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Urinary trace metals individually and in mixtures in association with preterm birth

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ABSTRACT

One in ten infants born in the United States is born preterm, or prior to 37 weeks gestation. Exposure to elevated levels of metals, such as lead and arsenic, has been linked to higher risk of preterm birth (PTB), but consequences of lower levels of exposure and less studied metals are unclear. We examined the associations between 17 urinary trace metals individually and in mixtures in relation to PTB. The LIFECODES birth cohort enrolled pregnant women at < 15 weeks gestation at Brigham and Women's Hospital in Boston. We selected cases of PTB (n = 99) and unmatched controls (n = 291) and analyzed urine samples for a panel of trace metals (median: 26 weeks gestation). We used logistic regression models to calculate the odds ratio (OR) for PTB and subtypes of PTB based on presentation at delivery. Subtypes included spontaneous and placental PTB. We used elastic net (ENET) regularization to identify individual metals or pairwise interactions that had the strongest associations with PTB, and principal components analysis (PCA) to identify classes of exposures associated with the outcome. We observed increased odds of PTB (OR: 1.41, 95% Confidence Interval [CI]: 1.12, 1.78) in association with an interquartile range difference in urinary copper (Cu). We also observed an increased OR for selenium (OR: 1.33, 95% CI: 0.98, 1.81). ENET selected Cu as the most important trace metal associated with PTB. PCA identified 3 principal components (PCs) that roughly reflected exposure to toxic metals, essential metals, and metals with seafood as a common source of exposure. PCs reflecting essential metals were associated with increased odds of overall and spontaneous PTB. Maternal urinary copper in the third trimester was associated with increased risk of PTB, and statistical analyses for mixtures indicated that after accounting for correlation this metal was the most important statistical predictor of the outcome.

1. Introduction

Preterm birth (PTB), defined as birth prior to 37 weeks gestation, is one of the most important causes of neonatal morbidity and mortality and is associated with adverse health outcomes later in life (CDC, 2017). The Centers for Disease Control and Prevention (CDC) estimated that in 2016, one in ten infants in the United States was born preterm (CDC, 2017). Risk factors for PTB include, but are not limited to, maternal age, race, low socioeconomic status, illicit drug use, history of PTB, multiple pregnancy, pregnancy complications, and other medical disorders (Frey and Klebanoff, 2016; Goldenberg et al., 2008). PTB can be further classified into subtypes based on presentation at birth, and risk factors as well as mechanisms may differ between these subtypes (McElrath et al., 2008).

A growing body of evidence suggests associations between exposure to chemicals during pregnancy and an increased risk of PTB (Ferguson et al., 2013; Ferguson and Chin, 2017; Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; CHEAR, Children's Health and Exposure Assessment Resource; ENET, elastic net; GLM, generalized linear model; PCA, principal component analysis; PC, principal component; PTB, preterm birth; SG, specific gravity

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Outcomes, 2007; Simmons et al., 2010). For metals specifically, the evidence for the association between lead (Pb) and PTB is well-established (Cantonwine et al., 2010; Cheng et al., 2017; Jelliffe-Pawlowski et al., 2006; Perkins et al., 2014; Torres-Sanchez et al., 1999). Arsenic (As) and cadmium (Cd) exposure are also associated with increased risk of PTB (Ferguson and Chin, 2017). Most of these studies have examined populations with historically high exposure to metals, such as As in Bangladesh and Pb and Cd in China; as such, the findings may not predict effects in populations with lower levels of exposure (Myers et al., 2010; Wang et al., 2016; Yang et al., 2016).

Furthermore, most studies that have assessed the relationships between multiple metals and PTB have focused on single-pollutant models only (Shirai et al., 2010; Tsuji et al., 2018; Wai et al., 2017). Since exposures in humans never occur in isolation, it is an important next step to investigate multiple metals simultaneously (Braun et al., 2016; Claus Henn et al., 2014; Taylor et al., 2016). However, there is a small but growing number of analyses using advanced statistical methodologies to analyze metal mixtures and health outcomes to better understand aggregate effects or to identify “bad actors” within a correlated set of exposures (Bobb et al., 2015; Deyssenroth et al., 2018; Horton et al., 2018; Sanders et al., 2015; Valeri et al., 2017). These previous studies have used methods, such as Bayesian kernel machine regression (BKMR) and weight quantile sums (WQS) to explore metal mixtures in relation to health outcomes, however they have not been utilized in the study of PTB.

In the present study we analyzed a panel of 17 trace metals measured in urine samples from the 3rd trimester of pregnancy and estimated associations with PTB. In addition, because this study has the largest number of trace metal analytes to date to address this research question, we investigated the effects of mixtures using two approaches. First, we used elastic net (ENET) regularization to identify the individual metals and pairwise interactions from the mixture that are most strongly associated with PTB. Second, we used principal components analysis (PCA) to examine associations with correlated groupings.

2. Methods

The LIFECODES birth cohort, an on-going prospective cohort study originally designed to identify risk factors for preeclampsia, recruits pregnant women who are planning to deliver at Brigham and Women's Hospital in Boston, Massachusetts, USA. Women are enrolled and consented at < 15 weeks gestation and participate in four study visits (Cantonwine et al., 2016). At the first visit, participants complete a questionnaire providing demographic information, tobacco and alcohol use, and pregnancy as well as medical history. Urine samples are collected at up to four timepoints for each participant (median 10, 18, 26, and 35 weeks of gestation) and stored at −80 °C. The present analysis utilizes participants from a nested case-control study of PTB that includes women who were recruited from 2006 to 2008 (Ferguson et al., 2014). There were approximately 150 singleton preterm births and 1100 singleton term births recruited into the LIFECODES birth cohort during that period, and demographic characteristics of the overall cohort were very similar to those of the participants who were included in the case-control study (Cantonwine et al., 2016). The nested case-control study selected nearly all the cases of preterm birth as well as unmatched controls in a 3:1 ratio. Individuals from the case-control study were included in the present analysis if they had available urine samples from the third study visit.

Gestational age to determine preterm birth was calculated using the last menstrual period verified by ultrasound and two maternal-fetal medicine specialists. Preterm birth was defined as delivery before 37 weeks completed gestation. In addition, previous research suggests that cases of PTB differ by presentation at delivery. In a previous study of newborns born before 28 weeks gestation, deliveries with a spontaneous presentation (i.e., with preterm premature rupture of the membranes [PPROM] or spontaneous preterm labor) had similar placental characteristics indicative of inflammation (McElrath et al., 2008). Alternatively, PTB that occurred with presentation of intrauterine growth restriction or pre-eclampsia had evidence of poor placentation. Thus, in our study population, cases of PTB were further classified into spontaneous PTB (n = 46) and placental PTB (n = 22) for analysis based on these presentations at delivery. Cases that did not fall into either category were not examined separately, as we had no prior hypothesis about a unifying mechanism. The study was approved by the Institutional Review Board at Brigham and Women's Hospital and was deemed exempt by the University of Michigan and the National Institute of Environmental Health Sciences (NIEHS).

2.1. Urinary trace metals analysis

Urine samples from the visit at median 26 weeks gestation were analyzed at NSF International (Ann Arbor, MI, USA) as part of a pilot study for the Children's Health and Exposure Assessment Resource (CHEAR), a program designed to expand resources for analyzing environmental exposures in NIH-funded studies on children's health (Balshaw et al., 2017; NIEHS, 2018). Seventeen trace metals were analyzed on a Thermo Fisher (Waltham, MA, USA) ICAPRQ inductively coupled plasma mass spectrometry (ICPMS) and CETAC ASX-520 autosampler, including As, barium (Ba), beryllium (Be), Cd, copper (Cu), chromium (Cr), mercury (Hg), manganese (Mn), molybdenum (Mo), nickel (Ni), Pb, selenium (Se), tin (Sn), thallium (Tl), uranium (U), tungsten (W), and zinc (Zn). A PFA-ST nebulizer, quartz spray chamber, quartz torch, quartz injector tube, and nickel sample and skimmer cones were utilized in the analysis. An in-house method was developed based on the CDC Laboratory Procedure Manual for Urine Multi-Element ICP-DRC-MS (method no. 3018.3 and 3018A.2; revised 2012 March 19). The LOD was determined by calculating three times the standard deviation of the background level of the blanks. Additional methods on the analysis of trace metals are provided as Appendix 1 in the supplemental material.

Some metal concentrations below the limit of detection (LOD) were reported by the ICP-MS. These machine-reported values were kept as is and concentrations not reported by the ICP-MS were replaced with the LOD divided by the square root of two (Hornung and Reed, 1990). If a metal had > 70% of the participants below the LOD (i.e., either machine-reported or imputed), it was treated as detect versus non-detect in subsequent analyses. To account for urine dilution, we corrected for urinary specific gravity using the formula $M_{SG} = M\ [(1.015–1)/(SG-1)]$, where M_{SG} is the specific gravity-corrected metal concentration, M is the measured metal concentration in urine, 1.015 is the median specific gravity of all participants, and SG is the specific gravity for the individual sample (Ferguson et al., 2014).

2.2. Statistical analysis

We examined population characteristics and pregnancy-related variables of the cases and controls individually and overall, including maternal age, race/ethnicity, education, health insurance provider, pre-pregnancy body mass index (BMI), self-reported tobacco use during pregnancy, self-reported alcohol use during pregnancy, parity, use of assisted reproductive technology (ART), self-reported multivitamin use during pregnancy, and sex of the neonate.

We analyzed trace metal distributions by calculating geometric mean (GM) concentrations as well as 25th, 50th, 75th, and 95th percentiles. In addition, we calculated the median, 25th, and 75th percentile of the specific gravity-corrected metals concentrations in cases and controls separately. For those treated as detect versus non-detect, we calculated the number and percentage detected within each group. In addition to looking at the distribution of metals by case status, we calculated the GM by levels of demographic covariates and tested for differences between the groups using general linear models.

In our primary analysis, we used logistic regression models to