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Exposure to atmospheric metals using moss bioindicators and neonatal health outcomes in Portland, Oregon ☆

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ABSTRACT

Studying the impacts of prenatal atmospheric heavy-metal exposure is challenging, because biological exposure monitoring does not distinguish between specific sources, and high-resolution air monitoring data is lacking for heavy metals. Bioindicators - animal or plant species that can capture environmental quality - are a low-cost tool for evaluating exposure to atmospheric heavy-metal pollution that have received little attention in the public-health literature. We obtained birth records for Portland, Oregon live births (2008–2014) and modeled metal concentrations derived from 346 samples of moss bioindicators collected in 2013. Exposure estimates were assigned using mother's residential address at birth for six metals with known toxic and estrogenic effects (arsenic, cadmium, chromium, cobalt, nickel, lead). Associations were evaluated for continuous (cts) and quartile-based (Q) metal estimates and three birth outcomes (preterm birth (PTB; <37 weeks)), very PTB (vPTB; <32 weeks), small for gestational age (SGA; 10th percentile of weight by age and sex)) using logistic regression models with adjustment for demographic characteristics, and stratified by maternal race. Chromium and cobalt were associated with increased odds of vPTB (chromium - odds ratio $(OR)_{cts} = 1.09$, 95% CI: 1.00, 1.17; cobalt - $OR_{Q4\ vs\ Q1} = 1.33$, 95% CI: 1.03, 1.71). Cobalt, chromium and cadmium were significantly associated with odds of SGA, although the direction of association differed by metal (cobalt - $OR_{cts} = 1.04$, 95% CI: 1.01, 1.07; chromium - $OR_{Q3\ vs\ Q1} = 0.91$, 95% CI: 0.83, 0.99; cadmium - $OR_{cts} = 0.96$, 95% CI: 0.93, 1.00). In stratified analyses, odds of SGA were significantly different among non-white mothers compared to white mothers with exposure to chromium, cobalt, lead and nickel. This novel application of a moss-based exposure metric found that exposure to some atmospheric metals is associated with adverse birth outcomes. These findings are consistent with previous literature and suggest that moss bioindicators are a useful complement to traditional exposure-assessment methods.

1. Introduction

Preterm birth (PTB) and small for gestational age (SGA) are birth outcomes associated with immediate risk of infant mortality as well as lifelong illness and disability (Baer et al., 2016; Barker, 1995; Blencowe et al., 2012; Carmody and Charlton, 2013; Frey and Klebanoff, 2016; Mwaniki et al., 2012; Twilhaar et al., 2017). Exposure to heavy metals *in utero* is associated with both PTB and SGA (Chen et al., 2018; Cheng et al., 2017a; Khanam et al., 2021; Rahman et al., 2016). Most of the research demonstrating association between heavy-metal exposure and adverse birth outcomes used biological monitoring of metal concentrations in maternal urine and blood, umbilical cord blood, or placental tissue (Al-Saleh et al., 2014; Cheng et al., 2017a; Govarts et al., 2016; Khanam et al., 2021). However, biomonitoring provides little insight into the effects of different sources of pollution. In particular, biomonitoring is not specific to atmospheric heavy-metal pollution, a challenge if one is interested in investigating the relationship between specific sources of metal exposure and birth outcomes.

Instrumental monitoring is one approach that can be used to study the impact of atmospheric heavy-metal pollution on birth outcomes. However, due to the high cost of instrumental air monitors, many major cities in the United States have only one permanent monitor

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(Environmental Protection Agency, 2019). In addition, these monitors frequently provide data only on the most common air pollutants (such as lead), limiting their utility in investigating less common – but still potentially harmful – metals. As a result, few studies have examined the association between atmospheric metal exposure and adverse birth outcomes (Bell et al., 2010; Ebisu et al., 2014, 2018). Furthermore, metal concentrations in air can vary significantly across space, possibly resulting in exposure misclassification when a single measurement is used to represent the exposure of many individuals over a large geographic area, such as a city (Dias and Tchepel, 2018).

Bioindicators can be used as a low-cost complement to existing techniques for assessing atmospheric metal pollution. Bioindicators are animal or plant species that assess environmental quality over time (Holt and Miller, 2010). In particular, moss have been used as bioindicators of atmospheric metal concentration for decades, as they lack roots and obtain nutrients via airborne particles (Smodiš and Parr, 1999). Consequently, metal concentrations in moss solely reflect atmospheric sources (Smodiš and Parr, 1999). Several validation studies demonstrate that metal concentrations in moss correlate well with instrumental measures, although the strength of the relationship varies by element (Aboal et al., 2010; Ares et al., 2011; Fernández et al., 2015; Gerdol et al., 2014; Vuković et al., 2015). Moss can be sampled at high spatial density and low-cost and provide integrated exposure information via a single pathway (atmospheric) (Donovan et al., 2016). Metals may accumulate in moss tissues, such that concentrations at a given time represent atmospheric deposition over several years (Harmens et al., 2012). Moss bioindicators have been used to measure geographic and source variability in air pollution, finding that the metals and their relevant concentrations in mosses correspond well with the types of industries and degree of industrialization and urbanization in the region of measurement (Kapusta and Godzik, 2020). Recently, use of comparative moss samples from before and during the COVID-19 pandemic demonstrated geographic variability in metal emissions and sensitivity to emissions from industrial sources (Yushin et al., 2020). Thus, moss bioindicators are potentially an effective low-cost screening tool for identifying areas of concern that can then be investigated by more expensive instrumental-monitoring techniques.

While moss bioindicators are a useful environmental exposure assessment tool, they have not been widely used in epidemiologic studies as an exposure metric in assessing health risks. The one previously published study using moss bioindicators found that exposure to metals was associated with an increased risk of natural-cause mortality in France (Lequy et al., 2019).

We investigate the association between atmospheric metal exposure and PTB and SGA using a novel application of a moss bioindicator to assess individual prenatal exposure. We conducted this study in Portland, Oregon using birth records from the Oregon Health Authority from 2008 to 2014 and metal-concentration data from moss samples collected by the U.S. Forest Service in 2013. These samples provide higher spatial-resolution pollution maps for concentrations of arsenic, cadmium, chromium, cobalt, nickel and lead than instrumental monitors. Additionally, these maps revealed previously unknown sources of cadmium, arsenic, and nickel in close proximity to residential areas, including stained glass manufacturing and industrial sites, the neonatal health effects of which have not yet been investigated (Gatziolis et al., 2016). This study investigates the utility of these moss data for assessing the neonatal health risks of atmospheric metal pollution in Portland.

2. Methods

2.1. Study population

We conducted a retrospective cohort study of all live births in Portland, Oregon, from 2008 to 2014 for which state birth records were available (n = 66,942). Of the 66,942 subjects, 487 (<1%) maternal residential addresses could not be matched with an exposure (metal) value and were, therefore, excluded from the analysis. Analysis was restricted to singleton births (n = 2,426 excluded) for which birth weight was greater than 250 g (n = 10 excluded) and gestational age was more than 20 or less than 44 weeks (n = 33 excluded). Under these criteria, 63,986 births qualified for inclusion. All information on maternal residential address, maternal covariates, and birth characteristics came from the birth records collected and provided by the Oregon Health Authority (OHA).

Institutional review board approval for this study was obtained from the Yale University Human Subjects Committee and the OHA (protocol ID number: 2000023085).

2.2. Exposure assessment

Data on metal concentrations in moss samples were provided by the U.S. Forest Service (USFS), Pacific Northwest Research Station. The methodology for collecting and analyzing moss samples and modeling exposures has previously been published (Donovan et al., 2016; Gatziolis et al., 2016). Briefly, researchers collected 346 *Orthotrichum lyellii* moss samples using a gridded sampling design. *O.lyelli* was specifically chosen, because it grows throughout Portland, including in highly-polluted locations. The city was divided into 1 km grid cells, and an address was randomly chosen within each cell (n = 278). If a suitable deciduous tree was present at the address, then a sample of *O.lyelli* was collected from a height of at least 1 m and immediately refrigerated. If a suitable tree was not present, then an expanding search pattern was used to identify a suitable sample. The mean distance from the random address to the tree sampled was 91 m. An additional 68 samples were collected 0–100 m from the 1 km-grid samples. These additional samples helped characterize spatial correlation between sample points (Hasselbach et al., 2005). Debris was removed from the moss samples and the bases were trimmed leaving two-thirds green shoots. Samples were dried, ground into a powder, and digested with HNO_3 and H_2O_2. Digests were analyzed for heavy metals using inductively coupled plasma optical emission spectrometry (ICP-OES). Quality control consisted of independent check standards to monitor ICP calibration, reagent and method blanks, and repeat analysis of a bulk sample of *O.lyelli* collected in the Portland area (described by Donovan et al., 2016; Gatziolis et al., 2016).

An inverse-distance weighting interpolation algorithm was used to produce continuous surface maps of metal concentrations in moss; sample maps for cobalt and cadmium are presented in the Appendix (Figures A1 and A2). When co-located samples have high variability in moss measurements, special techniques that incorporate information from multiple points, such as inverse-distance weighting, helps reduce exposure misclassification by creating a smoother surface (Donovan et al., 2016; Hasselbach et al., 2005). Values at intermediate points were estimated as a function of the inverse distance to the 346 points with an actual measurement. A maximum of 12 nearest, in planar space, sample points were used in the interpolation. Given the rate of deposition for heavy metals, estimates were truncated at 1000 m. This meant that there some gaps in the map and, therefore, exposure metrics could not be calculated for 487 subjects. Moss-based estimates were correlated with contemporaneous instrumental readings of atmospheric cadmium concentrations by the Oregon Department of Environmental Quality (Donovan et al., 2016). However, the strength of relationship between moss concentrations and atmospheric concentrations may vary by element, due to differences in how elements bind to moss cells, retention, and displacement by other elements (Gatziolis et al., 2016). Confirmation via contemporaneous instrumental readings was not available for every element included in this study.

Of the 22 elements previously measured in the Portland moss sample, six (arsenic, cadmium, chromium (except Cr (III)), cobalt, nickel and lead) were included in this analysis, because they have high toxicity and are linked to reproductive, developmental, or endocrine disrupting outcomes, including PTB and fetal growth restrictions (Cotechini and

Graham, 2015; Dietert, 2012; Gatziolis et al., 2016; Gore et al., 2015).

Moss concentrations were originally reported in mg metal/kg moss (Gatziolis et al., 2016). To enhance interpretability and facilitate comparisons, we standardized all exposure metrics by subtracting the mean and dividing by the standard deviation. Exposure variables were analyzed as continuous and categorical (quartiles of exposure) variables.

Maternal exposure to metals was assigned by linking geocoded maternal residential address to metal concentrations on the continuous-surface maps. We used data collected at one point in time (December 2013) to represent maternal exposure from 2008 to 2014. Our use of samples from one point in time to represent exposure over a six-year period is justified for two reasons. First, unlike data from instrumental monitors, concentrations of heavy metals in moss tissue represent atmospheric deposition over several years (Harmens et al., 2012). Gatziolis et al. (2016) hypothesized that their moss samples directly represented approximately 3 years of atmospheric pollution. We extended this period to six years, because most atmospheric heavy-metal pollution in Portland comes from long-established industrial point sources. For example, the largest source of atmospheric cadmium pollution is an art-glass manufacturer that has operated in the same location since 1974 (Donovan et al., 2016). To check whether our results were sensitive to our assumption that moss represented exposure over six years, we conducted a sensitivity analysis in which we used a shorter three-year exposure window.

2.3. Outcome assessment

Birth weight and gestational age information were obtained from vital statistics records provided by OHA. These data were used to define three birth outcomes: PTB (gestational age <37 weeks), very PTB (vPTB) (<32 weeks), and SGA (10th percentile of weight by age and sex (Talge et al., 2014)). vPTB was examined as a separate outcome from PTB because it is a more serious adverse outcome: in 2015, vPTB represented just 1.6% of all US live births, but accounted for 52% of infant deaths (Barfield, 2018). We also evaluated SGA as the 15th percentile for birth weight by gestational age and sex, based on recent research suggesting that this is a clinically relevant endpoint definition (Xu et al., 2010).

2.4. Covariates evaluated

Covariate data were obtained from the vital statistics records provided by OHA. Based on a review of relevant literature to identify covariates thought to be associated with the exposure or outcome, we *a priori* considered the following covariates for inclusion in multivariate regression models: maternal age (years, continuous), infant sex, mother race/ethnicity (categorical), primiparity (yes/no), maternal smoking during pregnancy (yes/no), 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), payment method for delivery (private, public, self, other), prenatal care (none/one or more visits), previous preterm birth (yes/no), use of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) benefits (yes/no), use of alcohol during pregnancy (ever/never). We then examined the association between the potential covariates and both the exposure and outcome. 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. Mother's pre-pregnancy BMI was unknown for n = 1117 mothers. Chi-square tests of individuals with and without BMI data revealed some significant differences in demographic characteristics. Therefore, missing BMI values were imputed using multiple imputation, assuming BMI was missing at random and using ten iterations of the imputation process (Groenwold et al., 2012). We *a priori* did not include maternal gestational diabetes in the model to avoid introducing bias through adjustment of a potential mediator; there is some evidence that endocrine disrupting chemical mixtures have an inflammatory effect on the maternal-neonate system, and thus could be on the causal pathway between metal exposure and PTB (Kelley et al., 2019).

2.5. Statistical Analysis

The three outcomes in this study were PTB, vPTB and SGA. We estimated separate models for each metal (continuous and categorical) and outcome combination (30 total models). For categorical models, we split exposure metrics into quartiles. Logistic regression was used to test associations in univariate unadjusted models and multivariate models adjusted for potential confounders. All previously described covariates (section 2.4) were included in the starting model as potential confounders. Backwards selection was used to identify the most parsimonious model containing only statistically significant ($p < 0.05$) covariates. Categorical variables were retained if at least one level was statistically significant. The final adjusted models for all metals contained the following covariates: infant sex, maternal age, mother race/ethnicity, maternal smoking during pregnancy, maternal education level, payment method for delivery, prenatal care, mother's pre-pregnancy body mass index, previous preterm birth, and primiparity.

We examined potential effect modification by stratifying by maternal race (white vs. non-white) in adjusted multivariate models in which metal exposures were expressed continuously. Due to small percentages of people identifying in race categories other than white, we aggregated Black, Asian, Native American, Hawaiian, and other races into one category (non-white) for the stratified analyses.To formally test for heterogeneity across strata, we added an interaction term between the relevant metal and the stratification variable (maternal race). In stratified models, heterogeneity across strata was considered significant based on the significance of this interaction term.

We present the associations between each metal exposure and birth outcome as odds ratios (OR) and their corresponding 95% confidence interval (CI). For continuous metal exposures, ORs represent change in odds for each standardized unit increase in metal exposure. For categorical metal exposures, ORs represent change in odds for the specified quartile (second, third or fourth) relative to the first quartile of metal exposure. Results are presented for single-pollutant models and are not adjusted for other metals. Additionally, we conducted a sensitivity analysis restricting our sample to births from 2011 through 2014 and repeated the previously described statistical analysis. This restricted time period is consistent with the 3 years of exposure that Gatziolis et al. (2016) estimated that their moss samples represented.

All statistical analyses were performed in the SAS and STATA statistical software packages (SAS Institute, Inc., Cary, North Carolina; STATA 15, STATACorp, College Station, Texas) and p-values less than 0.05 were considered statistically significant.

3. Results

3.1. Demographic and exposure characteristics of the study population

Maternal sociodemographic and birth characteristics for the population are summarized in Table 1. Mothers were predominantly non-Hispanic white, did not use tobacco, paid for delivery privately, had previously given birth, and received prenatal care.

Density plots showing the distributions of the standardized and un-standardized metal concentrations from moss-based bioindicators are presented in Fig. 1. Variability in metal estimates across the study population were observed for all metals, with the biomarker identifying both low and high exposures (distributions span several standard deviations above and below the mean). The greatest range of metal exposure was observed for lead, with un-standardized values ranging from a minimum of 1.70 to a maximum of 20.44 (Table 2).

Table 1
Baseline characteristics of the study cohort (n = 63,986).

Characteristic	*Number (%)*[a]	*Characteristic*	*Number (%)*
Maternal Age (Years)		**Maternal Race**	
<20	3,673 (5.7)	Non-Hispanic White Only	40,135 (62.7)
20–24	11,137 (17.4)	Hispanic White	8,874 (13.9)
25–29	16,253 (25.4)	Black + Multi-Race Black	5,507 (8.6)
30–34	19,113 (29.9)	Asian + White-Asian	5,200 (8.1)
≥35	13,807 (21.6)	Other	4,087 (6.4)
Unknown	3 (0.0)	Unknown	183 (0.3)
Maternal Education		**Maternal BMI**[b]	
Less Than High School	10,685 (16.7)	Underweight	2,192 (3.4)
High School	11,776 (18.4)	Normal Weight	33,477 (53.3)
Some College	17,075 (26.7)	Overweight	14,814 (23.2)
Bachelor's Degree Or Above	24,064 (37.6)	Obese	12,386 (19.4)
Unknown	386 (0.6)	Unknown (Imputed)	1,117 (1.8)
Payment Method For Delivery		**Birth Order**	
Private	36,276 (56.7)	1	29,209 (45.7)
Public	25,222 (39.4)	>1	34,777 (54.4)
Self	1,468 (2.3)	**Previous Preterm Birth**	
Other	840 (1.3)	Yes	1829 (2.9)
Unknown	180 (0.3)	No	62,157 (97.1)
Number Of PNC Visits		**Mother Used Tobacco**	
None	543 (0.9)	Yes	5,624 (8.8)
≥1	63,441 (99.2)	No	58,086 (90.8)
Unknown	2 (0.00)	Unknown	276 (0.4)
Baby's Sex			
Female	31,257 (48.9)		
Male	32,729 (51.2)		

[a] Percentages may not sum to 100 due to rounding.
[b] A total of 1,117 (1.8%) of subjects were assigned imputed values for BMI.

3.2. Birth outcomes

During the study period (2008–2014), 3,667 cases of PTB and 508 cases of vPTB occurred. Chromium and cobalt exposure were associated with increased odds of vPTB. Chromium, as a continuous exposure metric, was significantly associated with increased odds of vPTB (OR_{cts} = 1.09, 95% CI: 1.00, 1.17). Cobalt in the highest quartile of exposure relative to the lowest was significantly associated with increased odds of vPTB ($OR_{Q4\ vs\ Q1}$ = 1.33, 95% CI: 1.03, 1.71) (Table 3). Results for arsenic were inconclusive, with only the second quartile of exposure significantly associated with PTB, and not higher quartiles or continuous exposure. No significant associations were observed between the other metals (cadmium, lead, nickel) and PTB or vPTB.

Results for SGA15 and SGA10 were nearly identical and, therefore, only results for SGA10 are presented. Exposure to cobalt (continuous exposure metric) was associated with increased odds of SGA (OR_{cts} = 1.04, 95% CI: 1.01, 1.07) (Table 3). Exposure to lead was associated with increased odds of SGA in the second quartile only. Inverse associations were observed between cadmium exposure and SGA, both for the continuous and categorical metric ($OR_{Q2\ vs\ Q1}$ = 0.90, 95% CI: 0.83, 0.98; $OR_{Q3\ vs\ Q1}$ = 0.88, 95% CI: 0.81, 0.96; $OR_{Q4\ vs\ Q1}$ = 0.88, 95% CI: 0.81, 0.96; OR_{cts} = 0.96, 95% CI: 0.93, 1.00). The highest quartile of chromium exposure was associated with significantly lower odds of SGA ($OR_{Q3\ vs\ Q1}$ = 0.91, 95% CI: 0.83, 0.99). No other metals were significantly associated with SGA.

When the sample was restricted to births occurring from 2011 to 2014 (n = 35,806) (Appendix Table A1), results were generally consistent with those in the full sample. Null findings were unchanged in terms of statistical significance. Observed associations for chromium and cobalt with vPTB and cobalt, lead and chromium with SGA were consistent with those observed in the full population with respect to direction and magnitude, but were no longer statistically significant (as expected for a smaller sample size). In the restricted sample, cadmium remained inversely related to SGA across all quartiles and continuously, although this result was only significant in the second and fourth quartiles of exposure (Appendix Table A1).

When models were stratified by maternal race, odds ratios for all metals and vPTB were higher among non-white mothers compared to white mothers (Fig. 2). However, we found no significant interaction between exposure to any metal and maternal race for PTB or vPTB (Fig. 2).

Odds of SGA were higher among non-white mothers compared to white mothers for all metals (Fig. 3). Tests for heterogeneity indicated that these differences between white and non-white mothers were statistically significant for exposure to chromium (p-value for interaction = 0.03), cobalt (p = 0.05), lead ($p < 0.01$) and nickel (p = 0.02) (Fig. 3). Within the non-white stratum, odds of SGA birth were significantly elevated with exposure to cobalt (OR = 1.07, 95% CI: 1.03, 1.12) and nickel (OR = 1.06, 95% CI: 1.01, 1.11), while the associations between SGA and cobalt and nickel were both null for white mothers. Odds ratios for the non-white strata were elevated but not statistically significant for chromium (OR = 1.03, 95% CI: 0.99, 1.08) and lead (OR = 1.03, 95% CI: 0.98, 1.07), whereas among white mothers, the odds ratio was below 1.0 but not significant for chromium (OR = 0.97, 95% CI: 0.93, 1.02) and was significantly decreased for lead (OR = 0.94, 95% CI: 0.90, 0.99). We found no significant interaction between exposure to arsenic or cadmium and maternal race for SGA.

4. Discussion

Very few previous studies have used moss biomonitoring to assess the relationship between atmospheric metal pollution and health outcomes (Lequy et al., 2019), and no previous studies (to our knowledge) have specifically examined neonatal health outcomes. We found that metal concentrations derived from moss samples were significantly associated with odds of adverse birth outcomes in this Portland, Oregon birth cohort. Specifically, chromium and cobalt were associated with increased odds of vPTB; cadmium and chromium were association with decreased odds of SGA; cobalt was associated with increased odds of SGA. Arsenic and lead are potentially associated with elevated odds of PTB and SGA, respectively, although results are inconclusive. In our stratified analysis, we found that non-white women had higher odds of SGA from exposure to chromium, cobalt, lead, and nickel, compared to white women.

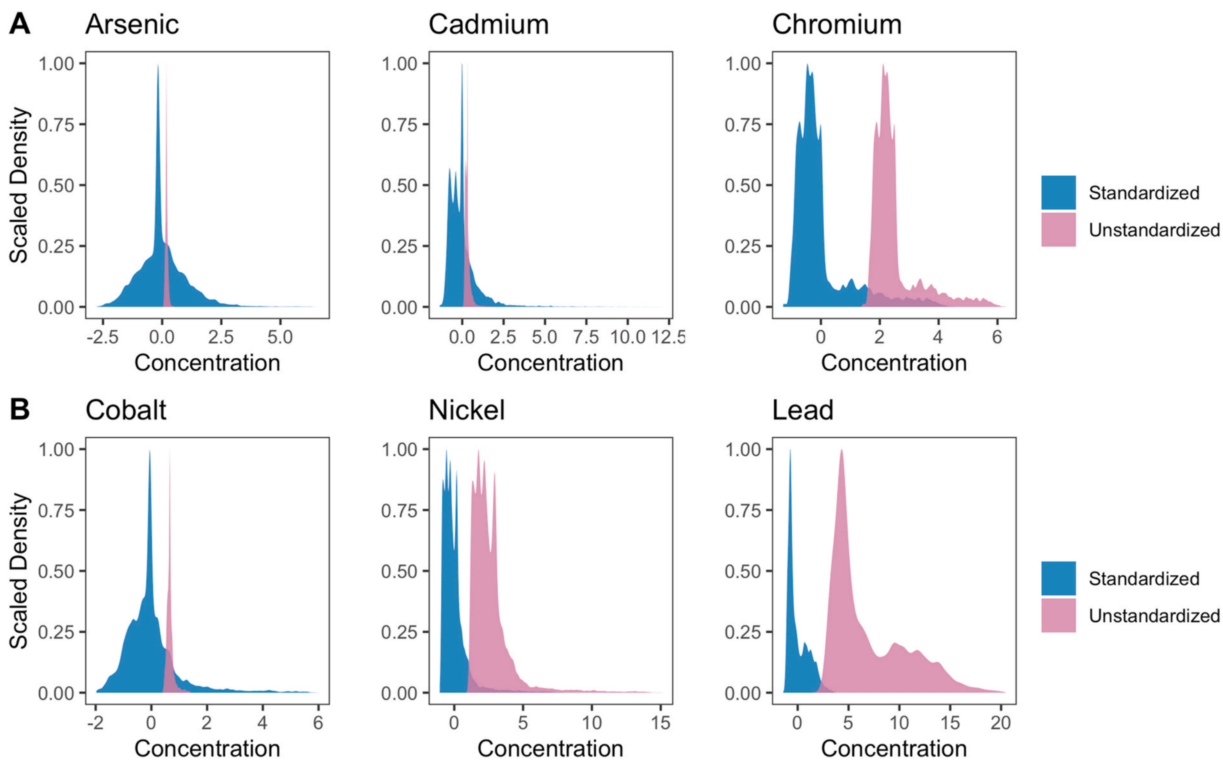

Fig. 1. (a and b). Distributions of metal concentrations (mg metal/kg moss), standardized and unstandardized.

Table 2
Distribution of Moss-Based Exposure Metric (Un-standardized Values, mg metal/kg moss).

Metal	Min	1st Quartile	Median	3rd Quartile	Max
Arsenic	0.05	0.16	0.18	0.21	0.52
Cadmium	0.06	0.21	0.32	0.35	2.58
Chromium	1.42	2.01	2.25	2.52	6.27
Cobalt	0.42	0.60	0.66	0.70	1.43
Lead	1.70	4.25	5.33	7.03	20.44
Nickel	0.97	1.74	2.29	2.98	15.10

Of all the metals evaluated, cadmium displayed the strongest association with an adverse birth outcome. Specifically, cadmium was associated with reduced odds of SGA when represented continuously and in a dose-dependent way when split into quartiles. This finding is consistent with previous research showing that cadmium has metallo-estrogenic effects, and estrogen-dependent tissues are highly sensitive to cadmium in women (Wallace, 2015). Animal toxicology studies in rats have demonstrated that cadmium disrupts the endocrine system of adult female rats by impacting sex steroid hormone production, development of the uterus, and quantity of ovarian follicles, and that hormonal changes induced by exposure to cadmium *in utero* can affect offspring (Li et al., 2018; Liu et al., 2020). Studies in pregnant mice and human cells have shown that cadmium causes changes in biochemical pathways that are associated with fetal growth restriction (Shi et al., 2020). The epidemiological literature on prenatal exposure to cadmium is mixed. Multiple studies have found that cadmium exposure is a risk factor for both SGA and PTB; however, these studies did not address solely atmospheric cadmium sources (Cheng et al., 2017b; Rahman et al., 2016; Sabra et al., 2017; Yang et al., 2016). However, consistent with our findings, some studies have also shown that cadmium exposure is associated with higher birth weight (Bloom et al., 2015), or have found inconsistent results (Al-Saleh et al., 2014).

The specific conditions in Portland may also explain why we found the strongest results for cadmium. Donovan et al. (2016) discovered that two art-glass manufacturers were emitting high levels of atmospheric heavy-metal pollution. Cadmium levels were particularly concerning. Instrumental monitoring 120 m from the larger of the two facilities in October and November of 2015 found that cadmium levels averaged 29.4 ng/m^3 (maximum of 195.4 ng/m^3). The average level was 49 times the State of Oregon's ambient benchmark of 0.6 ng/m^3 and approached the acute (1–14 day exposure) minimal risk level of 30.0 ng/m^3 established by the Agency for Toxic Substance and Disease Registry (Faroon et al., 2012).

Negative associations between metal concentrations and odds of SGA have several possible interpretations. Inverse associations may be due to chance or residual confounding. Alternatively, reduced odds of SGA from metal exposure may be viewed as a marker of endocrine disruption. Cadmium, in particular, is known to effect natural endocrine systems, adversely effecting human male and female reproduction, as well as pregnancy and birth outcomes (Kumar and Sharma, 2019). Endocrine disruption can lead to a range of adverse health outcomes, including obesity, diabetes, hormone-sensitive cancers, and disruption of reproductive, thyroid and neuroendocrine function (Gore et al., 2015). Previous studies have found that some endocrine disrupting metals can simultaneously be a risk factor both for SGA and large for gestational age (macrosomia) (Remy et al., 2017) and non-monotonic trends have been observed for many endocrine disrupting chemicals (Vandenberg et al., 2012). Our findings for cadmium are consistent across continuous and categorical representations of the exposure metric in the overall population, but further research should investigate the potential for inverse associations as observed here.

We also found that cobalt levels in moss were a risk factor for both vPTB and SGA. In the case of vPTB, only the highest quartile was statistically significant, which suggests that cobalt may only be a risk factor above a minimum threshold. Cobalt was also a risk factor for SGA when represented continuously, although not when split into quartiles. There have been very few studies of prenatal cobalt exposure. One of the few studies that focused on cobalt did not find significant associations with either birth weight or gestational age (Bloom et al., 2015). Therefore, our results suggest that additional studies of the risks of prenatal cobalt

Table 3
Adjusted[c] associations between preterm birth, SGA and metals, by quartiles and continuous exposure metrics.

	OR (95% CI) PTB[a] (n = 3,667 PTB)	OR (95% CI) PTB[a] (n = 508 vPTB)	OR (95% CI) SGA10 (n = 4,630 SGA10)
Arsenic			
Q2	1.10 (1.00, 1.21)[b]	1.05 (0.82, 1.34)	0.97 (0.89, 1.05)
Q3	1.04 (0.94, 1.15)	1.15 (0.90, 1.47)	1.02 (0.93, 1.11)
Q4	1.06 (0.97, 1.17)	0.95 (0.74, 1.22)	0.97 (0.89, 1.06)
Continuous	1.01 (0.97, 1.04)	0.95 (0.87, 1.04)	1.00 (0.97, 1.03)
Cadmium			
Q2	1.05 (0.96, 1.15)	1.00 (0.79, 1.27)	0.90 (0.83, 0.98)[b]
Q3	1.03 (0.93, 1.13)	0.97 (0.76, 1.24)	0.88 (0.81, 0.96)[b]
Q4	1.03 (0.94, 1.14)	1.08 (0.85, 1.38)	0.88 (0.81, 0.96)[b]
Continuous	1.02 (0.98, 1.05)	1.07 (0.99, 1.16)	0.96 (0.93, 1.00)[b]
Chromium			
Q2	0.95 (0.86, 1.04)	1.15 (0.90, 1.47)	0.98 (0.90, 1.07)
Q3	0.98 (0.89, 1.08)	1.26 (0.99, 1.61)	0.91 (0.83, 0.99)[b]
Q4	1.02 (0.92, 1.12)	1.19 (0.93, 1.52)	0.97 (0.89, 1.06)
Continuous	1.01 (0.97, 1.04)	1.09 (1.00, 1.17)[b]	1.00 (0.97, 1.03)
Cobalt			
Q2	1.00 (0.91, 1.10)	1.19 (0.92, 1.54)	1.00 (0.92, 1.09)
Q3	0.99 (0.90, 1.10)	1.28 (0.99, 1.65)	0.94 (0.86, 1.03)
Q4	1.03 (0.94, 1.13)	1.33 (1.03, 1.71)[b]	1.05 (0.96, 1.14)
Continuous	1.00 (0.97, 1.04)	1.05 (0.97, 1.14)	1.04 (1.01, 1.07)[b]
Lead			
Q2	1.09 (0.99, 1.19)	1.07 (0.84, 1.36)	1.10 (1.01, 1.20)[b]
Q3	0.93 (0.84, 1.03)	0.98 (0.75, 1.27)	0.97 (0.88, 1.06)
Q4	1.06 (0.96, 1.17)	1.19 (0.92, 1.53)	0.97 (0.89, 1.06)
Continuous	1.00 (0.97, 1.04)	1.06 (0.97, 1.16)	0.98 (0.94, 1.01)
Nickel			
Q2	1.00 (0.91, 1.10)	0.94 (0.73, 1.20)	1.06 (0.97, 1.15)
Q3	0.96 (0.87, 1.05)	1.06 (0.83, 1.36)	0.96 (0.88, 1.05)
Q4	0.96 (0.87, 1.06)	1.11 (0.87, 1.42)	1.01 (0.93, 1.11)
Continuous	0.99 (0.95, 1.02)	1.00 (0.91, 1.09)	1.01 (0.98, 1.04)

[a] Reference group is Quartile 1 (Q1); [b] $p < 0.05$.
[c] Models adjusted for infant sex, maternal age, mother race/ethnicity, maternal smoking during pregnancy, maternal education level, payment method for delivery, prenatal care, mother's pre-pregnancy body mass index, previous preterm birth, and primiparity.
Abbreviations: CI, confidence interval; OR, odds ratio; Q, quartile; PTB, preterm birth; vPTB, very preterm birth; SGA, small for gestational age.

exposure may be warranted.

Chromium was also a risk factor for vPTB, which is consistent with previous research (Remy et al., 2017). In addition, chromium was associated with decreased odds of SGA in the third quartile of exposure. However, the association we observed between chromium and SGA should be interpreted cautiously, as only the third quartile was significant. Previous studies have shown that prenatal chromium exposure can be a risk factor both for large-for-gestational-age and SGA births, indicating the potential complexity of this relationship (Remy et al., 2017).

We found some associations between arsenic and lead in moss and odds of PTB (arsenic) and SGA (lead). However, in both cases only the second quartile of exposure was significant, which is not suggestive of an underlying causal relationship and requires further investigation. A recent literature review found consistently higher incidence of PTB with lead exposure, but inconclusive results for arsenic (Khanam et al., 2021). It is possible that our findings are due to chance, or that elevated odds in the second quartile are due to a nonmonotonic trend, as has been observed for many endocrine disrupting chemicals (Vandenberg et al., 2012). Finally, we found no association between nickel and the probability of any adverse birth outcome in non-stratified analyses.

Our stratified analysis showed that exposures to chromium, cobalt, lead, and nickel were greater risk factors for SGA among non-white women. Among white women, the ORs for SGA and exposure to lead and chromium are less than 1.0, while among non-white women the ORs are greater than 1.0. Tests for heterogeneity indicated that these odds were significantly different when comparing white and non-white women. However, neither metal was significantly ($p < 0.05$) associated with increased (or decreased) odds of SGA, when examining the significance of ORs within strata. Differences in associations that we observed may reflect multiple factors, such as differences in co-exposures to other pollutants, social stressors, or susceptibility (e.g., baseline health status, access to or quality of health care, comorbidities). Additionally, white and non-white women may have disparities in access to care which are not entirely accounted for by adjusting for "number of prenatal care visits." Although we confirmed in our data that non-white women do not have systematically higher pollution exposure than white women, it is also possible that non-white women had higher exposure to non-atmospheric sources of heavy metals that are not reflected in moss measurements; there are multiple examples in the literature of ethnic minorities being exposed to higher levels of heavy-metal pollution for a variety of reasons (Cassidy-Bushrow et al., 2017; Davis et al., 2016; Nguyen et al., 2020).

Our study has several limitations. This was an observational study, so we were unable to establish causal relationships between heavy-metal exposure and birth outcomes. Additionally, residual confounding is possible: the birth-registry data we used has limited information on paternal characteristics, which may be a significant predictor of adverse birth outcomes (Meng and Groth, 2018), and maternal lifestyle and behavioral factors such as diet (Gete et al., 2019) and stress (Lilliecreutz et al., 2016). We were not able to distinguish between spontaneous or medically indicated PTB, which have potentially distinct etiologies (Savitz et al., 2005) and therefore may have differing relationships with metal exposure. In addition, some data were self-reported. Smoking was a particular concern, because self-reported data can be biased (Northam and Knapp, 2006), and cigarette smoking is not only a risk factor for adverse birth outcomes but also a major source of cadmium.

Our exposure metric was based on moss collected during December 2013, so exposure misclassification is a possibility. However, we think this is a reasonable measure of exposure because mosses integrate exposure over multiple years (Harmens et al., 2012) and long-standing industrial point sources are responsible for significant amounts of atmospheric heavy metals in Portland. We additionally repeated our analysis restricting the data to births from 2011 to 2014 and found that results in this smaller sample are generally consistent with associations in the larger sample. Residential mobility may also contribute to exposure misclassification. We only had a mother's address at the time of birth, and some women may have moved during pregnancy. Previous research on maternal residential mobility, however, suggests this is likely not a major source of exposure misclassification (Lupo et al., 2010). The strength of relationship between moss concentrations and atmospheric concentrations may vary by element, and in this study, calibration via comparisons between moss measures and contemporaneous instrumental readings was only available for cadmium (Gatziolis et al., 2016). Although such exposure-metric validation is outside the scope of this study, future research should explore these aspects of moss bioindicator measurements. Additionally, using a smoothing approach (such as inverse distance weighting) to assign exposure may limit the influence of abrupt changes in metal concentrations that Gatziolis et al. observed. There is additional potential for exposure misclassification due to edge effects associated with inverse distance weighting. However, we do not expect this to be a major source of exposure misclassification in this study due to the original sampling design for the moss. The original sampling reported in Donovan et al. (2016) included a 1 km buffer around the city in order to avoid edge effects in the spatial models. Less than 3% of our sample falls within this buffer; therefore, any edge effect would not be a major source of misclassification.

Our study has several strengths. First, although moss have been used as bioindicators of atmospheric metal concentrations for decades (Smodiš and Parr, 1999), we believe this to be the first study to use moss bioindicators as an exposure metric in a birth cohort study and among the first studies using moss in epidemiologic investigations. Using moss bioindicators highlights exposure to metals from a specific route, namely atmospheric pollution. Data derived from moss provide

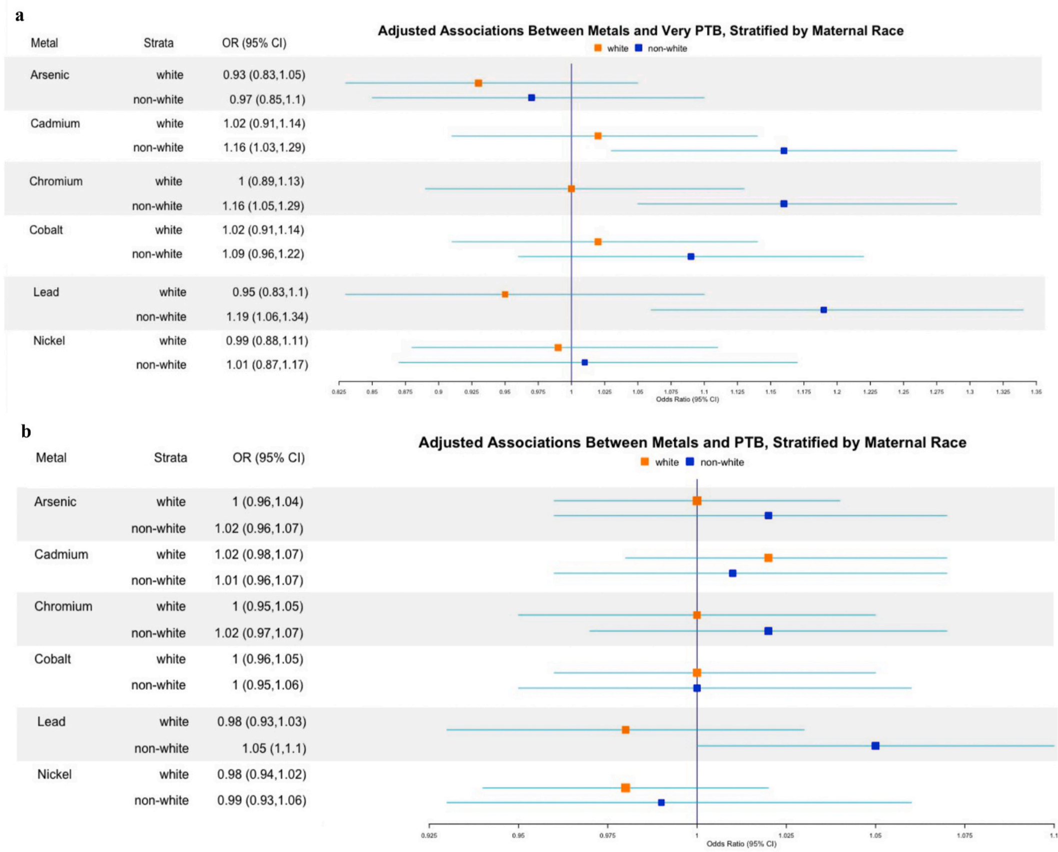

Fig. 2. a). Odds ratios (with 95% confidence intervals) for the adjusted[a] associations between metals and vPTB stratified by maternal race. Tests for heterogeneity not significant (at $p < 0.05$ level) for any metals. [a] Models adjusted for infant sex, maternal age, mother race/ethnicity, maternal smoking during pregnancy, maternal education level, payment method for delivery, prenatal care, mother's pre-pregnancy body mass index, previous preterm birth, and primiparity. **b).** Odds ratios (with 95% confidence intervals) for the adjusted[a] associations between metals and PTB stratified by maternal race. Tests for heterogeneity not significant (at $p < 0.05$ level) for any metals. [a] Models adjusted for infant sex, maternal age, mother race/ethnicity, maternal smoking during pregnancy, maternal education level, payment method for delivery, prenatal care, mother's pre-pregnancy body mass index, previous preterm birth, and primiparity.

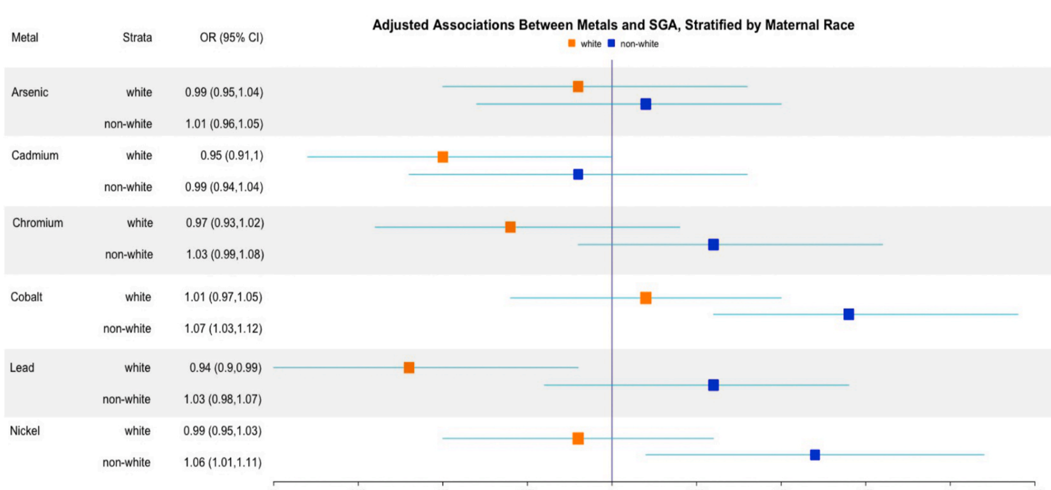

Fig. 3. Odds ratios (with 95% confidence intervals) for the adjusted[a] associations between metals and SGA stratified by maternal race. Tests for heterogeneity significant ($p < 0.05$) for chromium, cobalt, lead, nickel. [a] Models adjusted for infant sex, maternal age, mother race/ethnicity, maternal smoking during pregnancy, maternal education level, payment method for delivery, prenatal care, mother's pre-pregnancy body mass index, previous preterm birth, and primiparity.

exposure information at an improved spatial resolution relative to what can be obtained from the limited number of instrumental monitors in the city. Additionally, moss measurements integrate all atmospheric sources of metals, allowing for large scale estimation of atmospheric pollution (Lequy et al., 2019). Furthermore, this study uses a large sample size and is registry-based, reducing the potential for selection bias.

Lastly, we believe this work has important practical implications despite its limitations. The magnitude of effect is relatively small.

However, this is to be expected since PTB and SGA have a multifactorial etiology and metals exposure is likely not the dominant driver of PTB and SGA (Finken et al., 2018; Goldenberg et al., 2008). Additionally, we observed some inconsistencies in trends and effects, perhaps due to limitations of the exposure metric and assignment. However, the results are practically important for two reasons: (1) Even small odds ratios can result in a large absolute number of adverse outcomes for a common occurrence, such as births, in a large population (such as our population of >60,000 births); and (2) Exposure to heavy metals, particularly from industrial point sources, is a modifiable risk, which makes understanding potential health effects even more important.

5. Conclusions

The results of this observational study demonstrate that bioindicators may be a viable low-cost screening tool for analyzing the public health effects of exposure to atmospheric pollution. Results are consistent with the current literature on prenatal exposure to heavy metals. In particular, the cadmium results are supported by studies that did not use bioindicators and are consistent with Portland's documented history of high atmospheric cadmium emissions. The finding that cobalt may be a risk factor for adverse birth outcomes warrants further investigation with conventional monitoring methods.

Author statement

Conceptualization and Methodology- S.C., G.D. and N.C. Data curation- S.C. and D.G. Formal analysis- S.C. and G.D. Writing- S.C. (original draft, review and editing); S.C., G.D. and N.C. (review and editing), The final draft has been approved by all authors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A

Table A1
Adjusted[a] Associations Between Preterm Birth, SGA and Metals, by Quartiles and Continuous Exposure Metrics for Births between 2011 and 2014 and Percent Change Relative to Measures of Association in Full Study Population (n = 5,806)

	OR (95% CI) PTB (n = 2,037)	% change[b]	OR (95% CI) vPTB (n = 296)	% change[b]	OR (95% CI) SGA 10 (n = 2,571)	% change[b]
Arsenic						
Q2	1.13 (0.99, 1.28)	2.27	0.94 (0.68, 1.30)	−11.25	0.93 (0.83, 1.04)	−4.30
Q3	1.08 (0.94, 1.24)	3.65	1.07 (0.77, 1.49)	−7.07	1.00 (0.89, 1.12)	−2.00
Q4	1.03 (0.90, 1.18)	−2.67	0.82 (0.58, 1.15)	−16.30	1.05 (0.85, 1.06)	7.62
Continuous	0.99 (0.95, 1.04)	−1.71	0.91 (0.81, 1.03)	−4.37	1.00 (0.96, 1.04)	0.00
Cadmium						
Q2	1.04 (0.92, 1.19)	−0.61	1.08 (0.79, 1.48)	7.51	**0.88 (0.78, 0.98)**	−2.27
Q3	1.04 (0.91, 1.18)	0.54	0.94 (0.67, 1.31)	−3.47	0.90 (0.81, 1.01)	2.22
Q4	1.06 (0.93, 1.21)	3.01	1.01 (0.72, 1.41)	−7.28	**0.88 (0.78, 0.99)**	0.00
Continuous	1.03 (0.98, 1.08)	0.80	1.04 (0.92, 1.16)	−3.17	0.97 (0.93, 1.01)	1.03
Chromium						
Q2	0.89 (0.78, 1.01)	−6.58	1.17 (0.84, 1.63)	1.82	0.98 (0.87, 1.10)	0.00
Q3	0.94 (0.83, 1.07)	−4.37	1.12 (0.80, 1.56)	−12.61	0.93 (0.83, 1.04)	2.15
Q4	0.97 (0.85, 1.10)	−5.25	1.15 (0.82, 1.60)	−3.86	0.98 (0.88, 1.10)	1.02
Continuous	0.99 (0.95, 1.04)	−2.01	1.08 (0.97, 1.20)	−1.34	1.00 (0.96, 1.04)	0.00
Cobalt						
Q2	0.96 (0.85, 1.10)	−3.69	1.14 (0.81, 1.59)	−4.56	0.97 (0.86, 1.09)	−3.09
Q3	0.98 (0.86, 1.12)	−0.63	1.01 (0.72, 1.43)	−26.16	0.97 (0.86, 1.09)	3.09
Q4	0.95 (0.84, 1.09)	−7.95	1.20 (0.86, 1.67)	−10.72	1.03 (0.92, 1.15)	−1.94
Continuous	0.97 (0.92, 1.01)	−3.32	0.99 (0.88, 1.11)	−6.14	1.03 (0.99, 1.07)	−0.97
Lead						
Q2	1.03 (0.91, 1.17)	−6.06	1.13 (0.82, 1.55)	4.94	1.03 (0.92, 1.16)	−6.80
Q3	0.88 (0.76, 1.01)	−6.12	0.93 (0.65, 1.33)	−5.89	0.95 (0.84, 1.08)	−2.11
Q4	1.04 (0.91, 1.19)	−2.24	1.23 (0.87, 1.73)	3.33	0.96 (0.84, 1.08)	−1.04
Continuous	1.01 (0.96, 1.06)	0.71	1.07 (0.96, 1.21)	1.38	0.98 (0.94, 1.02)	0.00
Nickel						
Q2	0.97 (0.85, 1.10)	−2.91	0.95 (0.68, 1.33)	1.42	1.00 (0.89, 1.13)	−6.00
Q3	0.92 (0.81, 1.0[a])	−4.29	0.98 (0.70, 1.38)	−7.63	0.91 (0.81, 1.03)	−5.49
Q4	0.91 (0.80, 1.04)	−5.40	1.13 (0.81, 1.57)	1.35	1.03 (0.91, 1.16)	1.94
Continuous	0.98 (0.93, 1.03)	−1.19	1.01 (0.89, 1.14)	0.75	1.00 (0.96, 1[b]05)	−1.00

[a] Models adjusted for infant sex, maternal age, mother race/ethnicity, maternal smoking during pregnancy, maternal education level, payment method for delivery, prenatal care, mother's pre-pregnancy body mass index, previous preterm birth, and primiparity.

[b] % change $= \frac{OR_{sub} - OR_{full}}{OR_{sub}}$

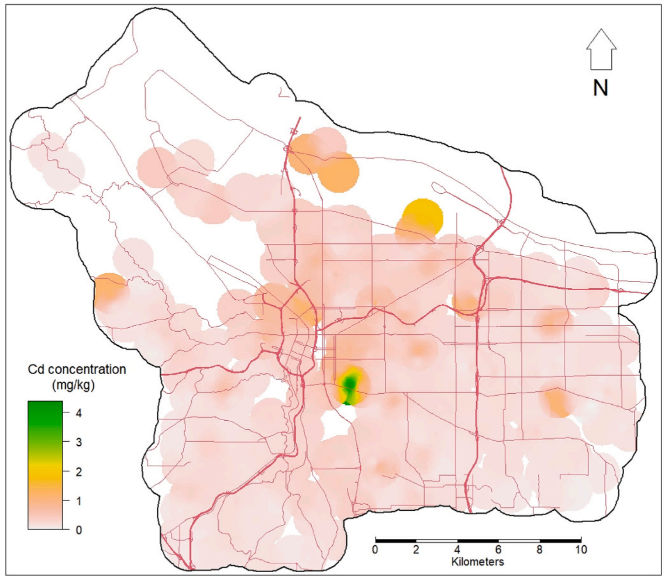

Fig. A1. Distribution of Inverse Distance Weighted Cadmium Concentrations in Study Area

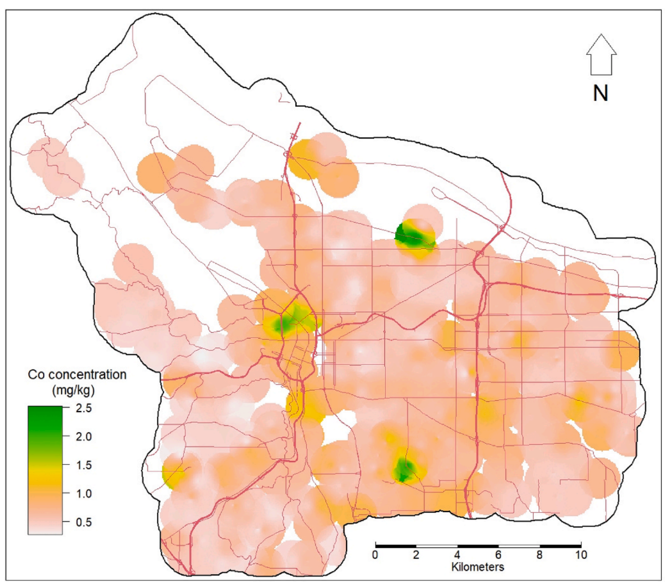

Fig. A2. Distribution of Inverse Distance Weighted Cobalt Concentrations in Study Area

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