In utero metal exposures measured in deciduous teeth and birth outcomes in a racially-diverse urban cohort

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ABSTRACT

A growing number of studies have examined associations of metal exposures with birth outcomes, however, results from these studies have been inconsistent, and hampered by methodological limitations. We measured direct fetal exposure to three metals (lead, manganese and zinc) during the second and third trimester and examined its association with birth weight and gestational age at delivery. Participants in the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS), a population-based birth cohort established between September 2003 and December 2007, were invited to donate teeth to the study. Lead, manganese and zinc during the second and third trimesters were measured via high-resolution microspatial mapping of dentin growth rings, a validated biomarker for prenatal metal exposure. Gestational age at delivery and infant birth weight were obtained from the delivery medical record. A total of 145 children had tooth metal measurements and birth outcome data. Mean birth weight was $3431 \pm 472 \, g$ and mean gestational age at delivery was 39.0 ± 1.3 weeks. Overall, there was a positive association between second ($\beta = 0.21$, 95% CI: 0.05, 0.37, P = 0.01) and third trimester ($\beta = 0.21$, 95% CI: 0.05, 0.37, P = 0.01) tooth manganese and birth weight Z-score; this remained statistically significant after covariate adjustment. There was also a negative association between second trimester tooth lead level and birth weight Z-score ($\beta = -0.20$, 95% CI: -0.38, -0.02, P = 0.02), however, this was attenuated after adjusting for covariates. Mixture analysis revealed similar findings. There was evidence for a sex-specific effect of manganese with birth weight Z-score, with the association stronger in female compared to male infants. Overall, we found evidence suggesting that higher *in utero* manganese is associated with larger birth weight Z-scores and that these associations may vary by infant sex.

1. Introduction

In contrast to other developed countries, rates of preterm birth and low birth weight are among the highest in the United States, at 9.6% and 8%, respectively, in 2015 (Goldenberg et al., 2008; Martin et al., 2017). As they undergo rapid and complex development, fetuses are at increased susceptibility to negative health effects of environmental exposures, including toxic metals (Perera et al., 1999, 2002; Grason and Misra, 2009). Prenatal exposure to toxic metals such as lead and

atypical levels of essential metals such as manganese have been shown to be associated with adverse birth outcomes. In a large study in New York State, even low maternal blood lead levels were associated with decreased infant birth weight (Zhu et al., 2010). Similarly, manganese is also associated with lower birth weight, however, this appears to be a non-linear relationship, with both low and high maternal manganese levels associated with lower birth weight (Zota et al., 2009; Eum et al., 2014). Less is known about the association of the essential element zinc with birth outcomes; in a systematic review, lower maternal blood zinc

level was associated with lower birth weight, however, this was nearly entirely in populations where zinc deficiency is common, and the effects of excessive zinc levels could not be adequately studied (Wilson et al., 2016).

While studies have used surrogate measures of fetal exposures to metals (e.g. maternal blood sample or hair sample from pregnancy) or single measures of direct fetal exposure (cord blood), to our knowledge no study has examined if direct fetal exposure to metals in the second versus third trimester are associated with negative birth outcomes. We utilized elemental mapping of human primary teeth with laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) to examine an unbiased "map" of metal exposures (lead, manganese and zinc) during fetal development (Hare et al., 2011). This novel approach not only quantifies prenatal exposures, but also estimates the timing of the exposure (i.e. within trimester), as early as the 14th week of intrauterine development (Hare et al., 2011; Arora et al., 2012, 2006; Sabel et al., 2008). The goal of this study was to examine if there are associations of direct fetal exposure to lead, manganese and zinc, by trimester (second or third), with birth outcomes, including birth weight and gestational age at delivery in the racially and socioeconomically diverse Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) (Cassidy-Bushrow et al., 2012; Havstad et al., 2011; Wegienka et al., 2011).

2. Methods

2.1. Study population

WHEALS is a birth cohort study that recruited pregnant women with due dates from September 2003 through December 2007, who were seeing a Henry Ford Health System (HFHS) obstetrics practitioner at one of five clinics, were in their second trimester or later, were aged 21–49 years, and were living in a predefined geographic area in Wayne and Oakland counties that included the city of Detroit as well as the suburban areas immediately surrounding the city (Cassidy-Bushrow et al., 2012; Havstad et al., 2011; Wegienka et al., 2011). WHEALS originally included 1258 maternal-child pairs.

Details of the WHEALS Tooth Fairy Study have previously been reported (Cassidy-Bushrow et al., 2017). Briefly, advertisements for the WHEALS Tooth Fairy Study were placed in study newsletters, a save-the-tooth refrigerator magnet was sent in a holiday mailer to all participants, and families were asked if they wanted to donate a tooth for the study during planned recruitment phone calls for other WHEALS activities. A total of 373 teeth were received from 156 participants between December 2011 and January 2015. Teeth were selected for metal measurement if (1) the child had at least some outcome data available (birth outcomes and/or a 2-year clinic visit); and (2) the tooth was relatively intact. After excluding participants with missing data, the final sample sizes were 138 children with tooth metal measurements and birth weight data and 145 children with tooth metal measurements and gestational age at delivery data. All participants provided written, informed consent. Study protocols were approved by the HFHS Institutional Review Board.

2.2. Outcome measurement

Prenatal and delivery records for WHEALS mothers were abstracted to obtain birth weight and gestational age at delivery. Sex- and gestational-age adjusted birth weight Z-scores were calculated using the US population as a reference (Oken et al., 2003). Low birth weight was defined as a birth weight < 2500 g and preterm delivery was defined as gestational age at delivery < 37 weeks and are presented for descriptive purposes.

2.3. Covariate measurement

Maternal race, household income, marital status, exposure to environmental tobacco smoke (ETS), smoking during pregnancy, year home was built, and exposure to indoor pets prenatally were self-reported. Year residence was built was dichotomized as 1980 or after or before 1980, to indicate risk of lead exposure due to lead-based paint (Dixon et al., 2009). Address during pregnancy was recorded and used to define whether the fetus was mainly exposed to an urban residence (defined as within the confines of the city of Detroit) or a suburban residence. Prenatal and delivery records for WHEALS women were abstracted to obtain body mass index at the first prenatal care visit, prenatal hemoglobin levels, and delivery type. As done previously, prenatal maternal anemia was defined as the mother ever having a hemoglobin < 10.5 g/dL during the WHEALS pregnancy (Cassidy-Bushrow et al., 2017).

2.4. Analysis of metals in tooth samples

We directly measured metals in baby teeth using laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) and assigned developmental times as detailed elsewhere (Arora et al., 2012, 2014). Teeth were sectioned and the neonatal line (a histological feature formed in enamel and dentine at the time of birth) and incremental markings were used to assign temporal information to sampling points. Second and third trimester metal levels were distinguished using previously validated methods that rely on incremental markings in teeth (akin to growth rings in trees) (Arora et al., 2012, 2014). We used an ArF excimer laser ablation system (ESI, USA) attached to an Agilent Technologies 8800 triple-quad ICP-MS. Data were analysed as metal-to-calcium ratios (e.g. $^{208}Pb:^{43}Ca$) to control for variations in mineral content within a tooth and between samples. Samples were analysed in two batches. Tooth attrition, which is the amount of tooth lost due to grinding or wear, was also measured; teeth with excessive attrition that would impede the chemical analysis are excluded. National Institute of Standards and Technology SRM 612 was used for calibration and quality control. The detection limit was 0.05 µg/g for lead, zinc and manganese. Across all time points and metals < 5% are below the detection limit; values below the detection limit are excluded from statistical analysis.

A small number of children (N = 17) had two teeth analysed for quality control procedures; in these cases, metals levels were averaged over teeth within each child. We have previously shown moderate to high agreement in second and third trimester lead (intraclass correlation coefficient [ICC] = 0.55 for second trimester and ICC = 0.74 for third trimester) and manganese (ICC = 0.84 for second trimester and ICC = 0.59 for third trimester, after removing one tooth pair with a manganese outlier) in children with two tooth measures in the study (Cassidy-Bushrow et al., 2017). There was also good to excellent agreement in zinc measures from children contributing two teeth to the analysis (second trimester ICC = 0.82; third trimester ICC = 0.72).

2.5. Statistical analysis

Our primary outcomes of interest were the continuous variables birth weight Z-score and gestational age at delivery; normality assumptions were met. Each metal was centered and standardized within batch before statistical analysis. Differences in metal levels between the second and third trimester was examined with a paired *t*-test.

Linear regression modeling was used with birth weight Z-score and gestational age as separate outcomes and individual centered and standardized metal measures in the second and third trimesters as the exposures. Models were fit separately for the second and third trimester. All analyses were adjusted for batch, tooth attrition, and tooth type. Additional potential clinical and demographic confounders of birth weight Z-score and gestational age were incrementally added to

the model if they were potentially associated with birth outcomes and/ or metal levels, including race, maternal age, maternal anemia, urban residence, year the house was built and ETS (Institute of Medicine, 1985; Shiue and Bramley, 2015). Because many of these variables could also be considered to be on the causal pathway (i.e. urban residence, maternal anemia, maternal age, year the house was built, ETS) for the main analysis we fit models without (Model 2) and with (Model 3) these variables. In order to compare whether the effect of a metal in the second and third trimester was the same, a contrast statement of effect estimates from the second trimester and third trimester was used. Interaction terms and stratified models were also fit to explore potential differences by race and sex.

We used weighted quantile sum (WQS) regression to study the mixture effects of metals on birth outcomes. WQS was developed (Carrico et al., 2015) to assess mixture effects in a single coherent model, thereby minimizing Type 1 errors, while also quantifying the contribution of individual "bad actors" among a multitude of correlated exposures. This is done by the calculation of a weighted index, $WQS = \sum w_j q_{ij}$, which integrates an empirically-estimated weight (w) for each exposure variable (j) with the ranked concentration of that exposure per subject (q_{ij}). The WQS index calculated for each subject thus captures the extent of their exposure to a chemical mixture, and the significance of this mixture with respect to health outcomes can be tested in the standard linear model $Y_i = \alpha_0 + \beta_1 WQS + \alpha_1 X_i + \varepsilon_i$, with a powerful single degree of freedom test of the significance of β_1 measuring the "mixture effect" related to the health outcome Y_i. The model intercept, α_0, and parameters for covariates, $\alpha_1 X_i$, and model error, ε_i, are interpreted as in standard linear models. In models where the mixture effect is significant, the identification of "bad actors" can be assessed by a comparison of the weights, w, estimated for each chemical, with heavily-weighted components contributing most strongly to the mixtures effect on the modeled health outcome. WQS regression is particularly robust against multicollinearity because of the constraints imposed in parameter estimation, in that all weights are constrained to an estimate between 0 and 1, and to sum to 1, thereby capturing a normalized effect estimate. The standardization of exposures to rankings (generally quartiles or deciles) further reduces the impact of extreme values and improves interpretability. WQS was fit constraining all parameters in the positive direction (i.e. to estimate effect on increased birth weight Z-score) or in the negative direction (i.e. to estimate the effect on decreased birth weight Z-score).

For all analyses, a P-value < 0.05 was used to define statistical significance. Interaction P-value < 0.1 was used to define statistical significance for interactions (Selvin, 1996).

3. Results

Among the 145 children included in analyses, mean birth weight was 3431 ± 472 g and mean birth weight Z-score was 0.06 ± 0.96, with 3 (2.1%) children born low birth weight. Mean gestational age at delivery was 39.0 ± 1.3 weeks and 6 (4.1%) children were born preterm. Participant characteristics are provided in Table 1. Race was statistically significantly associated with birth weight Z-score, with African-American mothers having lower birth weight infants than white mothers (P = 0.034). No other covariates were statistically significantly associated with birth weight Z-score or gestational age at birth.

The distribution of manganese, lead and zinc in teeth, by trimester, is presented in Fig. 1 in metal-to-calcium ratio of ion counts. Tooth zinc levels in the second (mean ± standard deviation (SD) = 14.02 ± 5.47) and third trimester (mean ± SD = 14.27 ± 5.63) were similar (P = 0.70). Tooth manganese levels decreased between the second (mean ± SD = 1.87 ± 0.97) and third trimester (mean ± SD = 1.08 ± 0.61; P < 0.001). In contrast, tooth lead levels increased between the second (mean ± SD = 0.04 ± 0.03) and third trimester (mean ± SD = 0.05 ± 0.04; P = 0.001). Results were similar by sex (Fig. 1). The correlation across tooth metals was also examined (Fig. 2);

Table 1
Distribution of maternal and delivery characteristics and their univariable association with birth weight Z-score and gestational age at delivery.

Characteristic	N (%) or mean ± std	Birth weight Z-score mean ± std or r	Gestational age at delivery (in weeks) mean ± std or r
Age (years)	31.0 ± 5.1	r = 0.22	r = −0.12
Race			
White	54 (36.5%)	0.32 ± 1.06	38.9 ± 1.6
African-American	65 (43.9%)	− 0.07 ± 0.89[*]	39.0 ± 1.3
Other	29 (19.6%)	− 0.08 ± 0.85	39.3 ± 1.0
Education			
College degree or higher	67 (45.3%)	0.15 ± 0.9	39.2 ± 1.3
Less than college degree	81 (54.7%)	− 0.02 ± 1.0	38.9 ± 1.4
Household income			
< $80k	87 (58.8%)	− 0.10 ± 0.88	39.0 ± 1.3
> $80k	42 (28.4%)	0.26 ± 1.09	39.1 ± 1.3
Refused to answer	19 (12.8%)	0.35 ± 0.88	39.1 ± 1.5
Marital Status			
Married	106 (71.6%)	0.06 ± 0.97	39.1 ± 1.4
Not Married	42 (28.4%)	0.07 ± 0.94	38.9 ± 1.2
Residence			
Urban	63 (42.6%)	− 0.12 ± 0.87	38.9 ± 1.3
Suburban	85 (57.4%)	0.20 ± 1.00	39.1 ± 1.3
Smoked during pregnancy			
Yes	9 (6.1%)	− 0.21 ± 0.87	39.0 ± 1.4
No	139 (93.9%)	0.08 ± 0.96	39.0 ± 1.3
Prenatal ETS exposure			
Yes	32 (21.6%)	− 0.23 ± 0.84	39.0 ± 1.2
No	116 (78.4%)	0.14 ± 0.97	39.0 ± 1.4
Prenatal indoor pets			
Yes	64 (43.2%)	0.17 ± 0.91	39.1 ± 1.3
No	84 (56.8%)	− 0.02 ± 0.99	39.0 ± 1.3
Ever anemic prenatally			
Yes	21 (14.2%)	0.45 ± 0.79	39.5 ± 1.1
No	127 (85.1%)	− 0.002 ± 0.97	39.0 ± 1.4
First BMI measured in pregnancy (kg/m²)	29.6 ± 8.1	r = −0.05	r = −0.13
Parity			
Nulliparous	57 (38.5%)	− 0.13 ± 0.93	39.1 ± 1.5
Multiparous	91 (61.5%)	0.17 ± 0.96	39.0 ± 1.2
Infant sex			
Male	72 (48.7%)	0.15 ± 0.98	38.9 ± 1.5
Female	76 (51.4%)	− 0.02 ± 0.93	39.2 ± 1.1
Year house built			
1980 or after	25 (16.9%)	0.14 ± 1.11	39.2 ± 1.6
Before 1980	116 (78.4%)	0.04 ± 0.94	39.0 ± 1.3
Missing	7 (4.7%)	0.12 ± 0.78	39.1 ± 0.7

  * P-value comparing African-American to white (P = 0.034).

as expected, for each metal, there was high correlation across trimester.

3.1. Association of tooth metals with birth weight Z-score and gestational age at delivery

Multivariable regression modeling revealed associations between tooth metal measures and birth weight Z-score (Table 2). Specifically, after adjusting for batch, tooth attrition and tooth type, manganese in the second (β = 0.21, 95% CI: 0.05, 0.37; P = 0.01) and third trimester (β = 0.21, 95% CI: 0.05, 0.37; P = 0.01) were positively associated with birth weight Z-score and lead in the second trimester was negatively associated with birth weight Z-score (β = − 0.20, 95% CI: −0.38, −0.02, P = 0.02). Results were similar for manganese after covariate adjustment (Table 2 Models 2 and 3). However, after full covariate adjustment, results were attenuated and no longer statistically significant for lead. There was no evidence for a trimester-specific effect of each metal with birth weight Z-score (Table 2; all P-values for effect by time > 0.26).

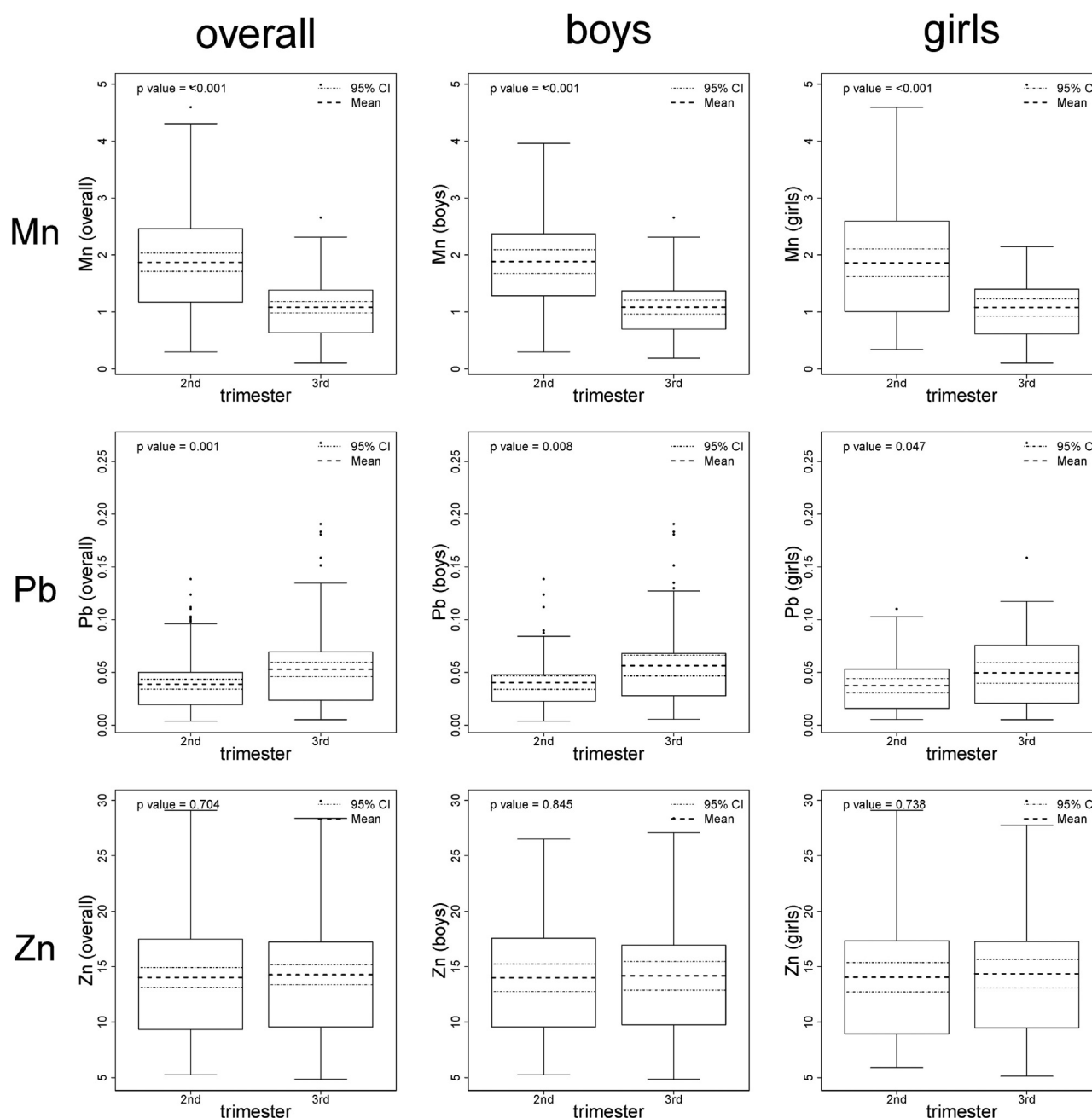When we examined the effects of the three metals jointly as a

Fig. 1. Distribution of manganese (Mn), lead (Pb), and zinc (Zn) by trimester of measurement, overall and by sex. Tooth metal data are presented in metal-to-calcium ratio of ion counts and are not centered/standardized for graphical purposes. P-value is for difference by trimester. CI, confidence interval.

mixture we saw significant associations with birth weight Z-score (Table 3). In our WQS regression analyses, when we constrained the association of metals with birth weight Z-score to be positive (i.e. to see which metals increased birth weight), we observed that second trimester metal mixture was significantly associated with birth weight Z-score (P = 0.047). This association was almost entirely attributed to manganese (75% of observed association) and zinc (23%). The third trimester metal mixture was also driven largely by manganese and zinc but was not statistically significant (P = 0.085). When we constrained the association of metals with birth weight Z-score to be negative (i.e. to see which metals decreased birth weight Z-score), much of the association, albeit not statistically significant, was driven by lead. Results were similar after full covariate adjustment (Table 3, Model 2).

None of the metals showed a significant association with gestational age at delivery (Table 2). Similarly, we did not observe any appreciable

mixture effects with gestational age (data not shown).

3.2. Sex and race specific effects of tooth metals on birth outcomes

Mean birth weight was slightly higher in male (3514.4 ± 509.9 g) compared to female infants (3354.6 ± 424.3 g) (P = 0.045). As expected, there was no difference by sex in birth weight Z-score (0.15 ± 0.98 in males and −0.02 ± 0.93 in females; P = 0.29). There was also no difference in gestational age at delivery by sex (38.9 ± 1.5 in males and 39.2 ± 1.1 weeks in females; P = 0.16). There were no sex differences in any metal level in either trimester (all P > 0.13).

There was evidence for sex-specific associations of tooth metals with birth weight Z-score (Supplemental Table). There was a statistically significant sex-by-trimester tooth lead interaction with birth weight Z-score (P = 0.07 in the model adjusted for batch, attrition and tooth
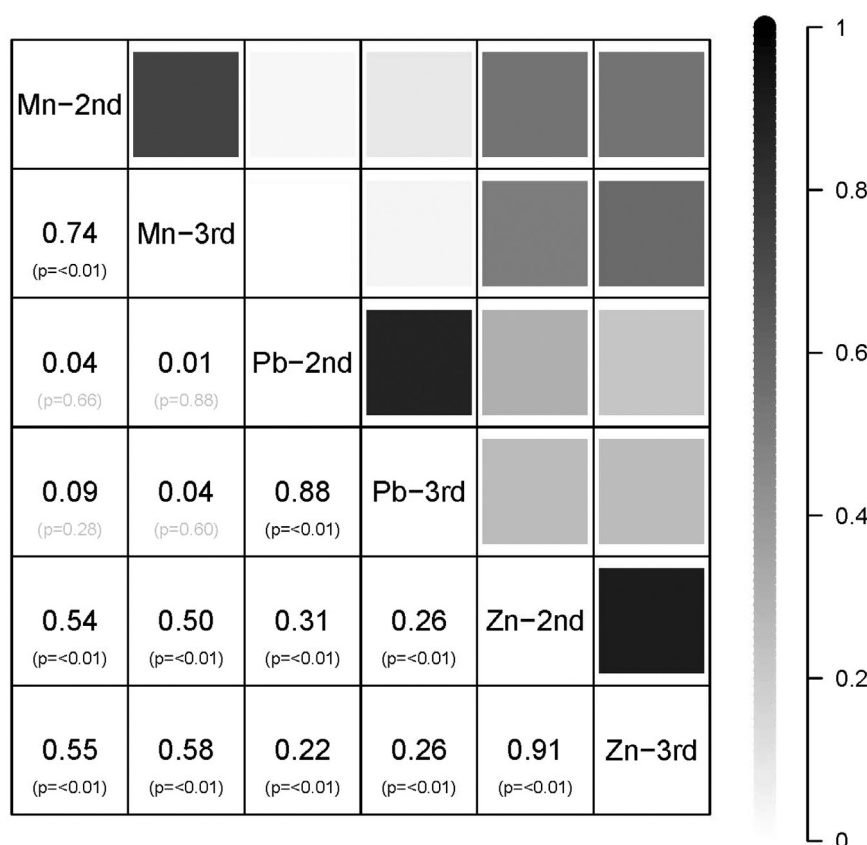
Fig. 2. Correlations between centered and standardized tooth metals across trimester of measure. Shading indicates strength of correlation. Data are correlation coefficient (P-value). Mn, manganese; Pb, lead; Zn, zinc; 2nd, second trimester; 3rd, third trimester.

type; P = 0.09 in the fully adjusted model). After adjusting for batch, tooth attrition, and tooth type, tooth lead level in the second trimester was negatively associated with birth weight Z-score among male ($\beta = -0.39$, 95% CI: -0.64, -0.14, P = 0.01) but not female ($\beta = -0.10$, 95% CI: -0.34, 0.14, P = 0.42) infants. In the fully adjusted model, however, the male-specific effect of lead on birth weight was attenuated and no longer statistically significant ($\beta = -0.20$, 95% CI: -0.47, 0.07, P = 0.15). While there was no evidence for a manganese-sex interaction with birth weight Z-score (all P > 0.45), in stratified models there were potential differences by sex in the manganese-birth weight Z-score association. Among females, tooth manganese levels in both the second ($\beta = 0.28$, 95% CI: 0.08, 0.48, P = 0.01) and third trimester ($\beta = 0.24$, 95% CI: 0.04, 0.44, P = 0.02) were positively associated with birth weight Z-score; there was no association with second ($\beta = 0.11$, 95% CI: -0.16, 0.38, P = 0.44) or third trimester ($\beta = 0.16$, 95% CI: -0.15, 0.47, P = 0.33) manganese in males. In females, after full covariate adjustment, the association of manganese in the second trimester ($\beta = 0.23$, 95% CI: 0.01, 0.45, P = 0.04) remained statistically significant with birth weight Z-score while the association of third trimester manganese ($\beta = 0.19$, 95% CI: -0.03, 0.41, P = 0.07) with birth weight Z-score was slightly attenuated and no longer statistically significant. There was no evidence for a sex-specific effect of zinc on birth weight Z-score.

There was no evidence for a race-specific effect of tooth metal levels with either birth weight Z-score or gestational age at delivery (all interaction P > 0.11).

4. Discussion

In the current study, we utilized the novel elemental bio-imaging of human primary teeth to examine direct fetal exposure to zinc, lead and manganese with birth outcomes, including birth weight and gestational

age at delivery. We found evidence consistent with previous studies showing positive associations between prenatal tooth manganese with birth weight Z-score and inverse associations of tooth lead with birth weight Z-score, however, after covariate adjustment, the associations with lead were attenuated. Associations between tooth metals and birth outcomes appeared to be sex-specific.

Potential mechanisms linking prenatal lead exposure with impaired fetal growth and preterm delivery include competition of lead with calcium for deposition into bone and impact on collagen synthesis which may impact chorioamniotic membrane structure (Zhu et al., 2010). While a number of studies have shown that lead increases the risk of poorer birth outcomes, not all studies have consistently demonstrated such associations (Zhu et al., 2010; Perkins et al., 2014; Taylor et al., 2015; Rabito et al., 2014; Xie et al., 2013; Kaji and Nishi, 2006). In the current study, before covariate adjustment, we did find an association between tooth lead level in the second trimester and birth weight Z-score, however, after covariate adjustment, this association was attenuated. These findings are similar to those found in Project Viva, which showed that mid-pregnancy maternal red blood cell lead level was not associated with infant birth weight or gestational age at delivery after adjusting for confounding factors (Perkins et al., 2014). In the CANDLE study which had maternal blood lead level measures in the second and third trimester as well as cord blood lead levels in 98 women, after adjusting for gravidity, marital status and gestational age at blood draw, second trimester maternal blood lead level was associated with a marginally statistically significant lower birth weight and statistically significant greater odds of preterm delivery (Rabito et al., 2014). Similarly, in the Project Viva study, maternal red blood cell lead level was associated with increased risk of preterm delivery (Perkins et al., 2014). With only 6 children in our sample born preterm, we were unable to examine if tooth metals were associated with preterm delivery.

Table 2

Association of centered and standardized tooth metals measured in second or third trimester with birth weight Z-score and gestational age at delivery. Bolded values highlight all P-values < 0.05.

Metal	Second trimester			Third trimester			Effect by time		
	β	95% CI	P	β	95% CI	P	β[a]	95% CI	P
Birth Weight Z-score									
Model 1									
Mn	0.21	(0.05, 0.37)	**0.01**	0.21	(0.05, 0.37)	**0.01**	−0.02	(−0.49, 0.45)	0.92
Pb	−0.20	(−0.38, −0.02)	**0.02**	−0.13	(−0.29, 0.03)	0.12	−0.34	(−0.93, 0.25)	0.26
Zn	0.12	(−0.06, 0.30)	0.16	0.12	(−0.04, 0.28)	0.16	0.14	(−0.72, 1.00)	0.76
Model 2									
Mn	0.19	(0.03, 0.35)	**0.02**	0.16	(0.00, 0.32)	0.05	0.10	(−0.35, 0.55)	0.68
Pb	−0.12	(−0.32, 0.08)	0.23	−0.04	(−0.22, 0.14)	0.69	−0.34	(−0.93, 0.25)	0.26
Zn	0.09	(−0.07, 0.25)	0.27	0.09	(−0.07, 0.25)	0.31	0.23	(−0.61, 1.07)	0.59
Model 3									
Mn	0.17	(0.01, 0.33)	**0.03**	0.16	(0.00, 0.32)	0.05	0.03	(−0.42, 0.48)	0.89
Pb	−0.15	(−0.35, 0.05)	0.12	−0.06	(−0.24, 0.12)	0.53	−0.31	(−0.90, 0.28)	0.30
Zn	0.07	(−0.09, 0.23)	0.39	0.07	(−0.09, 0.23)	0.42	0.16	(−0.66, 0.98)	0.70
Gestational Age at Delivery									
Model 1									
Mn	0.03	(−0.19, 0.25)	0.80	0.01	(−0.21, 0.23)	0.90	0.05	(−0.60, 0.70)	0.87
Pb	0.01	(−0.23, 0.25)	0.96	0.08	(−0.14, 0.30)	0.48	−0.27	(−1.07, 0.53)	0.51
Zn	−0.05	(−0.29, 0.19)	0.66	−0.04	(−0.28, 0.20)	0.72	−0.22	(−1.40, 0.96)	0.71
Model 2									
Mn	0.03	(−0.19, 0.25)	0.79	0.03	(−0.21, 0.27)	0.80	0.04	(−0.61, 0.69)	0.90
Pb	0.07	(−0.20, 0.34)	0.62	0.10	(−0.14, 0.34)	0.42	−0.15	(−0.97, 0.67)	0.73
Zn	−0.03	(−0.27, 0.21)	0.79	−0.02	(−0.26, 0.22)	0.85	−0.14	(−1.32, 1.04)	0.82
Model 3									
Mn	0.02	(−0.22, 0.26)	0.86	0.00	(−0.24, 0.24)	1.00	0.11	(−0.56, 0.78)	0.76
Pb	0.08	(−0.19, 0.35)	0.55	0.14	(−0.11, 0.39)	0.26	−0.22	(−1.08, 0.64)	0.61
Zn	−0.03	(−0.27, 0.21)	0.83	−0.01	(−0.25, 0.23)	0.92	−0.11	(−1.31, 1.09)	0.86

Mn, manganese; Pb, lead; Zn, Zinc; β, Beta; CI, Confidence Interval.
Model 1: Adjusted for batch, tooth attrition, and tooth type.
Model 2: Adjusted for batch, tooth attrition, tooth type, and race.
Model 3: Adjusted for batch, tooth attrition, tooth type, race, urban, ETS, anemic, maternal age, and year house built.
[a] β for the effect by time is the difference in effect estimates from the 2nd and 3rd trimesters.

Table 3

Weighted quantile sum (WQS) index for metals mixtures (using decile score) during second and third trimesters, related to birth weight Z-score. Bolded values highlight all P-values < 0.05.

	Model 1				Model 2			
	Positive direction[a]		Negative direction[a]		Positive direction[a]		Negative direction[a]	
	Second trimester	Third trimester	Second trimester	Third trimester	Second trimester	Third trimester	Second trimester	Third trimester
Beta	0.075	0.067	−0.03	−0.003	0.116	0.134	−0.09	−0.025
SE	0.038	0.039	0.04	0.04	0.069	0.073	0.06	0.067
P-value	**0.047**	0.085	0.348	0.946	0.094	0.065	0.148	0.711
Metal	Weights	Weights	Weights	Weights	Weights	Weights	Weights	Weights
Mn	0.75	0.83	0.01	0.05	0.93	0.84	0.00	0.02
Pb	0.02	0.07	0.98	0.85	0.00	0.03	0.98	0.93
Zn	0.23	0.10	0.01	0.10	0.07	0.13	0.01	0.05

SE, standard error; Mn, manganese; Pb, lead; Zn, Zinc.
Model 1: Adjusted for batch, tooth attrition, tooth type, and race.
Model 2: Adjusted for batch, tooth attrition, tooth type, race, urban, ETS, anemic, maternal age, and year house built.
[a] Positive direction indicates the association of metals with birth weight Z-score constrained to be positive; Negative direction indicates the association of metals with birth weight Z-score constrained to be negative.

Manganese is an essential nutrient and as such, is necessary for proper growth and development, however, manganese at higher levels can also be toxic (Xia et al., 2016; Crossgrove and Zheng, 2004). Similar to lead, there is a growing body of literature showing the importance of manganese in healthy birth outcomes. Data from 172 mother-infant-pairs born in Shanghai showed both lower and higher maternal manganese levels in blood measured near delivery were associated with lower birth weight (Chen et al., 2014). Similar findings were obtained in a case-control study conducted in Hubei Province, China, which showed both lower and higher maternal urinary manganese measured at delivery was associated with low birth weight (Xia et al., 2016). In contrast, in a study in Taiwan, first and second, but not third trimester maternal erythrocyte manganese levels were inversely associated with infant birth weight (Tsai et al., 2015). We found that tooth manganese levels in the second and third trimester were positively associated with birth weight, even after adjustment for covariates. Future studies that establish ideal manganese levels during pregnancy may be needed.

Like manganese, zinc is an essential nutrient that is needed for cell growth, differentiation and survival (Wang et al., 2016; Hirano et al., 2008). A systematic review of the role of maternal zinc status and pregnancy complications revealed that there is sufficient evidence to suggest there is an association between maternal circulating zinc levels

and low birth weight in populations where zinc deficiency is prevalent, but insufficient studies examining the association of maternal zinc with preterm birth (Wilson et al., 2016). In the China-Anhui birth cohort study, lower maternal serum zinc level in the first but not second trimester was associated with greater risk for preterm birth (Wang et al., 2016). In a recent study conducted in Spain, cord blood zinc levels were higher in infants with appropriate-for-age growth compared to those with intrauterine growth restriction or small-for-gestational-age growth (Sabra et al., 2017). In the National Birth Defects Prevention Study, lower maternal self-reported zinc intake was associated with greater odds of preterm delivery (before 32 weeks gestation) (Carmichael et al., 2013). Overall, we found no association of tooth zinc level with birth outcomes in the WHEALS cohort.

We explored potential race and sex specific effects of metals in teeth with birth outcomes. In a study of infants born in Shanghai there was a statistically significant inverse association of cord blood lead level with birth weight among male but not female infants (Wang et al., 2017). Similar results were found in the Project Viva cohort, showing higher maternal blood lead level was associated with lower birth weight in male but not female infants; however, this was attenuated after covariate adjustment (Perkins et al., 2014). In the Project Viva cohort, maternal blood lead level was also statistically significantly associated with preterm birth and suggestively associated with decreased gestational age at delivery in male but not female infants (Perkins et al., 2014). In contrast, there was no sex-specific relationship of cord blood lead and birth weight in the Tohoku Study of Child Development (Tatsuta et al., 2017). Before covariate adjustment, we found that second trimester tooth lead level was inversely associated with birth weight Z-score in male but not female infants, however, this was attenuated after adjusting for covariates. Wang et al. (2017) postulate that male fetuses have a higher growth rate and nutritional demands, and thus may be at higher risk of poorer growth with lead exposure if lead negatively impacts placental function (Wang et al., 2017). Previous studies have shown that higher maternal blood lead is inversely associated with placental thickness (Al-Saleh et al., 2014). In contrast, we found that higher manganese level was associated with greater birth weight Z-score in female but not male infants. In a study in Hubei Province, China, maternal pre-delivery urine manganese levels demonstrated a curvilinear association with low birth weight in female infants but a linear association in male infants (Xia et al., 2016). Additional work to confirm our findings is needed.

Data from NHANES suggests that only 59.4% of pregnant women (1988–1994) in the US had adequate zinc intake (Briefel et al., 2000). In the US, NHANES data also suggest that reproductive age women have higher blood manganese levels than similarly aged men (Oulhote et al., 2014). Among US women 20–44 years, pregnant women also have higher blood manganese levels than their non-pregnant counterparts (Oulhote et al., 2014). There is no evidence to suggest that women/fetuses from WHEALS would have zinc or manganese intake that differs from the rest of the United States. Prenatal tooth manganese level in WHEALS is higher than that from a cohort in Mexico, however, which may reflect underlying dietary differences in mothers from the US compared to Mexico (Gunier et al., 2015). Finally, we have previously shown, based on data from routine blood lead screening, that children from the WHEALS cohort have rates of elevated blood lead levels that are similar to that of the US (Wheeler and Brown, 2013; Cassidy-Bushrow et al., 2016), suggesting that our population is neither disproportionately burdened by, nor protected from, lead exposure.

The current study has a number of strengths and limitations. We have previously shown that children from WHEALS who donated a tooth to the study were of slightly older gestational age at delivery (39.1 ± 1.3 weeks compared to 38.7 ± 1.8 weeks) and higher birth weight Z-score (0.06 ± 0.95 compared to −0.15 ± 0.99 weeks) than WHEALS children who did not donate a tooth to the study (Cassidy-Bushrow et al., 2017). As reported elsewhere, the propensity for participation in research studies by healthier volunteers (with respect to

both outcomes of interest and potential exposures) may bias the results of a study (Froom et al., 1999), potentially toward the null. There are known sex differences in the vulnerability to prenatal exposures (DiPietro and Voegtline, 2017); we found evidence for sex-specific effects of tooth manganese on birth weight Z-score in stratified models but not when tested with interaction terms, which may suggest that sex acts as an effect modifier rather than an interaction variable (VanderWeele, 2009). However, we also may be underpowered to detect some associations, particularly those that are sex or race specific, which may be why we have several associations that are marginally statistically significant. Further, in our fully-adjusted models, the associations of some metals were attenuated and no longer statistically significant; it is possible that we adjusted for covariates that are on the causal pathway from exposure to outcome, and thus we have over-adjusted our models and biased the results to the null (Schisterman et al., 2009). Utilizing the novel tooth-matrix methodology overcomes several limitations of previous studies, including precluding the need for multiple measures of maternal blood or urine over time and the direct measurement of fetal exposure rather than relying on maternal exposure as a surrogate. Tooth biomarkers have been used in earlier studies and have shown differences in exposure to lead and other metals (Gulson, 1996; Bellinger et al., 1991; Kim et al., 1996; Leviton et al., 1993; Needleman, 1993; Needleman et al., 1992, 1974, 1990; Needleman and Gatsonis, 1990; Needleman and Shapiro, 1974). However, levels of metals reported by our methods are not directly comparable to those studies using other analytical methods. It is also known that the distribution of elements in dental hard tissue is heterogeneous (de Souza-Guerra et al., 2014). Our racially diverse cohort is a strength, as well as the distribution of residence across both urban and suburban areas.

4.1. Conclusions

Overall, we found evidence suggesting that higher *in utero* manganese is associated with larger birth weight Z-scores and that these associations may vary by infant sex. Future studies are needed to better understand the mechanisms by which manganese could impact birth weight differentially by sex.

Funding sources

Human subjects protections

This study was reviewed and approved by the Henry Ford Health System Institutional Review Board (Federal Wide Assurance Number 00005846; IRB# 00000253 and IRB# 00008660); IRB approval #1881. Parents/guardians provided written, informed consent.

Declarations of interest

None.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2019.01.054.

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