quantifying the relevant exposure window when using moss samples.

6. TABLES

Table 1. Baseline Characteristics of the Study Cohort^ (n=62,869)

Characteristic	Number (Column Percent)*
Mother Age (years)	
<20	3608 (5.74)
20-24	10933 (17.39)
25-29	15949 (25.37)
30-34	18815 (29.93)
>=35	13562 (21.57)
Unknown	2 (0.00)
Mother Race	
Non-Hispanic white Only	39578 (62.95)
Hispanic white	8664 (13.78)
Black + Multi-race Black	5355 (8.52)
Asian + white-Asian	5115 (8.14)
Other	3988 (6.34)
Unknown	169 (0.27)
Mother Education	
Less than high school	10369 (16.49)
High school	11549 (18.37)
Some College	16816 (26.75)
Bachelor's degree or above	23791 (37.84)
Unknown	344 (0.55)
Mother BMI Category	
Underweight	2192 (3.49)
Normal Weight	33477 (53.25)
Overweight	14814 (23.56)
Obese	12386 (19.70)
Mother Using WIC benefits	
Yes	23059 (36.68)
No	38766 (61.66)
Unknown	1044 (1.66)
Mother Used Alcohol	
Yes	643 (1.02)
No	54695 (87.00)
Unknown	7531 (11.98)
Payment Method for Delivery	

Private	35846 (57.02)
Public	24653 (39.21)
Self	1377 (2.19)
Other	826 (1.31)
Unknown	167 (0.27)
Birth Order	
First Baby	28833 (45.86)
Not First Baby	34036 (54.14)
Number of PNC Visits	
No prenatal care	455 (0.72)
Had prenatal care	62412 (99.27)
Unknown	2 (0.00)
Mother Used Tobacco	
Yes	5528 (8.79)
No	57117 (90.85)
Unknown	224 (0.36)
Pre pregnancy diabetes	
Yes	489 (0.78)
No	62380 (99.22)
Pre pregnancy Hypertension	
Yes	908 (1.44)
No	61961 (98.56)
Gestational Diabetes	
Yes	3991 (6.35)
No	58878 (93.65)
Gestational Hypertension	
Yes	2953 (4.70)
No	59916 (95.30)
Previous preterm birth	
Yes	1786 (2.84)
No	61083 (97.16)
Baby's Sex	
Female	30710 (48.85)
Male	32159 (51.15)

^ Complete BMI Data Cases Only- EXCLUDING individuals with BMI data missing

*Percentages may not sum to 100 due to rounding

Table 2. Unadjusted and Adjusted Associations Between Preterm Birth and Individual Metals^

	Preterm (<37 weeks) (n=3667 preterm; 62869 total)		Very Preterm (<32 weeks) (n=508 very preterm; 62869 total)	
	OR (95% CI) Unadjusted Association	OR (95% CI) Adjusted Association*	OR (95% CI) Unadjusted Association	OR (95% CI) Adjusted Association*
Arsenic	1.022 (0.989, 1.056)	1.006 (0.973, 1.041)	0.987 (0.904, 1.077)	0.962 (0.879, 1.052)
Cadmium	0.988 (0.955, 1.022)	1.018 (0.984, 1.054)	1.032 (0.951, 1.120)	1.069 (0.985, 1.160)
Chromium	1.011 (0.978, 1.045)	1.010 (0.977, 1.045)	**1.103 (1.019, 1.194)**	**1.097 (1.013, 1.189)**
Cobalt	1.024 (0.992, 1.058)	1.005 (0.972, 1.040)	1.084 (1.000, 1.174)	1.059 (0.974, 1.151)
Lead	0.972 (0.939, 1.005)	1.007 (0.971, 1.044)	1.034 (0.949, 1.127)	1.078 (0.986, 1.179)
Nickel	0.970 (0.937, 1.005)	0.987 (0.953, 1.023)	0.985 (0.900, 1.077)	1.002 (0.915, 1.097)

^ Complete BMI Data Cases Only- EXCLUDING individuals with BMI data missing
Bold indicates significant at the p=0.05 level (odds ratio does not contain the null value 1.000).

*Table 3. Adjusted Associations Between Preterm Birth and Metal Quartiles^*

		Preterm (<37 weeks) (OR (95% CI))	Very Preterm (<32 weeks) (OR (95% CI))
Arsenic	Quartile 2 (25%-50%)	1.094 (0.994, 1.203)	1.026 (0.798, 1.318)
	Quartile 3 (50%-75%)	1.032 (0.933, 1.142)	1.140 (0.882, 1.473)
	Quartile 4 (75%-100%)	1.067 (0.969, 1.176)	0.987 (0.765, 1.274)
Cadmium	Quartile 2	1.037 (0.943, 1.140)	0.965 (0.754, 1.234)
	Quartile 3	1.015 (0.921, 1.117)	0.956 (0.744, 1.229)
	Quartile 4	1.032 (0.935, 1.139)	1.089 (0.848, 1.398)
Chromium	Quartile 2	0.944 (0.857, 1.039)	1.151 (0.890, 1.488)
	Quartile 3	0.970 (0.882, 1.068)	1.241 (0.964, 1.599)
	Quartile 4	1.019 (0.926, 1.121)	1.244 (0.964, 1.605)
Cobalt	Quartile 2	1.001 (0.908, 1.103)	1.212 (0.928, 1.583)
	Quartile 3	0.982 (0.890, 1.083)	1.277 (0.980, 1.664)
	Quartile 4	1.031 (0.937, 1.136)	**1.344 (1.038, 1.741)**
Lead	Quartile 2	**1.100 (1.002, 1.209)**	1.073 (0.838, 1.375)
	Quartile 3	0.933 (0.842, 1.034)	1.011 (0.773, 1.321)
	Quartile 4	1.077 (0.974, 1.192)	1.237 (0.953, 1.604)
Nickel	Quartile 2	1.014 (0.922, 1.116)	0.960 (0.742, 1.242)
	Quartile 3	0.974 (0.883, 1.073)	1.096 (0.852, 1.409)
	Quartile 4	0.964 (0.874, 1.064)	1.120 (0.868, 1.444)

^ Complete BMI Data Cases Only- EXCLUDING individuals with BMI data missing
Bold indicates significant at the p=0.05 level (odds ratio does not contain the null value 1.000).

*Table 4. Stratified Analysis by Race (white / Non-white)^*

	White				**Non-White**			
	Preterm (<37 weeks) (n=2049 preterm; 39578 total)		Very Preterm (<32 weeks) (n=267 very preterm)		Preterm (<37 weeks) (n=1617 preterm; 23291 total)		Very Preterm (<32 weeks) (n=241 very preterm)	
	OR Unadjusted	OR Adjusted	OR Unadjusted	OR Adjusted	OR Unadjusted	OR Adjusted	OR Unadjusted	OR Adjusted
Arsenic	1.011 (0.968, 1.056)	1.000 (0.956, 1.045)	0.972 (0.862, 1.096)	0.948 (0.839, 1.072)	1.027 (0.976, 1.082)	1.017 (0.965, 1.072)	0.991 (0.869, 1.131)	0.978 (0.856, 1.117)
Cadmium	0.995 (0.954, 1.038)	1.025 (0.982, 1.069)	0.987 (0.879, 1.108)	1.018 (0.908, 1.143)	1.006 (0.950, 1.065)	1.017 (0.960, 1.078)	**1.133 (1.008, 1.273)**	**1.149 (1.023, 1.291)**
Chromium	0.993 (0.949, 1.040)	1.002 (0.957, 1.050)	1.004 (0.888, 1.135)	1.011 (0.894, 1.144)	1.027 (0.979, 1.077)	1.027 (0.978, 1.078)	**1.188 (1.070, 1.318)**	**1.182 (1.065, 1.313)**
Cobalt	1.026 (0.983, 1.070)	1.004 (0.960, 1.050)	1.063 (0.952, 1.187)	1.031 (0.918, 1.158)	1.010 (0.959, 1.063)	1.005 (0.953, 1.060)	1.094 (0.971, 1.232)	1.090 (0.964, 1.232)
Lead	**0.940 (0.899, 0.984)**	0.982 (0.935, 1.032)	0.912 (0.804, 1.033)	0.955 (0.835, 1.093)	1.037 (0.987, 1.091)	**1.056 (1.002, 1.112)**	**1.204 (1.073, 1.352)**	**1.223 (1.086, 1.378)**
Nickel	0.976 (0.935, 1.018)	0.982 (0.940, 1.025)	0.984 (0.877, 1.103)	0.988 (0.880, 1.109)	0.990 (0.932, 1.052)	0.998 (0.938, 1.061)	1.025 (0.888, 1.185)	1.030 (0.889, 1.193)

^ Complete BMI Data Cases Only- EXCLUDING individuals with BMI data missing
Bold indicates significant at the p=0.05 level (odds ratio does not contain the null value 1.000).

7. APPENDIX

Supplemental Table A: Descriptive statistics of the sample comparing population with complete vs. missing BMI data

	BMI Data Complete (n=62869)	BMI Data Missing* (n=1117)	P value (Chi-Square)
	# (Column %)	# (Column %)	
Mother Age (years)			
<20	3608 (5.74)	65 (5.82)	0.0003
20-24	10933 (17.39)	204 (18.26)	
25-29	15949 (25.37)	304 (27.22)	
30-34	18815 (29.93)	304 (26.68)	
>=35	13562 (21.57)	245 (21.93)	
Unknown	2 (0.00)	1 (0.09)	
Mother Race			
Non-Hispanic white Only	39578 (62.95)	557 (49.87)	<.0001
Hispanic white	8664 (13.78)	210 (18.80)	
Black + Multi-race Black	5355 (8.52)	152 (13.61)	
Asian + white-Asian	5115 (8.14)	85 (7.61)	
Other	3988 (6.34)	99 (8.86)	
Unknown	169 (0.27)	14 (1.25)	
Mother Education			
Less than high school	10369 (16.49)	316 (28.29)	<.0001
High school	11549 (18.37)	227 (20.32)	
Some College	16816 (26.75)	259 (23.19)	
Bachelor's degree or above	23791 (37.84)	273 (24.44)	
Unknown	344 (0.55)	42 (3.76)	
Mother Using WIC benefits			
Yes	23059 (36.68)	428 (38.32)	<.0001
No	38766 (61.66)	560 (50.13)	
Unknown	1044 (1.66)	129 (11.55)	
Mother Used Alcohol			
Yes	643 (1.02)	13 (1.16)	<.0001
No	54695 (87.00)	911 (81.56)	
Unknown	7531 (11.98)	193 (17.28)	

Payment Method for Delivery			
Private	35846 (57.02)	430 (38.50)	<.0001
Public	24653 (39.21)	569 (50.94)	
Self	1377 (2.19)	91 (8.15)	
Other	826 (1.31)	14 (1.25)	
Unknown	167 (0.27)	13 (1.16)	
Birth Order			
First Baby	28833 (45.86)	376 (33.66)	<.0001
Not First Baby	34036 (54.14)	741 (66.34)	
Number of PNC Visits			
No prenatal care	455 (0.72)	88 (7.88)	<.0001
Had prenatal care	62412 (99.27)	1029 (92.12)	
Unknown	2 (0.00)	0 (0.00)	
Mother Used Tobacco			
Yes	5528 (8.79)	96 (8.59)	<.0001
No	57117 (90.85)	969 (86.75)	
Unknown	224 (0.36)	52 (4.66)	
Pre pregnancy diabetes			
Yes	489 (0.78)	7 (0.63)	0.5681
No	62380 (99.22)	1110 (99.37)	
Pre pregnancy Hypertension			
Yes	908 (1.44)	16 (1.43)	0.9737
No	61961 (98.56)	1101 (98.57)	
Gestational Diabetes			
Yes	3991 (6.35)	98 (8.77)	0.0010
No	58878 (93.65)	1019 (91.23)	
Gestational Hypertension			
Yes	2953 (4.70)	56 (5.01)	0.6205
No	59916 (95.30)	1061 (94.99)	
Previous pre term birth			
Yes	1786 (2.84)	43 (3.85)	0.0449
No	61083 (97.16)	1074 (96.15)	
Baby's Sex			
Female	30710 (48.85)	547 (48.97)	0.9351
Male	32159 (51.15)	570 (51.03)	

*BMI was calculated from information reported on the birth record about mother height and weight. BMI data was missing for 1117 women due to missing height and weight data points.

Supplemental Table B. Unadjusted and Adjusted Associations Between Individual Metals and Preterm Birth (Including individuals with BMI data missing)

	Preterm (<37 weeks)		Very Preterm	
	OR (95% CI) Unadjusted Association	OR (95% CI) Adjusted Association*	OR (95% CI) Unadjusted Association	OR (95% CI) Adjusted Association*
Arsenic	1.022 (0.989, 1.056)	1.006 (0.972, 1.040)	0.976 (0.896, 1.064) #	0.950 (0.870, 1.038) #
Cadmium	0.985 (0.952, 1.018)	1.016 (0.982, 1.051)	1.032 (0.952, 1.117)	1.070 (0.988, 1.158)
Chromium	1.007 (0.975, 1.040)	1.006 (0.973, 1.040)	**1.091 (1.009, 1.179)**	**1.084 (1.002, 1.173)**
Cobalt	1.022 (0.990, 1.055)	1.003 (0.969, 1.037)	1.078 (0.997, 1.165)	1.052 (0.970, 1.142)
Lead	0.968 (0.937, 1.001)	1.002 (0.967, 1.038)	1.020 (0.938, 1.110) #	1.058 (0.969, 1.155) #
Nickel	0.969 (0.937, 1.003)	0.985 (0.951, 1.020)	0.981 (0.899, 1.071)	0.995 (0.909, 1.088)

#: Indicates change by greater than or equal to 10% (greater or equal to +/- 0.1 in the OR) compared to the OR for excluding missing BMI data

Bold indicates significant at the p=0.05 level (odds ratio does not contain the null value 1.000).

Supplemental Table C. Adjusted Associations Between Preterm Birth and Metal Quartiles (Including individuals with BMI data missing)

		Preterm (<37 weeks) (OR (95% CI))	Very Preterm (<32 weeks) (OR (95% CI))
Arsenic	Quartile 2 (25%-50%)	**1.102 (1.003, 1.211)**	1.059 (0.831, 1.349)
	Quartile 3 (50%-75%)	1.037 (0.939, 1.146)	1.144 (0.892, 1.467)
	Quartile 4 (75%-100%)	1.065 (0.967, 1.172)	0.946 (0.737, 1.215)
Cadmium	Quartile 2	1.050 (0.956, 1.152)	0.992 (0.782, 1.259)
	Quartile 3	1.028 (0.935, 1.131)	0.980 (0.766, 1.252)
	Quartile 4	1.035 (0.939, 1.141)	1.083 (0.848, 1.384)
Chromium	Quartile 2	0.950 (0.864, 1.045)	1.151 (0.897, 1.476)
	Quartile 3	0.982 (0.894, 1.078)	1.268 (0.993, 1.619)
	Quartile 4	1.017 (0.925, 1.117)	1.191 (0.928, 1.528)
Cobalt	Quartile 2	1.000 (0.908, 1.101)	1.195 (0.922, 1.549)
	Quartile 3	0.998 (0.907, 1.099)	**1.293 (1.001, 1.671)**
	Quartile 4	1.030 (0.937, 1.133)	**1.329 (1.034, 1.708)**
Lead	Quartile 2	1.084 (0.988, 1.189)	1.060 (0.834, 1.346)
	Quartile 3	0.926 (0.838, 1.024)	0.972 (0.749, 1.262)
	Quartile 4	1.059 (0.958, 1.170)	1.178 (0.914, 1.518)
Nickel	Quartile 2	0.999 (0.909, 1.098)	0.932 (0.725, 1.197)
	Quartile 3	0.953 (0.865, 1.048)	1.052 (0.824, 1.345)
	Quartile 4	0.954 (0.865, 1.051)	1.097 (0.857, 1.403)

*Odds ratios are relative to quartile 1

Bold indicates significant at the p=0.05 level (odds ratio does not contain the null value 1.000).

Supplemental Table D. Unadjusted and Adjusted Associations Between Preterm Birth and Individual Metals in Same Model (Including individuals with BMI data missing)

	Preterm (<37 weeks)		Very Preterm (<32 weeks)	
	OR (95% CI) Unadjusted Association	OR (95% CI) Adjusted Association*	OR (95% CI) Unadjusted Association	OR (95% CI) Adjusted Association*
Arsenic	1.033 (0.996, 1.070)	1.008 (0.971, 1.045)	0.959 (0.871, 1.055)	0.926 (0.841, 1.019)
Cadmium	0.981 (0.944, 1.020)	1.014 (0.975, 1.054)	1.022 (0.926, 1.127)	1.070 (0.971, 1.179)
Chromium	1.026 (0.973, 1.083)	1.009 (0.955, 1.065)	1.091 (0.957, 1.244)	1.072 (0.941, 1.222)
Cobalt	1.031 (0.982, 1.083)	1.003 (0.955, 1.055)	1.069 (0.948, 1.205)	1.032 (0.915, 1.164)
Lead	0.968 (0.919, 1.021)	0.995 (0.941, 1.051)	0.963 (0.843, 1.101)	0.985 (0.857, 1.133)
Nickel	**0.947 (0.908, 0.988)**	0.980 (0.938, 1.023)	0.946 (0.847, 1.057)	0.985 (0.879, 1.105)

Bold indicates significant at the p=0.05 level (odds ratio does not contain the null value 1.000).

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