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Prenatal Metal(loid) Mixtures and Birth Weight for Gestational Age: A Pooled Analysis of Three Cohorts Participating in the ECHO Program

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Declaration of interests

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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Abstract

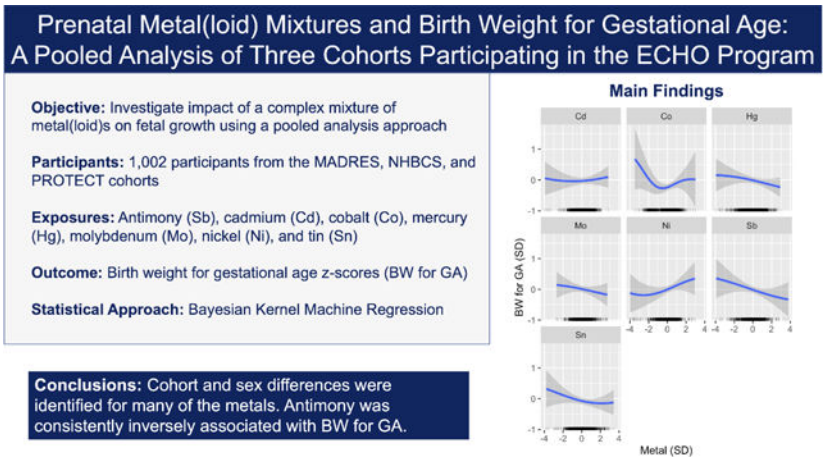
Background: A growing number of studies have identified both toxic and essential metals which influence fetal growth. However, most studies have conducted single-cohort analyses, which are often limited by narrow exposure ranges, and evaluated metals individually. The objective of the current study was to conduct an environmental mixture analysis of metal impacts on fetal growth, pooling data from three geographically and demographically diverse cohorts in the United States participating in the Environmental Influences on Child Health Outcomes program.

Methods: The pooled sample (N=1,002) included participants from the MADRES, NHBCS, and PROTECT cohorts. Associations between seven metals (antimony, cadmium, cobalt, mercury, molybdenum, nickel, tin) measured in maternal urine samples collected during pregnancy (median: 16.0 weeks gestation) and birth weight for gestational age z-scores (BW for GA) were investigated using Bayesian Kernel Machine Regression (BKMR). Models were also stratified by cohort and infant sex to investigate possible heterogeneity. Chromium and uranium concentrations fell below the limits of detection for most participants and were evaluated separately as binary variables using pooled linear regression models.

Results: In the pooled BKMR analysis, antimony, mercury, and tin were inversely and linearly associated with BW for GA, while a positive linear association was identified for nickel. The inverse association between antimony and BW for GA was observed in both males and females and for all three cohorts but was strongest for MADRES, a predominantly low-income Hispanic cohort in Los Angeles. A reverse j-shaped association was identified between cobalt and BW for GA, which was driven by female infants. Pooled associations were null for cadmium, chromium, molybdenum, and uranium, and BKMR did not identify potential interactions between metal pairs.

Conclusions: Findings suggest that antimony, an understudied metalloid, may adversely impact fetal growth. Cohort- and/or sex-dependent associations were identified for many of the metals, which merit additional investigation.

Graphical Abstract



Keywords

mixtures; metals; metalloids; fetal growth; pooled analysis; BKMR

1. Introduction

Fetal growth is an important indicator of future health (Crispi et al. 2018; Reyes and Mañalich 2005; Shenkin et al. 2004; Whincup et al. 2008). Infants born small for gestational age experience greater neonatal mortality compared to infants born an appropriate weight for gestational age and are at greater risk of neurocognitive impairment in childhood and cardiometabolic disease later in life (Kesavan and Devaskar 2019; Sacchi et al. 2020). Continuous associations have also been identified between size at birth and future disease risk (Gluckman et al. 2008). Thus, even modest reductions in fetal growth may have important implications for disease burden at the population level. It is therefore critical to identify modifiable exposures that influence fetal growth.

Size at birth is influenced by the diverse exposures experienced *in utero* (Gluckman et al. 2008; Padula et al. 2020), and exposure to toxic metals and metalloids (hereafter referred to collectively as “metals”) has been identified as one factor contributing to reduced fetal growth (Ballester et al. 2018; Cabrera-Rodríguez et al. 2018; Freire et al. 2019; Gonzalez-Nahm et al. 2020 p.; Gustin et al. 2020; Johnston et al. 2014; Khoshhali et al. 2020; Kim et al. 2017, 2020; Punshon et al. 2019; Shirai et al. 2010; Vejrup et al. 2014; Vigeh et al. 2018; Xia et al. 2016; Zhang et al. 2004). Because metals are ubiquitous in the environment due to contamination from both natural and anthropogenic sources, metal exposures are prevalent, with major sources including ingestion of contaminated food and drinking water and inhalation of polluted air and dust (Davis et al. 2014; Tchounwou et al. 2012). Many metals cross the placenta and can therefore directly impact the developing fetus (Gundacker and Hengstschläger 2012). Metals can also indirectly impact growth by adversely affecting placental function (Chen et al. 2014; Punshon et al. 2019; Zhao et al. 2020). Several toxic metals, including cadmium (Cd) and mercury (Hg), have been associated with reduced fetal growth and other adverse birth outcomes across multiple studies (Ballester et al. 2018; Freire et al. 2019; Gonzalez-Nahm et al. 2020; Gustin et al. 2020; Johnston et al. 2014;

Khoshhali et al. 2020; Kim et al. 2017, 2020; Punshon et al. 2019; Shirai et al. 2010; Vejrup et al. 2014; Vigeh et al. 2018; Zhang et al. 2004). However, others such as chromium (Cr), antimony (Sb), tin (Sn), and uranium (U) have been less well-studied (Cabrera-Rodríguez et al. 2018; Freire et al. 2019; Kim et al. 2020; Peng et al. 2018; Shirai et al. 2010; Xia et al. 2016; Zhang et al. 2020). In contrast with toxic metals, which have no biological function, essential metals, including cobalt (Co) and molybdenum (Mo), are important physiologically in low-to-moderate quantities, but can also be toxic at high levels of exposure (Barceloux 1999; Cao et al. 2016; Howe et al. 2021; Novotny and Peterson 2018; Shi et al. 2019; Shih et al. 2021; Shiue and Hristova 2014). Associations between many essential elements and fetal growth have therefore been inconsistent across studies and may depend on the specific population and exposure range (Eum et al. 2014; Howe et al. 2020b; Mikelson et al. 2019; Signes-Pastor et al. 2019).

Traditionally, metals have been evaluated individually in relation to fetal growth. However, metal exposures typically co-occur due to common sources and may be correlated and interact in complex ways to impact health (Shim et al. 2017). Evaluating metals individually may therefore lead to the possible misestimation of their effects on growth. As a result, a growing number of studies have applied environmental mixture modeling approaches to simultaneously investigate impacts of co-occurring metals on fetal growth (Ashrap et al. 2020a; Cabrera-Rodríguez et al. 2018; Cassidy-Bushrow et al. 2019; Govarts et al. 2016; Howe et al. 2020b, 2020a; Hu et al. 2021; Kim et al. 2020; Signes-Pastor et al. 2019). These studies have identified several understudied metals of concern, including Sb and Sn, to be associated with reduced fetal growth, as well as novel interactions between metal pairs (Cabrera-Rodríguez et al. 2018; Howe et al. 2020b, 2020a; Kim et al. 2020). However, many environmental mixture modeling methods require large data sets. Single-cohort analyses are also typically limited by relatively narrow exposure ranges.

For the current study, we therefore pooled data from three geographically and demographically diverse cohorts participating in the Environmental Influences on Child Health Outcomes (ECHO) Program with the goals of improving statistical power and capturing wider exposure ranges to simultaneously investigate the impacts of multiple metals on fetal growth (Padula et al. 2020). ECHO is a national, multidisciplinary research initiative launched by the National Institutes of Health to examine the impacts of early life environmental exposure impacts on the health and development of approximately 50,000 children from diverse populations across the United States (Gillman and Blaisdell 2018). We focused on metal concentrations that were measured in maternal urine samples collected at the earliest study visit for each cohort, as findings from previous studies suggest that early pregnancy may be a particularly susceptible exposure window (Huang et al. 2019; Peng et al. 2018; Vigeh et al. 2018). In secondary analyses, we stratified by cohort to investigate potential heterogeneity. Given prior evidence that fetal sex may modify individual metal associations with growth (Gilbert-Diamond et al. 2016; Govarts et al. 2016; Signes-Pastor et al. 2019; Tatsuta et al. 2017; Taylor et al. 2016; Zhang et al. 2018), metal impacts on fetal growth were also investigated separately for males and females in secondary analyses.

2. Materials and Methods

2.1 Participating Cohorts

Cohorts in the ECHO Program were invited to participate in the current study if they had 1) previously measured a panel of multiple metals in maternal urine samples during pregnancy, 2) available birth outcomes data for participants, and 3) the ability to share data for a pooled analysis by December 2020. Three cohorts contributed data: the Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) Study, the New Hampshire Birth Cohort Study (NHBCS), and the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) Study. Participants from each cohort were included in the pooled analysis if they had complete data for maternal urinary metal measurements from the cohort's earliest study visit (median 12.5 weeks gestation for MADRES, 12.3 weeks gestation for the NHBCS, and 17.3 weeks gestation for PROTECT), birth outcomes (weight and gestational age), and relevant covariates for statistical analyses. Extreme outliers for urinary metals (mean ± 4 SD on the log-scale) (N=44) and one participant from the PROTECT cohort who had a particularly high birth weight for gestational age z-score (6.62 SD) were excluded, leaving a total of 1,002 participants for the pooled analysis. Flowcharts for each cohort are shown in Figure S1.

2.1.1 MADRES—MADRES is an ongoing prospective pregnancy cohort, which began enrolling participants in November 2015 (Bastain et al. 2019). Participants are recruited from four prenatal care providers in Los Angeles, California, including two community health clinics, one county hospital prenatal clinic, and one private obstetrics and gynecology practice. Most of these clinics serve predominately lower income Hispanic populations. Women are eligible to participate in MADRES if they are at least 18 years old, can speak English or Spanish fluently, and their pregnancy is at <30 weeks gestation at the time of recruitment. For the current study, we included participants who enrolled in early pregnancy (median: 12.5 weeks gestation). MADRES exclusion criteria include multiple gestation; HIV positive status; current incarceration; and having a physical, mental, or cognitive disability that would prevent the participant's ability to participate or provide informed consent. The study protocol was approved by the University of Southern California's Institutional Review Board, and all participants provided informed consent at study entry.

2.1.2 NHBCS—The NHBCS is an ongoing prospective pregnancy cohort, which began enrolling participants in January 2009 (Muse et al. 2020). Participants were initially recruited between ~24 and 28 weeks gestation from prenatal clinics in New Hampshire. However, in March 2017 an additional wave of participant recruitment began at ~12 weeks gestation. Given our interest in early pregnancy metals exposure, we included NHBCS participants who were recruited at ~12 weeks gestation. Women were eligible to participate in the NHBCS if they were between 18–45 years old, had a singleton pregnancy, could speak English fluently, used a private unregulated water system at their home, and were not planning to move. All participants provided written informed consent at study entry, and all study procedures were approved by the Institutional Review Board at Dartmouth College.

2.1.3 PROTECT—In 2010, the PROTECT cohort began recruiting pregnant women who resided in Northern Puerto Rico (Ferguson et al. 2019). Study participants were recruited in the first or second trimester of pregnancy (median: 14 weeks gestation). Spot urine samples, pregnancy characteristics, and additional demographics were obtained at three subsequent study visits (Visit 1 mean ± SD: 18 ± 2 weeks gestation, Visit 2 mean ± SD: 22 ± 2 weeks gestation, and Visit 3 mean ± SD: 26 ± 2 weeks gestation). Women were eligible to participate if they 1) were between 18 and 40 years of age; 2) resided in the Northern Karst aquifer region; 3) stopped using oral contraceptives three months prior to their pregnancy; 4) did not use *in vitro* fertilization to conceive; and 5) did not have any major preexisting medical or obstetric conditions, including diabetes; hypertension; or liver, kidney, or cardiovascular disease. Participants provided written informed consent prior to enrollment in the cohort, and the research protocols were approved by the ethics and research committees at the University of Puerto Rico and participating clinics, as well as at the University of Michigan and Northeastern University.

2.2 Urine Collection & Urinary Metals

Metal mixture analyses focused on seven metals, which were selected because they were commonly measured across the three cohorts, exceeded the cohort-specific limits of detection (LOD) for at least 60% of participants in the pooled sample, and can be reliably measured in urine (ATSDR 2019; Basu et al. 2018; Faroon and Keith 2004; Fay 2005; Harper 2005; Todd et al. 2020; Vacchi-Suzzi et al. 2016). These elements included antimony (Sb), cadmium (Cd), cobalt (Co), mercury (Hg), molybdenum (Mo), nickel (Ni), and tin (Sn). Cohort-specific LODs are shown for each metal in Table S1. If a metal concentration fell below the cohort-specific LOD, the machine value was used. Machine values ≤0 were set to the smallest positive value divided by 2. Urinary metal concentrations were adjusted for specific gravity, measured separately for each cohort using a refractometer, to account for urine dilution. Two metals, chromium (Cr) and uranium (U), which did not meet the detection thresholds to be included in the mixture analysis but can be reliably measured in urine were evaluated separately as binary variables (above versus below the cohort-specific LOD) using traditional linear regression models (Keith et al. 2013; Wilbur 2000).

Metal concentrations were measured by inductively coupled plasma mass spectrometry in spot urine samples, collected from participants during pregnancy. For MADRES and PROTECT, urinary metals were measured through the Children's Health Exposure Analysis Resource Program (CHEAR) (now the Human Health Exposure Analysis Resource) at NSF international, which is affiliated with the University of Michigan CHEAR Laboratory Hub, as described previously (Ashrap et al. 2020b, 2020a; Howe et al. 2020b, 2020a). For the NHBCS, urinary metals were measured by the Dartmouth Trace Element Analysis Core (Farzan et al. 2021; Romano et al. 2019).

2.3 Birth Outcomes

For the NHBCS and PROTECT, birth weight (BW) information was abstracted from the medical records. For MADRES, BW information from the medical records was prioritized. However, maternal reported BW measures were used for 1.7% of participants for whom abstracted values could not be obtained. Gestational age (GA) at birth was determined for

each cohort using a hierarchy of methods as described previously (Ferguson et al. 2019; Gilbert-Diamond et al. 2016; Howe et al. 2020a). Infant sex was also abstracted from the medical records for PROTECT and the NHBCS. For MADRES, infant sex information from the medical records was prioritized. However, maternal reported infant sex was used for 3.1% of participants for whom abstracted information could not be obtained. Sex-specific BW for GA z-scores were calculated for each participant using a U.S. reference, which was selected because it was updated recently and uses obstetric estimates of GA at birth (Aris et al. 2019).

2.4 Covariates

Information on the highest attained maternal education and parity were determined using questionnaires administered during pregnancy (MADRES, PROTECT) or at enrollment (NHBCS). As the majority of NHBCS and PROTECT participants had completed some college, a collapsed attained maternal education variable with two categories was created for all cohorts: completed some college versus did not complete any college. Parity was also collapsed into three categories: first pregnancy, second pregnancy, and third or higher pregnancy. Information on maternal smoking during the pregnancy was obtained by questionnaires administered during pregnancy (MADRES, PROTECT) or postpartum (NHBCS). Information on secondhand smoke exposure during the pregnancy was obtained by questionnaires administered during pregnancy (MADRES, PROTECT) and, for the NHBCS, also at enrollment. For each cohort, a combined variable was created for any *in utero* tobacco smoke exposure during pregnancy, which was defined as any maternal or secondhand tobacco smoke exposure. For MADRES, maternal pre-pregnancy BMI was calculated using the participant's self-reported pre-pregnancy weight, obtained by a questionnaire administered during pregnancy, and standing height, which was measured twice by stadiometer (Perspectives Enterprises Model PE-AIM-101). For the NHBCS, pre-pregnancy BMI was computed using maternal height values abstracted from the medical records and usual weight when not pregnant. If this information was not available from the medical records, self-reported values from the prenatal or postpartum questionnaires were used. For PROTECT, pre-pregnancy BMI was calculated using self-reported pre-pregnancy weight and height measures, obtained at the first study visit.

2.5 Statistical Analyses

Urinary metals were $\log_2$-transformed, mean-centered, and standard deviation scaled prior to inclusion in statistical analyses. Descriptive statistics were calculated for each exposure, outcome, and covariate. Pearson correlations were used to evaluate pairwise relationships between metal concentrations. Bayesian Kernel Machine Regression (BKMR) was used to simultaneously investigate associations between the seven selected metals (Cd, Co, Hg, Mo, Ni, Sb, Sn) and BW for GA z-scores, using the "bkmr" package in R (Bobb et al. 2018). BKMR is a flexible method that can identify mixture components of importance, cumulative mixture impacts, and both synergistic and antagonistic interactions between mixture components in the context of correlated exposures, allowing for non-linear exposure-response relationships (Bobb et al. 2015). 100,000 posterior samples of model parameters were obtained using a Markov chain Monte Carlo (MCMC) sampler. Model convergence was inspected using trace plots. The default noninformative priors specified in

the R package were used for primary analyses (Bobb et al. 2018). For each BKMR model, the difference in BW for GA z-score and corresponding 95% credible interval was estimated for a change in each metal from its 25th to 75th percentile, holding all other metals constant at their medians. Individual mixture component associations with BW for GA were ranked using posterior inclusion probabilities (PIPs). Potential interactions between metal pairs and cumulative mixture impacts (i.e., difference in BW for GA for a simultaneous increase in quantiles of all metals) were also investigated. In secondary analyses, models were stratified by cohort and infant sex. As interactions between metals and categorical variables cannot be investigated formally using BKMR, we also ran single-metal traditional linear regression models using metal*cohort and metal*sex cross product terms to examine whether any of the metal and BW for GA associations differed significantly ($P<0.05$) by cohort or infant sex.

We also ran a series of sensitivity analyses. Given that BKMR can be sensitive to the choice of prior distributions, we first investigated whether results from the primary model were robust to alternative prior assumptions, as described previously (Howe et al. 2020b, 2020a). Specifically, we compared both a higher (b=1000) and lower (b=50) degree of smoothness for the exposure-response relationships. For the model investigating the lower degree of smoothness, 200,000 posterior samples of model parameters were obtained, as this model did not converge after 100,000 iterations. As BKMR can be sensitive to the random seed selected for initializing the MCMC (Nunez et al. 2021), we also ran a sensitivity analysis varying the seed to evaluate whether results were similar. For a subset of participants (10.4%), urine collection for metals assessment did not occur until the second half of pregnancy (≥20 weeks gestation); we therefore also compared results after excluding these individuals. Finally, since adjusting for GA at birth through the generation of BW for GA z-scores can potentially induce collider bias if it is an intermediate between the exposure and outcome, we ran a BKMR model which evaluated GA at birth as the outcome to evaluate its association with each metal (Wilcox et al. 2011).

Metals which did not reach the detection thresholds (above the LOD for ≥60% of participants) for inclusion in the BKMR (Cr and U) were investigated separately using pooled traditional linear regression models. These metals were evaluated as binary variables (i.e., ≥ vs < the LOD), and associations with a p-value<0.05 were considered statistically significant.

Potential confounders and precision variables were determined using a directed acyclic graph (Figure S2). Final models were adjusted for maternal age, maternal pre-pregnancy BMI, maternal education, parity, *in utero* tobacco smoke exposure, GA at urine collection, and cohort (for the primary and sex-stratified models). Fish/seafood consumption, prenatal vitamin use, and maternal anemia were also identified as potential confounders in our directed acyclic graph but could not be included as covariates in statistical models due to a high proportion of missingness in one or more cohort and/or the inability to harmonize the variable across the three cohorts. Although maternal race/ethnicity was also identified as a potential confounder, 93% of participants in the NHBCS identified as non-Hispanic white and >99% of PROTECT participants identified as Hispanic. We were therefore unable to adjust for this variable in statistical models. However, cohort was included as a covariate to

account for these and other differences across the three study populations. In preliminary analyses, results were similar when including cohort as a random intercept versus as a fixed effect. Cohort was therefore modeled as a fixed effect, as it more stringently controls for potential confounding by cohort and is recommended when the pooled sample size exceeds 500 (Basagaña et al. 2018).

3. Results

A total of 350 participants from MADRES, 184 participants from the NHBCS, and 468 participants from PROTECT contributed to the pooled analysis. The majority of participants from MADRES (78.9%) and PROTECT (99.6%) identified as Hispanic, while the majority of participants from the NHBCS (96.7%) identified as non-Hispanic. Additional characteristics of participants from each cohort are shown in Table S2. On average, NHBCS participants were older, and MADRES participants were more likely to be obese and less likely to have completed any college (Table S2). MADRES participants were also more likely to report that they were in their third or higher pregnancy, and their infants were less likely to have been exposed *in utero* to tobacco smoke (Table S2). On average, urine collection for metals assessment occurred later in pregnancy for PROTECT participants, and the prevalence of *in utero* tobacco smoke exposure was highest among PROTECT infants (Table S2). Although BW for GA differences by cohort were small, they were statistically significant; on average, NHBCS participants had the highest BW for GA z-scores and PROTECT participants had the lowest BW for GA z-scores (Table S2). Participants included in the pooled analysis were generally similar to the larger cohorts from which they were sampled, although there was a lower percentage of women who had previously been pregnant at least twice in the NHBCS and PROTECT subsets (Table S3).

Descriptive characteristics of the pooled sample (N=1,002) are shown in Table 1. On average, women were 28.6 (SD: 5.7) years of age at enrollment and contributed a urine sample for metals analysis at 15.3 (SD: 4.0) weeks gestation. More than half of the participants were either overweight (29%) or obese (24.1%). Three-quarters (74.5%) of participants identified as Hispanic, and the majority (70.6%) reported completing some college. Most women (42.8%) were pregnant with their first child, while 37.6% reported that this was their second pregnancy, and 19.6% reported that this was their third or higher pregnancy. Slightly more than half (51.7%) of infants were male, and 86.7% did not experience any *in utero* tobacco smoke exposure.

Urinary metal concentrations for the pooled sample are shown in Table 2 and separately by cohort in Table S4. For most metals, concentrations exceeded the LOD for >75% of study participants with the exceptions of Cr and U, which were detectable in only 15% and 34% of participants, respectively. On average, urinary metal concentrations were lowest among the NHBCS participants (Table S4). Co, Mo, Ni, and Sn were highest among the PROTECT participants, while Cd and Hg were highest among the MADRES participants (Table S4).

Urinary Sb concentrations were generally similar for MADRES and PROTECT participants, although the range was wider for MADRES participants (Table S4). In the pooled sample, Pearson correlations between the urinary metals were uniformly positive and generally

modest in magnitude, with somewhat larger correlations observed between Co and Ni, Co and Sn, and Ni and Sn (Figure 1). Urinary metal correlations are also shown stratified by cohort in Figure S3. For all three cohorts, positive correlations were generally observed between metal pairs, although in MADRES inverse correlations were observed for the following metal pairs: Cd and Hg, Co and Hg, Sb and Hg.

In the pooled sample, the BKMR PIPs ranked Co and Sb most highly with respect to their associations with BW for GA (Table 3). A reverse j-shaped association was identified for Co, while an inverse linear association was identified for Sb (Figure 2). Inverse linear associations were also identified for Hg and Sn, and a positive linear association was identified for Ni (Table 3, Figure 2). The difference in BW for GA for a 25^{th} to 75^{th} percentile change in each metal is shown in Table 3. Among metals that were linearly associated with BW for GA, the magnitude of association was strongest for Ni. A change in Ni from its 25^{th} to 75^{th} percentile was associated with a 0.15 (95% CI: −0.01, 0.30) SD difference in BW for GA z-score. BKMR results were similar when varying the random seed (Figure S4) and were generally similar when varying the model priors, although evidence of overfitting was observed for Co and Ni when specifying a lower degree of smoothness (b=50) (Figure S5). Patterns of association were also similar when restricting to participants with urinary metals measured at <20 weeks gestation (Figure S6). Visually, we did not observe strong evidence of interactions between metal pairs (Figure S7) or a cumulative association between the overall metal mixture and BW for GA (Figure 3). For most metals, associations with GA at birth were null (Figure S8). However, a positive association was observed between Hg and GA at birth (Figure S8).

Many of the metal-BW for GA associations identified using BKMR appeared to vary by cohort (Table S5 and Figure S9). For example, Co was inversely associated with BW for GA in the NHBCS (effect estimate (95% CI): −0.35 (−0.60, −0.10)) but positively in PROTECT (effect estimate (95% CI): 0.19 (0.03, 0.35)). The association between Sn and BW for GA also appeared to vary by cohort. Sn was inversely associated with BW for GA in MADRES, whereas a positive trend was observed in the NHBCS, and a null association was observed in PROTECT (Table S5, Figure S9). Hg and Ni associations with BW for GA were consistent for MADRES and PROTECT, with inverse associations observed for Hg and positive associations for Ni. In contrast, associations between these metals and BW for GA were null in the NHBCS. Sb was consistently inversely associated with BW for GA in all three cohorts, with the strongest association observed in MADRES and the weakest association observed in PROTECT (Table S5, Figure S9). For example, a change in Sb from its 25^{th} to 75^{th} percentile was associated with a −0.18 (95% CI: −0.36, −0.01) SD difference in BW for GA z-score in MADRES compared with a −0.05 (95% CI: −0.17, 0.07) SD difference in BW for GA z-score in PROTECT (Table S5). The association between Cd and BW for GA was null for all three cohorts (Table S5, Figure S9). Notably, BW for GA z-scores and urinary concentrations of all seven metals differed by cohort (Table S2, Table S4, Figure S9). In single-metal traditional regression models, we identified a significant interaction between Co and cohort (P=0.03 comparing MADRES to the NHBCS and P<0.01 comparing PROTECT to the NHBCS) (Table S6). Other metal*cohort cross product terms were not statistically significant (P≥0.05) (Table S6).

Sex-stratified BKMR results are presented in Table S7 and Figure S10. BKMR PIPs ranked Co and Sn most highly for females and Hg and Sb most highly for males with respect to their associations with BW for GA (Table S7). Among female infants, an inverse and linear association was identified between Sn and BW for GA and a U-shaped association was identified between Co and BW for GA. In contrast, these associations appeared null among male infants. Holding all other metals in the mixture constant at their medians, a change in Sn from its 25th to 75th percentile was associated with a −0.15 (95% CI: −0.34, 0.04) SD difference in BW for GA among females compared with a −0.01 (95% CI: −0.20, 0.18) SD difference among males. A positive linear association between Ni and BW for GA was observed in both males and females, although this association appeared to be somewhat stronger among females (Figure S10). Holding all other metals in the mixture constant at their medians, a change in Ni from its 25th to 75th percentile was associated with a 0.15 (95% CI: −0.06, 0.36) SD difference in BW for GA among females compared with a 0.08 (95% CI: −0.13, 0.29) SD difference among males. An inverse linear association between Sb and BW for GA was also observed in both males and females, with similar effect estimates for the two groups (Table S7, Figure S10). Urinary metal concentrations did not differ for women carrying male compared with female infants (P≥0.05) (Figure S10). In single-metal traditional regression models, none of the metal*sex cross product terms were statistically significant (P≥0.05) (Table S8).

In pooled traditional linear regression models, associations between Cr and U, evaluated as binary variables (above versus below the LOD), and BW for GA z-scores were null (Cr β (95% CI): 0.05 (−0.14, 0.24); U β (95% CI): −0.01 (−0.15, 0.13)).

4. Discussion

Using a flexible environmental mixture modeling approach, we simultaneously evaluated associations between urinary concentrations of seven metals (Cd, Co, Hg, Mo, Ni, Sb, and Sn) and BW for GA in a pooled analysis of three cohorts participating in the ECHO Program. We did not observe a cumulative impact of the overall metal mixture on BW for GA. However, we identified potential associations between several metals and BW for GA after accounting for co-exposure to other metals in the mixture. Inverse associations with BW for GA were identified for Hg, Sb, and Sn, while a positive association was identified for Ni, and a reverse j-shaped association was identified for Co. Associations for Cd and Mo were consistently weak or null across models. In stratified analyses, an inverse association between Sb and BW for GA was observed for each of the participating cohorts. This association was strongest in MADRES and was relatively weak in the NHBCS and PROTECT. In contrast, associations for Co, Hg, Ni, and Sn appeared to vary by cohort. In sex-stratified analyses, possible associations between Co and Sn with BW for GA were identified in female, but not male infants.

Of the nine metals evaluated in our pooled analyses, Cd and Hg have been studied most extensively. Prior studies have largely reported adverse impacts of Cd on fetal growth (Huang et al. 2019). However, results for this metal were consistently null in our analysis. This may be due to the relatively low Cd levels in our pooled sample (median 0.13 μg/L), as studies of pregnant women in China and Bangladesh with higher Cd exposures (median

maternal urinary Cd concentrations of 0.54 and 0.63 μg/L, respectively) have reported inverse associations between this metal and size at birth (Cheng et al. 2017; Kippler et al. 2012). Interestingly, most studies of Hg and fetal growth have measured Hg concentrations in whole blood, which primarily reflects methylHg, yet these studies have largely reported inverse associations with fetal growth, consistent with our findings for urinary Hg, which predominantly reflects inorganic Hg (Branco et al. 2017; Kim et al. 2017, 2020; Ramón et al. 2009; Sabra et al. 2017; Thomas et al. 2015; Vigeh et al. 2018).

Far fewer studies have investigated Sn's or Sb's impacts on fetal growth, but inverse associations have been reported between these metals and fetal growth, consistent with the results from our pooled analysis (Cabrera-Rodríguez et al. 2018; Kim et al. 2020; Shirai et al. 2010). The impacts of Co on fetal growth are also understudied, but two larger studies have identified positive associations with fetal growth at low concentrations and the opposite pattern at high concentrations (Hou et al. 2019; Mikelson et al. 2019). A non-linear relationship between Co and BW for GA was similarly identified in our pooled analysis. However, in contrast with prior studies, we observed a reverse j-shaped association which may have been driven by cohort differences.

While many studies evaluating Ni's impacts on fetal growth have been null, several studies have reported associations between Ni and reduced risk of small for gestational age or positive associations with fetal growth, consistent with our results (Deyssenroth et al. 2018; Jalali and Koski 2018; Vaktskjold et al. 2007). Although Ni is not an essential metal, it may have nutritional benefits. For example, evidence from both animal and human studies suggest that Ni can reverse vitamin B12 deficiency and elevated homocysteine, which are risk factors for reduced fetal growth (Hogeveen et al. 2012; Katko et al. 2008; Nielsen et al. 1993; Rogne et al. 2017; Stangl et al. 2000). Rodent studies have also demonstrated that Ni supplementation, in combination with vitamin B12, promotes growth (Nielsen et al. 1993).

Given that Cr and U concentrations fell below their LODs for a large portion of the pooled sample, they were evaluated individually as binary variables in traditional linear regression models. Associations with BW for GA were null for both metals. Prior studies evaluating U and fetal growth have also been null (Cabrera-Rodríguez et al. 2018; Deyssenroth et al. 2018; Zhang et al. 2020). However, results for Cr have been mixed, with several studies reporting inverse associations and others reporting null associations, possibly due to differences in the biomarkers evaluated and the exposure ranges represented (Bank-Nielsen et al. 2019; Cabrera-Rodríguez et al. 2018; Deyssenroth et al. 2018; Freire et al. 2019; Jalali and Koski 2018; Peng et al. 2018; Xia et al. 2016),

A growing number of studies have reported sex-specific associations between metals and fetal growth (Freire et al. 2019; Huang et al. 2019; Peng et al. 2018; Tatsuta et al. 2017), including a recent meta-analysis which concluded that Cd is inversely associated with birthweight among female, but not male infants (Huang et al. 2019). Although results for Cd were consistently null in our pooled analyses, possible sex differences were observed for Co and Sn. For both metals, associations with BW for GA were observed in female infants only, with a U-shaped association identified for Co and an inverse linear association identified for Sn. As urinary concentrations of Co and Sn were similar for women carrying male and

female infants, these sex-specific associations cannot be attributed to differences in maternal exposure. To our knowledge, only one study has investigated Co-fetal growth associations separately by sex, but no differences were observed (Mikelson et al. 2019), and we are not aware of any studies investigating possible sex differences in the association between Sn and fetal growth. Although we cannot rule out the possibility that these sex-specific associations may be chance findings, especially given that metal*sex cross product terms from traditional regression models were not statistically significant, there are several plausible mechanisms that could explain differential impacts on growth, including sex differences in the placental transfer of metals, metal metabolism, and placental function (Clifton 2010; Gabory et al. 2013; Li et al. 2019; Rosenfeld 2015; Vahter et al. 2007).

Many of the metal-growth associations also appeared to vary by cohort. Although these differences may be driven by a variety of factors, one potential explanation is the variability in metal distributions across the three cohorts, which may reflect different portions of the dose-response curve. For example, inverse associations between Hg and BW for GA were observed for both MADRES and PROTECT, which had similar urinary Hg concentrations (MADRES range: 0.06–16.33 μg/L, PROTECT range: 0.02–24.50 μg/L). However, this association was null in the NHBCS, possibly due to the lower and narrower range of urinary Hg (0.00–3.00 μg/L). The most pronounced cohort difference was observed for Co, with negative, null, and positive associations observed for the NHBCS, MADRES, and PROTECT, respectively. Consistent with this finding, we identified a significant Co*cohort interaction in traditional linear regression models. Although Co levels varied by cohort, with the three cohorts generally representing low, moderate, and high Co concentrations, respectively, this is unlikely to explain the heterogeneity in the Co-growth associations, as essential metals typically demonstrate protective effects at low concentrations and toxic effects at high concentrations (Dror et al. 2018). A more plausible explanation is therefore differences in population characteristics, which may modify Co's impacts on fetal growth. Differences in unmeasured co-pollutants and confounders may also explain some of the heterogeneity in the metal-fetal growth relationships, as exposure sources likely differ for the three cohorts given their distinct geographic locations.

The urban locations of MADRES and PROTECT may have contributed to the higher Sb concentrations observed in these cohorts, as traffic-related air pollution from brake wear and tear is an importance source of Sb exposure, as are smelters, coal-fired plants, and waste incinerators (Belzile et al. 2011; Fort et al. 2016). In contrast, bottled water may be a relevant source of Sb exposure for all three cohorts, as this metalloid is used as a catalyst in the production of polyethylene terephthalate (Belzile et al. 2011). Hg concentrations were also higher in MADRES and PROTECT compared with the NHBCS, likely due to differences in diet and other behavioral patterns, as urinary Hg can reflect a mixture of demethylated methylHg from fish and seafood consumption in addition to elemental and inorganic Hg exposure from dental amalgams and the use of certain cosmetics and personal care products (Copan et al. 2015; Du et al. 2021; Peregrino et al. 2011). Urinary Sn concentrations were highest in PROTECT. However, while canned food and seafood consumption are important sources of Sn exposure in the general population, prior studies in PROTECT indicate that these dietary factors do not explain the higher urinary Sn concentrations in this cohort (Ashrap et al. 2020b). Co concentrations also varied by

cohort. Most individuals are exposed to Co through their diet, although tobacco smoke exposure has also been identified as a possible source of exposure in PROTECT (Ashrap et al. 2020b; Faroon and Keith 2004). In urban areas, air pollution also contributes to Co exposure due to municipal waste incineration and fossil fuel combustion, which may explain the higher urinary Co concentrations observed in MADRES and PROTECT compared with the NHBCS (Faroon and Keith 2004). Future studies which identify specific metal exposure sources for these diverse populations will be critical for better understanding the heterogeneity in our findings and designing the most effective public health interventions.

Although the biological pathways which contribute to metal impacts on fetal growth are largely unknown, several general mechanisms may be relevant to multiple metals and merit future investigation. Such mechanisms include alterations in inflammation, oxidative stress, and angiogenesis/endothelial function, which impact placental structure and function and consequently the transfer of nutrients and oxygen to the fetus (Dimasuay et al. 2016; Kirshenbaum et al. 2021; Schoots et al. 2018). Incorporating markers of oxidative stress and vascular function is therefore an important next step for mechanistic research. A growing body of evidence also suggests that metals perturb epigenetic programming, which may have important consequences for fetal growth (Bommarito et al. 2017; Küpers et al. 2019). Investigating epigenetic mediators of metal-growth relationships, especially in the context of complex mixtures, is therefore also a promising avenue for understanding metal impacts on fetal growth. Importantly, many metals (e.g., Hg, Mo, Ni, Sb, Sn) can also cross the placenta and thus directly impact fetal metabolism and growth (Gundacker and Hengstschläger 2012). Investigating the mechanisms which contribute to the placental transfer of metals is also a key area for future research, which requires the collection of complementary samples, such as placental tissue and cord blood.

The current study was strengthened by its prospective design; the large sample size; the evaluation of multiple metals; our use of an environmental mixture modeling approach; and our inclusion of participants from diverse geographic areas within the U.S., the majority of whom (74.5%) identify as Hispanic, a group that has been historically underrepresented in epidemiologic research. However, there are also several important limitations. First, while the metals selected for the current study can be reliably measured in urine, it is important to note that their half-lives differ, with urinary concentrations of some metals (e.g., Co, Mo, Ni, Sb, Sn) reflecting exposures that occurred over the past few days to weeks and others reflecting exposures over the past several months (e.g., Hg) or decades (e.g., Cd) (ATSDR 2019; Basu et al. 2018; Faroon and Keith 2004; Fay 2005; Harper 2005; Tallkvist and Oskarsson 2014; Todd et al. 2020; Vacchi-Suzzi et al. 2016; Ye et al. 2016). Many metals also exist in multiple chemical forms which are differentially excreted into urine. For example, urinary Hg predominately reflects inorganic Hg and is therefore a reasonable biomarker of inorganic and elemental Hg but is less useful as a biomarker of methylHg (Basu et al. 2018). Another limitation of our study was the inability to adjust for potential dietary confounders due to data missingness and differences in how dietary information was acquired for the three participating cohorts. An important dietary confounder that we could not adjust for was fish and seafood consumption. Fish and seafood are sources of Hg and Sn, as well as nutrients that promote growth; thus, fish and seafood consumption is likely a negative confounder which would have biased associations between these metals and BW

for GA toward the null. An additional consideration is that several additional metals which may also impact fetal growth, such as arsenic, manganese, and lead, were excluded from our study, either because urine is not a suitable matrix or because the metal was not measured in all three cohorts (e.g., speciated arsenic was not available for PROTECT). These metals could potentially confound some of the metal-BW for GA associations identified in our study. It is also important to note that while associations between six of the seven metals and GA at birth were null, a positive association was identified between Hg and GA at birth. We therefore cannot rule out the possibility that the inverse association between Hg and BW for GA may be impacted by collider bias (Wilcox et al. 2011). Finally, it is important to note that the MADRES and PROTECT cohorts are predominantly Hispanic, while the NHBCS is predominantly non-Hispanic white, which precluded our ability to adjust for or investigate potential differences by race or ethnicity. However, by adjusting for and stratifying by cohort, we may have indirectly accounted for some of these differences.

5. Conclusions

Pooling data from three geographically and demographically diverse cohorts participating in the ECHO Program and using a flexible mixture modeling approach, we identified inverse associations for Hg, Sb, and Sn; a positive association for Ni; and a non-linear association for Co in relation to BW for GA. For many of these metals, associations appeared to vary by cohort and/or sex. However, the inverse association between Sb and BW for GA was consistently observed across all three cohorts and in both males and females, which suggests that this understudied metalloid may adversely impact fetal growth. Future studies are needed to identify the major sources of Sb exposure for these populations and to better understand the heterogeneity observed for other metal-fetal growth associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BKMR	Bayesian Kernel Machine Regression

BW	birth weight
Cd	cadmium
CHEAR	Children's Health Exposure Analysis Resource
Co	cobalt
Cr	chromium
ECHO	Environmental Influences on Child Health Outcomes
GA	gestational age
Hg	mercury
LOD	limit of detection
MADRES	Maternal and Developmental Risks from Environmental and Social Stressors
MCMC	Markov chain Monte Carlo
Mo	molybdenum
NHBCS	New Hampshire Birth Cohort Study
Ni	nickel
PIP	posterior inclusion probability
PROTECT	Puerto Rico Testsite for Exploring Contamination Threats
Sb	antimony
Sn	tin
U	uranium

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Highlights

- Mercury, antimony, and tin were inversely associated with fetal growth
- Nickel was positively associated with fetal growth
- A non-linear association was identified between cobalt and fetal growth
- Associations were null for cadmium, chromium, molybdenum, and uranium

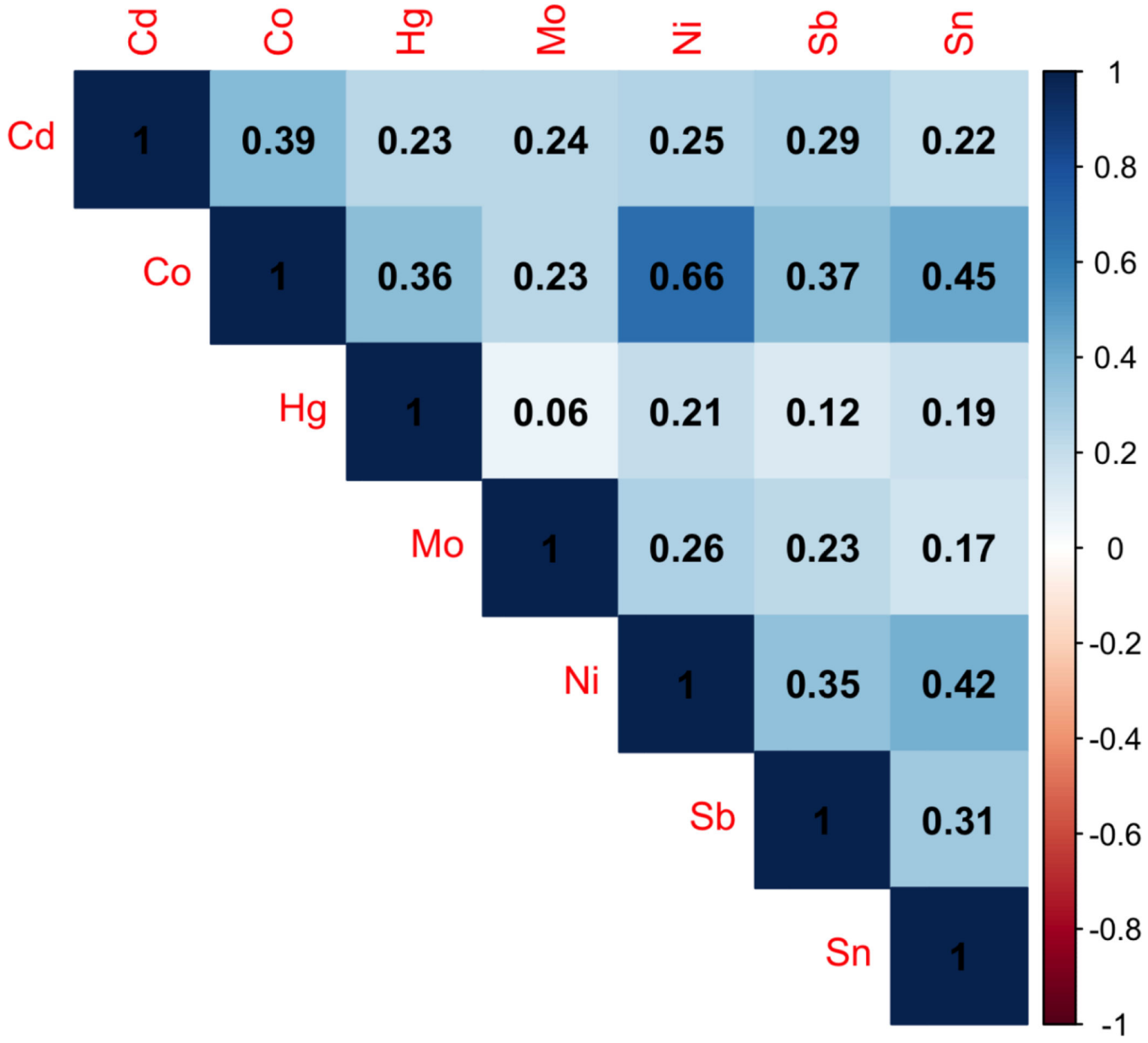

Fig. 1.

Pearson Correlations between Urinary Metal Pairs for the Pooled Sample (N = 1,002). Positive correlations are indicated in blue and negative correlations in red. Darker shades indicate stronger correlations. Numeric cor-relation coefficients are overlaid on the plot. All pairwise correlations were statistically significant ($P < 0.05$). Urinary metals were adjusted for specific gravity to account for urine dilution and $\log_2$-transformed. Abbreviations: Cd, cadmium; Co, cobalt; Hg, mercury; Mo, molybdenum; Ni, nickel; Sb, antimony; Sn, tin. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

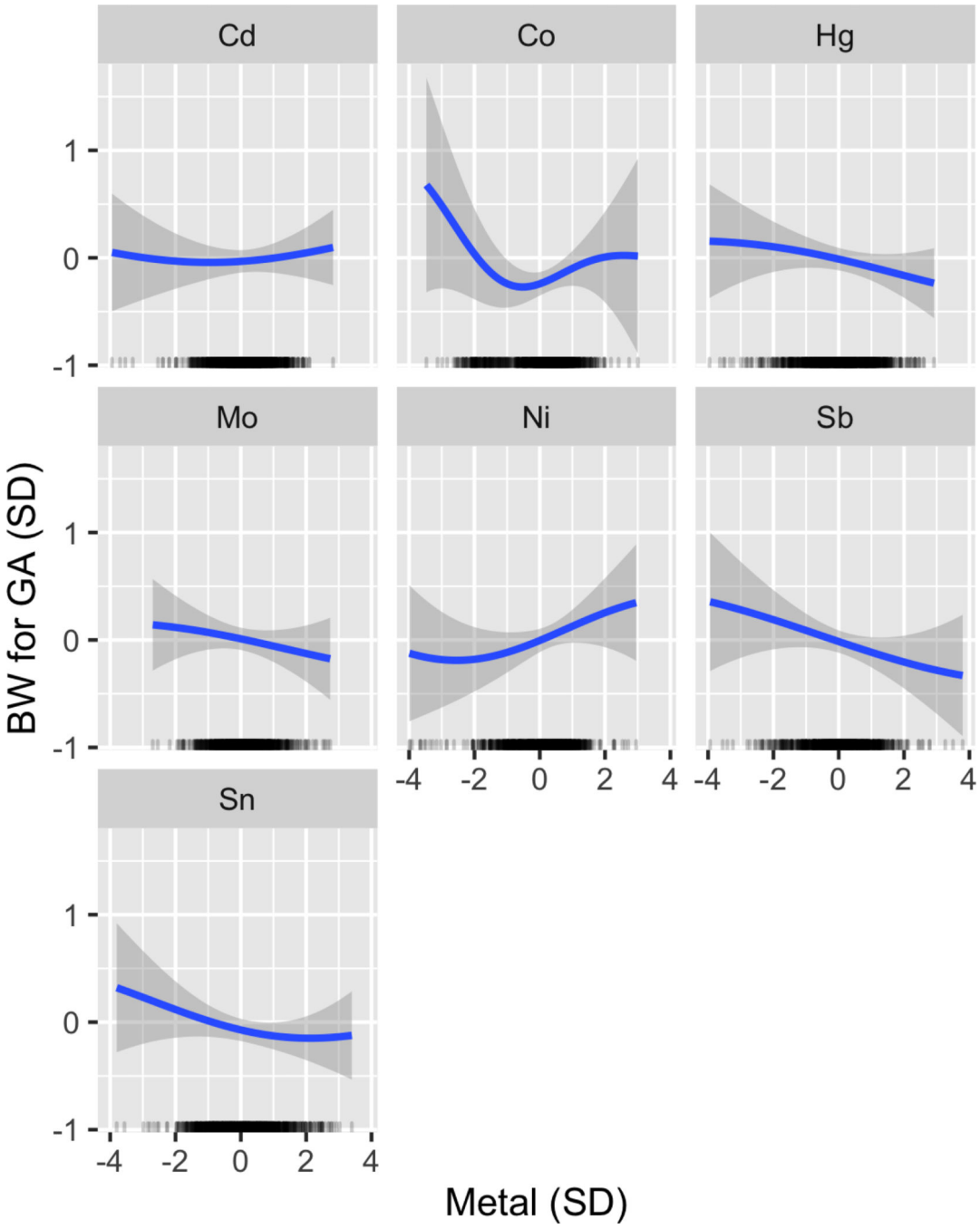

Fig. 2.

BKMR Metal-BW for GA Associations (N = 1,002). Each panel shows the association between the speciified metal and BW for GA, holding all other metals in the mixture at their median and adjusting for maternal age, pre-pregnancy BMI, education, parity, gestational age at urine collection, in utero tobacco smoke exposure, and cohort. Abbreviations: BKMR, Bayesian Kernel Ma-chine Regression; BW for GA, birth weight for gesta-tional age; Cd, cadmium; Co, cobalt; Hg, mercury; Mo, molybdenum; Ni, nickel; Sb, antimony; Sn, tin.

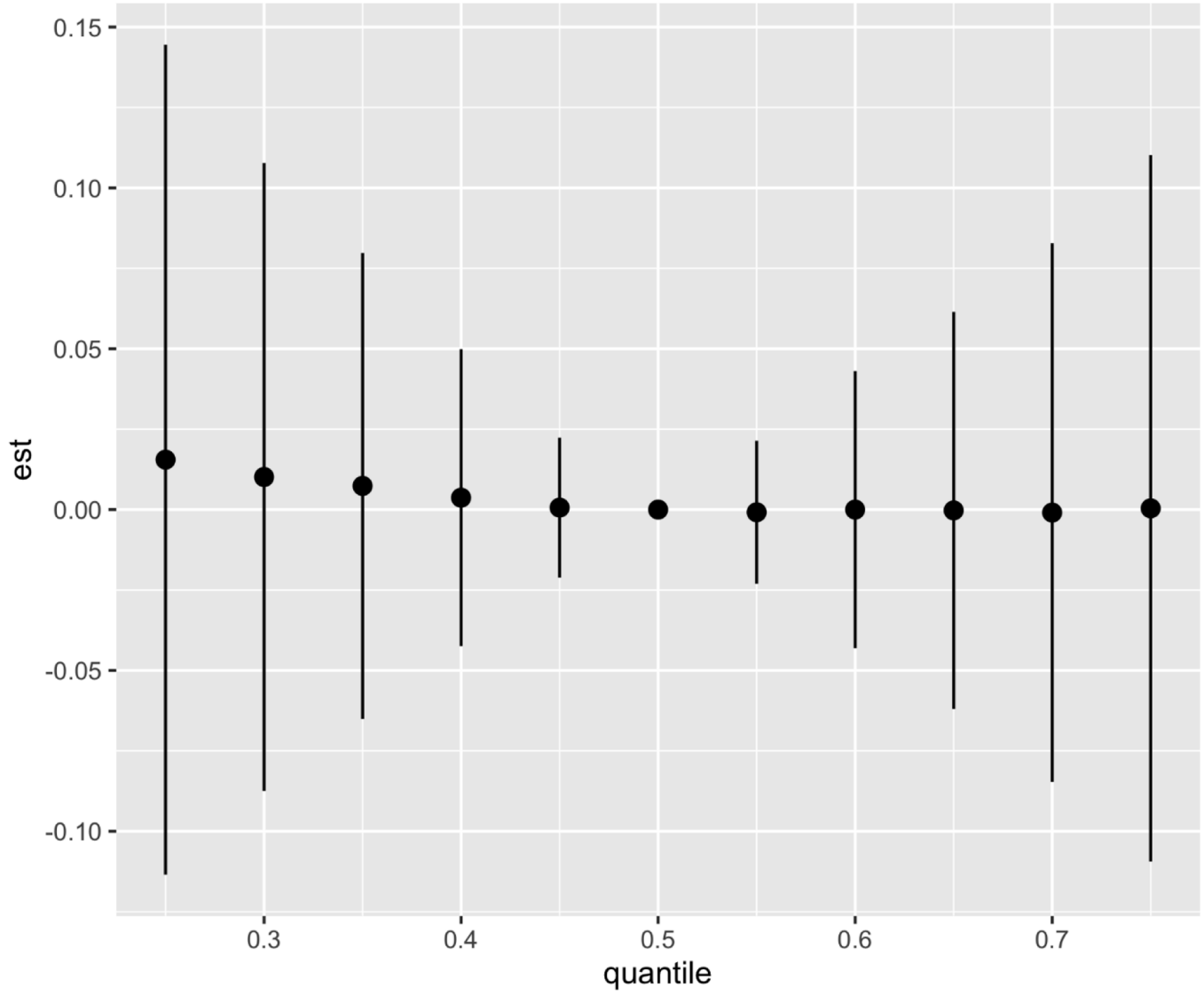

Fig. 3.

BKMR Cumulative Metal Mixture Association with BW for GA (N = 1,002). The y-axis shows the estimated difference in BW for GA when setting all metals to the quantile specified on the x-axis, compared with setting all metals to their median values. The BKMR model was adjusted for maternal age, pre-pregnancy BMI, education, parity, gestational age at urine collection, in utero tobacco smoke exposure, and cohort. Abbreviations: BW for GA, birth weight for gestational age.

Table 1.

Characteristics of the Pooled Sample (N=1,002)

	Mean ± SD or N (%)	Median (Range)
Maternal Characteristic		
GA Urine (weeks)	15.3 ± 4.0	16.0 (5.7–34.0)
Age (years)	28.6 ± 5.7	28.5 (18.0–45.5)
Pre-Pregnancy BMI (kg/m^2)	26.6 ± 6.2	25.6 (13.2–53.9)
Pre-Pregnancy BMI category		
Underweight (<18.5 kg/m^2)	42 (4.2%)	
Normal weight (18.5 to <25 kg/m^2)	423 (42.2%)	
Overweight (25 to <30 kg/m^2)	296 (29.5%)	
Obese (≥30 kg/m^2)	241 (24.1%)	
Ethnicity		
Non-Hispanic	254 (25.3%)	
Hispanic	746 (74.5%)	
Did Not Report	2 (0.2%)	
Educational Attainment		
Did Not Complete Any College	295 (29.4%)	
Completed Some College	707 (70.6%)	
Parity		
First Pregnancy	429 (42.8%)	
Second Pregnancy	377 (37.6%)	
Third or Higher Pregnancy	196 (19.6%)	
Infant Characteristic		
BW for GA Z-Score (SD)	−0.08 ± 1.10	−0.07 (−4.38–3.45)
BW (grams)	3280 ± 527	3310 (595–4904)
GA at Birth (weeks)	39.1 ± 1.6	39.2 (29.4–42.4)
Preterm Birth		
Yes (<37 weeks)	78 (7.8%)	
No (≥37 weeks)	924 (92.2%)	
Low Birth Weight		
Yes (<2500 grams)	61 (6.1%)	
No (≥2500 grams)	941 (93.9%)	
Sex		
Male	518 (51.7%)	
Female	484 (48.3%)	
In Utero Tobacco Smoke Exposure		
Any	134 (13.4%)	
None	868 (86.7%)	

Abbreviations: BW, birth weight; BW for GA, birth weight for gestational age; GA, gestational age

Table 2.

Urinary Metal Concentrations for the Pooled Sample

	N (%) ≥ LOD	Mean ± SD	Min	P5	P10	P25	P50	P75	P90	P95	Max
Cd, μg/L	752 (75.0)	0.19 ± 0.20	0.00	0.03	0.04	0.07	0.13	0.23	0.39	0.57	3.07
Co, μg/L	983 (98.1)	0.83 ± 0.71	0.02	0.09	0.13	0.39	0.73	1.07	1.51	1.91	9.82
Cr, μg/L	154 (15.4)	0.30 ± 0.42	0.00	0.01	0.04	0.10	0.22	0.36	0.61	0.94	7.36
Hg, μg/L	898 (89.6)	1.22 ± 1.94	0.00	0.07	0.12	0.28	0.65	1.42	2.64	3.91	24.50
Mo, μg/L	1002 (100.0)	71.2 ± 44.2	8.7	27.0	33.4	45.5	60.5	82.7	115.5	143.9	415.1
Ni, μg/L	870 (86.8)	4.6 ± 5.1	0.0	0.6	0.9	1.7	3.5	6.0	8.6	11.0	74.2
Sb, μg/L	920 (91.8)	0.10 ± 0.09	0.00	0.02	0.03	0.05	0.05	0.11	0.17	0.21	1.52
Sn, μg/L	920 (91.8)	2.4 ± 5.6	0.0	0.1	0.2	0.3	0.9	2.1	5.1	8.9	88.6
U, μg/L	339 (33.8)	0.02 ± 0.03	0.00	0.00	0.00	0.00	0.01	0.02	0.04	0.07	0.32

Abbreviations: Cd, cadmium; Co, cobalt; Cr, chromium; Hg, mercury; Mo, molybdenum; Ni, nickel; Sb, antimony; Sn, tin; U, uranium

Table 3.

BKMR Posterior Inclusion Probabilities and Effect Estimates for Each Metal in the Mixture

Metal	PIP	Effect Estimate (95% CI)
Cd	0.36	0.02 (−0.08, 0.13)
Co	0.68	0.12 (−0.06, 0.30)
Hg	0.44	−0.09 (−0.20, 0.03)
Mo	0.34	−0.05 (−0.15, 0.04)
Ni	0.49	0.15 (−0.01, 0.30)
Sb	0.62	−0.09 (−0.19, 0.01)
Sn	0.39	−0.09 (−0.22, 0.03)

Effect estimates reflect the difference in birth weight for gestational age z-score for a change in the specified metal from the 25^{th} to 75^{th} percentile, holding all other metals in the mixture at their median values and adjusting for maternal age, pre-pregnancy BMI, maternal education, parity, gestational age at urine collection, *in utero* tobacco smoke exposure, and cohort.

Abbreviations: BKMR, Bayesian Kernel Machine Regression; Cd, cadmium; Co, cobalt; Hg, mercury; Mo, molybdenum; Ni, nickel; PIP, posterior inclusion probability; Sb, antimony; Sn, tin