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The association of lead exposure during pregnancy and childhood anthropometry in the Mexican PROGRESS cohort

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Abstract

Lead exposure during pregnancy remains a public health problem with potential lifelong impacts on children's growth and development. Mexico is unique in that stunting and obesity are both major public health concerns in children. This situation might be exacerbated by lead exposure which remains more common in Mexico than in the United States due in part to the use of lead glazed pottery in food preparation and storage. Our objective is to determine how lead exposure during pregnancy is associated with children's growth parameters, including height, weight, body mass index and percentage body fat measured between ages 4–6 years old in a Mexico City pregnancy cohort. Blood lead was collected in the 2nd and 3rd trimester of pregnancy as well as at delivery. Bone lead was assessed in mothers as a long term exposure biomarker. We performed multivariable linear regression analyses to assess the association between each of these lead exposure biomarkers and child anthropometry.

We found a significant negative association between maternal 3rd trimester blood lead concentration and offspring height for age (β −0.10; 95% CI −0.19, −0.01), and a negative association between maternal 3rd trimester blood lead concentration and weight for age (β −0.11;

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95% CI −0.22, −0.003). Our results in this Mexican population add to previous findings of an association of lead and decreased stature and weight in early childhood. Ongoing follow-up and longitudinal analyses may help elucidate how this impacts growth trajectory and other children's health outcomes.

Keywords

lead; anthropometry; stunting; child; pregnancy

1. Introduction

In some developing and middle income countries such as Mexico as well as sporadic episodes in the US, lead exposure is still a concern. In particular, lead exposure remains a public health problem for childbearing women, their developing fetuses and may have lifelong impacts on children's growth and development. Mexico is unique in that both stunting and obesity are major public health concerns in children (Kroker-Lobos et al. 2014). There are many risk factors for lead exposure, the most common of which are use of traditional lead glazed pottery (the main exposure factor for the general population), pica (the eating of nonfood substances), occupational exposure (directly or indirectly from the inadvertent transfer of lead dust from the workplace on workers' clothing, shoes or bodies), use of alternative remedies or cosmetics, air pollutants and nutritional sources (due to food wrappers and water sources) (Bakhireva et al. 2013; Brown et al. 2000; Meneses-Gonzalez et al. 2003; Romieu et al. 1994; CDC 2010). Recent events in Washington DC and Flint Michigan highlight the importance of water as a source (Bellinger 2016). Lead is particularly dangerous for the fetus because it crosses the placenta and may cause adverse birth outcomes, including low birth weight and preterm birth (Chen et al. 2006 (location: Taiwan; biomarkers: blood; exposure level: mean 10.1 μg/dL, sd 10.4); Gundacker et al. 2010 (Austria; blood, placenta, cord blood, meconium; median: 24.9, 25.8, 13.4, 15.5 μg/dL); Gundacker and Hengstschläger 2012; Jedrychowsky et al. 2008 (Poland; cord blood; mean 1.42 μg/dL, sd 0.71); Schell et al. 2009 (New York; blood; mean 2.8 μg/dL, sd 2.63); Torres-Sanchèz et al. 1999 (Mexico; cord blood; median 9 μg/dL); Zhu et al. 2010 (New York; blood; median 2 μg/dL)).

There are many ways by which lead might interfere with growth in early life. Lead may alter bone cell function directly (through changes in circulating hormones or by impairing their ability to synthesize or secrete other components of the bone matrix) (Hamilton and O'Flaherty 1995) or indirectly (by perturbing the ability of bone cells to respond to hormonal regulation, or by effecting or replacing calcium in the active sites of its messenger system) (Pounds et al. 1991). It may induce a reduction of circulating maternal thyroid hormone that impacts overall growth trajectories (Hannigan et al. 1995; Hernandez-Avila et al. 2002 (Mexico; tibia, patella; mean 9.83, 14.14 μg/g, sd 8.9, 13.0)). Lead could disrupt heme-mediated generation of critical enzymes involved in metabolism and other metabolic functions such as the synthesis of vitamin D which regulates calcium metabolism (Mushak et al. 1989). Further, lead may impair growth by altering the hypothalamic-pituitary-growth axis function (Fleisch et al. 2013 (Russia; blood; median 3 μg/dL)).

Previous studies have investigated the association between lead exposure and children's growth. The majority of these studies focused on postnatal exposure and found some evidence of associations between lead exposure during childhood and children's growth. In particular, previous investigations identified significant negative correlations between blood lead (BlPb) levels during childhood and child stature and growth over time (Schwartz et al. 1986 (United States; blood; range 5 to 35 μg/dL); Vivoli et al. 1993 (Italy; blood; mean 7.8 μg/dL); Kafourou et al. 1997 (Greece; blood; mean 12.3 μg/dL, sd 8.9); Ballew et al. 1999 (United States; blood; mean 3.6 μg/dL); Frisancho and Ryan 1991 (United States; blood; mean 0.5 μmol/L); Cantoral et al. 2015 (Mexico; blood; median 0.17 μmol/L); Dallaire et al. 2014 (Canada; blood; mean 2.7 μg/dL sd 2.1)). Other studies observed negative associations between lead exposure during pregnancy and children's height and weight (Schell et al. 2009 (New York; blood; mean 2.8 μg/dL, sd 2.63); Afeiche et al. 2011 (Mexico; tibia, patella; mean 8.7 μg/g, 10.4 μg/g, sd 9.7, 11.8); Hong et al. 2014 (South Korea; blood; mean 1.25 μg/dL sd 1.5)). However, most previous studies focused on postnatal exposures and did not measure exposure to lead during pregnancy. Fetal development is a life state with high plasticity involving a series of delicately regulated processes that can be affected by environmental exposures. Alterations of fetal development may lead to long term consequences with persistent alterations of child phenotype, including growth, in postnatal life.

In the present analysis, we investigated the association of maternal biomarkers of lead exposure during pregnancy with children's anthropometric measures at 4–6 years of age. We examined the association of maternal lead levels with multiple measures related to growth including height, weight, body mass index (BMI) and percentage body fat (PBF).

2. Material and methods

2.1 Recruitment of the Study Participants

The Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) is an NIH funded ongoing prospective pre-birth cohort in Mexico City. Between July 2007 and February 2011, 1054 pregnant women receiving care through the Mexican Social Security System (IMSS) were enrolled after providing written informed consent. The study protocols were approved by the institutional review boards of the Brigham and Women's Hospital, the Icahn School of Medicine at Mount Sinai and the National Institute of Public Health in Mexico.

Women were considered eligible for enrollment if they were 18 years or older, pregnant at <20 weeks of gestation, free of heart or kidney disease, did not use steroids or anti-epilepsy drugs, did not consume alcohol on a daily basis, had access to a telephone, and planned to reside in Mexico City for the following three years. The follow-up for this analysis lasted from the 2nd trimester of pregnancy until the children reached 4–6 years old. All measures of interest were gathered during the planned visits at 2nd, 3rd trimester, delivery, one month and around 4 years after delivery. From the initial enrollment of 1054 mothers, 948 live births were assessed. On average ~550 children presented at each postnatal visit and a total of 760 returned for at least 2 postnatal visits. The study subjects for the present analysis were restricted to the 513 mothers and their children who presented to the 4–6 year visit and

completed measures of maternal BlPb, maternal bone lead, or cord BlPb, and at least one postnatal growth measurement at the follow-up visit at age 4–6 years and the LeadCare measurement at this stage. We did not find significant differences between the characteristics of the included pairs and the remainder of the cohort for maternal blood and bone lead, age, education, BMI, height, gestational age, parity, environmental tobacco smoking (ETS), delivery mode, breastfeeding, and child's age, sex, LeadCare at 4–6 years, and food frequency questionnaire (FFQ) total dietary intake (all $p>0.05$).

2.2 Lead measurements in maternal blood and cord blood

Maternal blood was collected at the second and third trimester visit. An additional maternal venous blood sample and an umbilical cord blood sample were collected within 12 hours of delivery. All blood specimens were drawn in trace metal free tubes and refrigerated at 2–6°C until analysis. Lead concentration was measured by external calibration using the Agilent 8800 ICP Triple Quad (ICP-QQQ) in MS/MS mode in the trace metals laboratory at the Icahn School of Medicine at Mount Sinai. The limit of detection was <0.2μg/dL and the instrument precision (given as %RSD) was approximately 5%. Blinded quality control samples obtained from the Maternal and Child Health Bureau and the Wisconsin State Laboratory of Hygiene Cooperative Blood Lead Proficiency Testing Program showed good precision and accuracy.

2.3 Bone lead measurements

One month postpartum mothers were recalled for a visit in which tibia (cortical bone) and patella (trabecular bone) lead concentrations were measured using a K-shell X-ray fluorescence instrument (Hu et al. 1991). We estimated lead concentration for 30 minutes for each leg and the measures were averaged by the inverse of the proportion of the measurement error corresponding to each determination. Bone lead content is thought to provide an indicator of exposure over the span of decades; in particular tibia measurements reflect longer time spans (> 10 years) compared to patella (1–5 years) (Hu et al. 1998). Sometimes negative values are obtained when the true bone lead concentration value is close to 0: the instrument produces a continuous unbiased point estimate that fluctuates around the true bone lead value (Kim et al. 1995). From the epidemiological point of view, useful information would be lost if we set the negative estimates equal to zero or we put them in a single category. Furthermore it was found that results obtained including the negative values or using simulated estimates randomly generated from a normal distribution were very similar (Téllez-Rojo et al. 2004). It is preferable to use all the values to maintain the true shape of the distribution of the measures and to give the relative position of each participant within the study population.

2.4. Measures of Children's Growth and Adiposity at the 4–6 year visit

Trained research assistants collected measures of anthropometry at the age 4–6 year visit in which child weight and standing height were measured using a professional digital scale (Health-o-meter), which was calibrated regularly to ensure accuracy. We used these measures to calculate BMI and to determine BMI z-score for age and sex based on WHO norms (WHO 2006). Tetrapolar bioelectrical impedance was measured using the InBody 370 or 230 (Biospace Co., Ltd.) to estimate body fat mass and PBF. Because values on these two

instruments differed systematically for children, we used a robust linear model fit on a calibration set of 36 children with concurrent measures to adjust the values (R^2 of 0.99 and 0.96 for body fat mass and PBF, respectively).

2.5 Covariates

Information on maternal age, years of education, parity and ETS were collected at the second trimester visit using a standardized questionnaire. Gestational age was calculated from the report of the last menstrual period. Maternal weight and height were measured at the second trimester visit and they were used to calculate BMI. Delivery mode was assessed at delivery and breastfeeding after the first month post delivery (none/non-exclusive/exclusive). LeadCare (children's blood lead measurement) and FFQ total dietary intake were collected at 4–6 year visit.

2.5 Statistical analysis

BlPb concentrations were $\log_2$ transformed to approximate a normal distribution. Bone lead concentration was used on its original scale. Covariates (maternal BMI, education, ETS, parity, delivery mode, breastfeeding, LeadCare and FFQ total dietary intake) were selected a priori based on biological and environmental considerations. We used multiple linear regression models to assess the association between each of the lead exposure biomarkers and the outcome variables. The outcome variables included BMI for age and sex z-score, PBF, weight for age and sex (WFA) z-score and height for age and sex (HFA) z-score. All models included as covariates maternal age, BMI (or height instead of BMI only for the model with HFA z-score as outcome), education, ETS, parity (primiparous, yes/no), gestational age, breast feeding, delivery mode, child's sex, LeadCare BlPb, FFQ total dietary intake (kcal/day) and age at measurement (only for the model with PBF as outcome because PBF is not standardized for child age and sex). A sensitivity analysis was applied to confirm that differences of the associations between the venous BlPb concentrations measured in each perinatal visit and each outcome were not due to different characteristics of the subjects by examining how the associations changed when restricted to subjects who had all three blood measures. We also limited the analysis to full term children to look for potential confounding. Furthermore we explored an interaction term between maternal BlPb concentration measured at 3rd trimester and child sex. We assessed the odds ratio for stunting (a measure of clinically short stature, dichotomized as HFA z-score < −2 standard deviations) using a logistic regression. We performed all the analyses using R version 3.2.2 (R: https://www.R-project.org/).

3. Results

The study sample consisted of 513 mother-child pairs with complete data on exposure, covariates and phenotypes at 4–6 years of age. Table 1 shows the demographic and anthropometric characteristics of the study participants and the association of each covariate with BlPb lead exposure at 3rd trimester. Average maternal age was 27 years. Most of the mothers had a high school education or less (74.3%), had previously given birth (52.4%) and did not report any smokers in their household (70.6%). The covariates significantly associated with BlPb exposure at 3rd trimester are maternal age, maternal height and

children's age at follow up. Descriptive data for child BMI z-score, PBF, WFA z-score, HFA z-score, and age at follow-up are also shown in Table 1.

Table 2 shows descriptive statistics of lead concentrations. The $\log_2$ transformed cord BlPb and maternal BlPb measured across prenatal visits were highly correlated (see Table 3) (Pearson's r from 0.62 to 0.82, all $p<0.001$; Spearman correlations were very similar) and concentrations slightly increased from 2nd to 3rd trimester to delivery (there was an increment of 5% and 10%, respectively from 2nd to 3rd to delivery). Modest correlations were found between bone and all BlPb concentrations (Pearson's r from 0.16 to 0.38, all $p<0.02$) and somewhat stronger correlations between patella and tibia lead concentrations (Pearson's $r=0.41$, $p<0.001$).

Tables 4 and 5 show the unadjusted and covariate-adjusted regression results for the associations of lead levels with the children's growth parameters. We observed a significant unadjusted negative association between maternal 3rd trimester BlPb concentration and child HFA z-score (β −0.14, 95% confidence interval (CI) −0.23, −0.05). The regression coefficient indicates that—on average—a two-fold higher BlPb concentration was associated with a 0.14 lower HFA z-score, which, translates to 0.7 cm lower for both an average 5 year old girl and boy. This association remained statistically significant although slightly attenuated in the adjusted model (β −0.10, CI −0.19, −0.01, which, translates to 0.5 cm lower for both an average 5 year old girl and boy). We can also see a significant association between HFA z-score and blood lead geometric mean in the unadjusted model, but it does not remain significant in the adjusted model. We found a negative, significant association between maternal 3rd trimester BlPb concentration and WFA (β −0.11, CI −0.22, 0.003) in the adjusted model. A two-fold higher BlPb concentration was associated with 0.11 lower WFA, which translates to 0.37 kg and 0.23 kg lower for an average 5 year old girl or boy, respectively. We also explored an interaction term between maternal BlPb concentration measured at 3rd trimester and child sex and we saw no statistically significant difference in the associations for boys and girls. From the R^2 of each model we can see that these models explain only a small proportion of the variance in children's growth parameters. PBF did not show any consistent associations with the exposure measures.

We observed that for the associations between all of the exposure measurements and the HFA z-score, all of the beta values and the p-values decrease when we drop the covariate maternal height from the model (apart from the association between bone lead concentration and the outcome: for tibia the coefficient beta didn't change and for patella the p-value increased) (Table 6). In particular we can see that for the BlPb concentration measured at 3rd trimester the association with HFA z-score becomes significant (β −0.16, CI −0.25, −0.06). This suggests that maternal height is a partially confounding variable for the association between maternal BlPb concentration and HFA z-score (Pearson's r between maternal height and BlPb concentration from −0.17 to −0.11, $p<0.01$; apart from tibia: r −0.06, p 0.22).

We performed a logistic regression to analyze the odds ratio for stunting in our cohort (prevalence of 4% at assessment in this sample). We found a positive significant association in the adjusted model between $\log_2$-transformed lead exposure during the 3rd trimester and stunting (OR 1.8, CI 1.02, 3.25). We also conducted a sensitivity analysis, restricting to

children born full term (>37 weeks gestation) to look for confounding, but we didn't find substantial changes in the results.

4. Discussion

In this study, we investigated the association between lead exposure during pregnancy and children's growth in a prospective pre-birth cohort. We found that there was a significant negative association between maternal BlPb concentration measured in the 3rd trimester and children's HFA z-score and a significant negative relationship between BlPb concentration measured in the 3rd trimester and children's WFA z-score.

Our findings have high biological plausibility. There are many ways by which lead could directly or indirectly affect bone cell function and then alter children's height and body composition (Pounds et al. 1991). There were some previous studies that performed an analysis similar to ours (Afeiche et al. 2011; Hong et al. 2014; Schell et al. 2009). They performed a prospective analysis looking at lead exposure during pregnancy related to children's growth. Hong et al. found a negative association between lead exposure during pregnancy and children's height at 2 years of age. Our results were in agreement with this study, although we investigated 4–6 year old children and thus show persistent associations at a later age. In Schell et al. there was a negative association only in children with higher BlPb concentrations (≥3 μg/dL) at 1 year old, but it was not statistically significant. Schell et al., Hong et al., and Afeiche et al. each found a negative relationship between lead exposure and children's weight respectively measuring exposures at 6 months, 2 years, and 2–5 years (findings only among females in the analysis by Afeiche and colleagues). Our study similarly found a significant association between prenatal BlPb and children's weight. Compared to previous studies in Mexico City, our study is more contemporary and reflects the lower exposure levels that are more current in Mexico City. This increases the generalizability to other populations with lower exposure levels and the relevance for current policy decisions, although the reduced exposure variability is likely to have decreased our power to detect associations.

In the present study, we report a statistically significant negative association between BlPb exposure measured in the 3rd trimester and children's growth at 4–6 years old. A strength of this analysis is the multiple different types and timing of exposure measurements (three maternal BlPb measures, cord BlPb and maternal bone lead concentrations). We found a significant relationship between maternal BlPb concentration and reduced children's height, and a significant association between the same exposure and stunting, although the low prevalence at follow-up limited power. We also found a significant association between maternal BlPb concentration and reduced children's weight. There was no association between maternal tibia lead concentration and any of the growth outcomes. This could be explained by the fact that in cortical bone, lead accumulates more slowly: this measure may not be as representative of the exposure of the fetus during pregnancy compared with other biomarkers. The total variance in growth parameters explained is quite low in all the models as many factors influence children's growth during the first years of life. Since we found a significant negative association with both height and weight, we don't see any association with the children's BMI z-score. This suggests that other studies interested in growth

parameters and body composition should look not only at BMI as an outcome but also consider weight and height separately.

We found that maternal height is a potential confounder in the relationship between lead exposure and children's height: maternal education was associated with maternal stature and BlPb concentration and both of these were associated with children's height. One possible explanation is that maternal lead exposure is itself a major source of lead for the fetus and if lead stunted growth in the mother, the reduced growth in her child is a form of a transgenerational toxic effect via bone remobilization. Nonetheless to be conservative, we decided to keep maternal height in the model recognizing that this may be an overadjustment.

Not much is known about the critical period of lead exposure during pregnancy. What we can see from our results is that the significant associations between the exposure and the outcomes are in maternal blood measured during the 3rd trimester. In this analysis, late pregnancy is the period in which we found a possible adverse association: the associations among BlPb concentration measured in the 3rd trimester and HFA and WFA are both measurements that reflected the exposure during the last period of pregnancy. The 3rd trimester is when most of the lead is mobilized from mom's bone and there is faster fetal growth (Ettinger et al. 2014; Téllez-Rojo et al. 2004). Thus, the higher exposure to lead coincides with a fetal growth spurt. This may be why we see a significant association between the exposure to lead measured in this period and a lower height and weight in early childhood. Based on our results, it may be advantageous for future studies to use exposure measures collected in the 3rd trimester as we did not find associations with childhood growth parameters using the more commonly collected cord blood biomarker.

The current study has some limitations. The first is that we did not control for the effects of other environmental pollutants that may impact growth. A second limitation may be selection bias if loss to follow up was associated with lead exposure and poor growth. Nonrandom loss to follow up might potentially bias the results. However, we did not find any significant differences between the participants included in this analysis and the remainder of the cohort. Another limitation was that we did not account for multiple comparisons resulting from testing multiple outcomes and exposure measures. Finally, we were unable to adjust for other potential confounders for which we lacked appropriate measures, such as maternal calcium levels during pregnancy, nor did we undertake mediation analyses to understand how associations related to growth trajectories at other ages.

This study also had several strengths. We utilized different types of lead exposure measures, which allowed for a comprehensive characterization of in utero exposure including assessing critical windows as well as cumulative lead exposure. We had a sizeable number of mother-child pairs and we adjusted all results for multiple predictors and potential confounders. We examined four different outcomes to extensively characterize children's growth more than 4 years after prenatal exposure, and found associations consistent with prior literature. While previous studies often relied on postnatal lead measurements, we found that the third

trimester exposure measure was most associated with children's growth and this association remained after adjustment for a childhood blood lead measure.

A future study could be a mediation analysis or latent trajectory analysis including the anthropometric measures of children at the earlier stages. Our results provide additional evidence of an association between lead exposure measured in blood during 3rd trimester of pregnancy and children's growth – as measured prospectively in a population-based Mexico City pre-birth cohort. Future analysis may benefit from the ongoing collection of longitudinal growth measures to better understand how prenatal exposures like lead impact growth trajectories.

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Abbreviations

BMI	body mass index
BlPb	blood lead
CI	confidence interval
ETS	environmental tobacco smoking
FFQ	food frequency questionnaire
HFA	height for age
PBF	percentage body fat
WFA	weight for age

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Highlights

- Maternal blood lead was negatively associated with children's height and weight.
- Third trimester maternal blood was associated with children's odds of stunting.
- Negative associations of lead and growth were specific to 3rd trimester blood.

Table 1

Demographic and anthropometric characteristics of 513 mothers at the second trimester of pregnancy and their children at the follow-up visit at 4–6 years, and the association between the covariates and the lead exposure at 3rd trimester

Variable	N (%)	Mean (SD)	(Min, Max)	β Coeff	(95% CI)
Mothers					
Age		27.1 (5.6)	(18, 44)	0.02	(0.004, 0.04)
2nd trimester BMI (kg/m^2)		26.1 (4.2)	(17.9, 43.9)	−0.002	(−0.02, 0.02)
Height (m)		1.6 (0.06)	(1.4, 1.7)	−2.70	(−4.36, −1.04)
Maternal Education					
Less Than High School	213 (41.5)			ref	
High School	168 (32.8)			0.20	(−0.002, 0.40)
College	132 (25.7)			0.15	(−0.07, 0.37)
Primiparous					
Yes	244 (47.6)			0.03	(−0.16, 0.22)
No	269 (52.4)			ref	
ETS					
Yes	151 (29.4)			0.07	(−0.12, 0.26)
No	362 (70.6)			ref	
Children					
Gestational age at birth (week)		38.4 (1.7)	(30, 43)	0.03	(−0.02, 0.08)
BMI z-score		0.2 (1.1)	(−3.8, 6.6)		
Percentage Body Fat * (%)		24.0 (6.1)	(5.0, 55.1)		
Weight for Age z-score		−0.2 (1.1)	(−3.6, 6.3)		
Height for Age z-score		−0.5 (0.9)	(−3.1, 2.7)		
Age at follow-up (years)		4.8 (0.6)	(4.0, 6.7)	0.19	(0.03, 0.35)
LeadCare BlPb at 48		4.0 (2.4)	(0.7, 26.4)	0.07	(−0.03, 0.10)
FFQ (kcal/day) **		1.66 (0.60)	(0.64, 4.25)	0.1	(−0.06, 0.22)
Sex					
Male	254 (49.5)			ref	
Female	259 (50.5)			0.02	(−0.16, 0.19)
Breastfeeding					

Variable	N (%)	Mean (SD)	(Min, Max)	β Coeff	(95% CI)
Not breastfed at 1 month	63 (12.3)			ref	
Non-exclusive at 1 month	314 (61.2)			0.13	(−0.14, 0.40)
Exclusive at 1 month	136 (26.5)			−0.03	(−0.33, 0.27)
Delivery mode					
Vaginal	241 (47.0)			ref	
Cesarean non-elective	174 (33.9)			0.15	(−0.05, 0.35)
Cesarean elective	98 (19.1)			0.14	(−0.10, 0.37)

* n=506 due to missing measurements

** values divided by 1000

Table 2

Lead concentration in maternal blood and bone (patella and tibia) at different time points during pregnancy, and in cord blood.

	N	Mean (SD)	GM	(Min, Max)
Maternal Blood				
2nd Trimester of Pregnancy (μg/dL)	487	3.7 (2.6)	3.0	(0.8, 17.8)
3rd Trimester of Pregnancy (μg/dL)	428	3.9 (2.8)	3.1	(0.3, 28.3)
At Delivery (μg/dL)	405	4.3 (3.1)	3.5	(0.7, 21.9)
Geometric Mean of all Measures (μg/dL)	513	3.7 (2.4)	3.2	(0.8, 15.5)
Cord Blood (μg/dL)	282	3.5 (2.7)	2.8	(0.4, 18.5)
Patella Lead Concentration (μg/g)	424	4.7 (8.8)		(−15.9, 43.2)
Tibia Lead Concentration (μg/g)	430	2.9 (8.6)		(−32.4, 30.1)

Table 3

Pearson's correlation matrix among lead biomarkers; log-transformed maternal blood at three timepoints, cord blood, and untransformed bone concentrations (patella and tibia).

	2nd Trimester	3rd Trimester	At Delivery	Cord Blood	Patella
3rd Trimester	0.76				
At Delivery	0.74	0.82			
Cord Blood	0.62	0.73	0.79		
Patella	0.31	0.26	0.38	0.31	
Tibia	0.20	0.16	0.26	0.17	0.41

Table 4

Association between $\log_2$ transformed lead concentrations in maternal pregnancy blood and cord blood, and children's BMI z-score, Percentage Body Fat, Weight for Age z-score, and Height for Age z-score at follow-up visits aged 4–6 years.

Outcome		Unadjusted				Adjusted*			
Exposure	**N**	**β Coeff**	**(95% CI)**	**R^2-adj**	**p-value**	**β Coeff**	**(95% CI)**	**R^2-adj**	**p-value**
BMI z-score									
Cord BlPb	282	0.04	(−0.08, 0.16)	−0.002	0.53	0.05	(−0.08, 0.17)	0.09	0.46
BlPb Geometric Mean	513	0.03	(−0.08, 0.14)	−0.002	0.61	0.04	(−0.07, 0.15)	0.06	0.51
BlPb at 2nd Trimester Visit	487	0.03	(−0.26, 0.45)	−0.002	0.59	0.04	(−0.07, 0.15)	0.07	0.51
BlPb at 3rd Trimester Visit	428	0.002	(−0.10, 0.11)	−0.002	0.97	−0.01	(−0.12, 0.10)	0.04	0.81
BlPb at Delivery	405	0.02	(−0.09, 0.13)	−0.002	0.72	−0.03	(−0.08, 0.14)	0.06	0.58
PBF									
Cord BlPb	278	0.16	(−0.52, 0.85)	−0.003	0.64	0.31	(−0.37, 0.99)	0.10	0.37
BlPb Geometric Mean	506	−0.19	(−0.82, 0.44)	−0.001	0.55	−0.09	(−0.73, 0.55)	0.08	0.78
BlPb at 2nd Trimester Visit	481	−0.22	(−0.83, 0.39)	−0.001	0.48	−0.13	(−0.75, 0.49)	0.09	0.68
BlPb at 3rd Trimester Visit	423	−0.16	(−0.77, 0.46)	−0.002	0.62	−0.21	(−0.82, 0.41)	0.07	0.52
BlPb at Delivery	399	−0.15	(−0.77, 0.47)	−0.002	0.64	−0.12	(−0.74, 0.50)	0.07	0.70
WFA z-score									
Cord BlPb	282	−0.03	(−0.15, 0.09)	−0.003	0.67	−0.03	(−0.15, 0.09)	0.08	0.64
BlPb Geometric Mean	513	−0.04	(−0.15, 0.06)	−0.001	0.42	−0.05	(−0.16, 0.06)	0.06	0.38
BlPb at 2nd Trimester Visit	487	−0.01	(−0.12, 0.09)	−0.002	0.79	−0.02	(−0.13, 0.09)	0.06	0.68
BlPb at 3rd Trimester Visit	428	−0.09	(−0.19, 0.02)	0.004	0.11	−0.11	(−0.22, −0.003)	0.05	0.04
BlPb at Delivery	405	−0.03	(−0.13, 0.07)	−0.002	0.58	−0.03	(−0.13, 0.08)	0.06	0.58
HFA z-score									
Cord BlPb	282	−0.09	(−0.19, 0.02)	0.007	0.09	−0.04	(−0.14, 0.06)	0.17	0.39
BlPb Geometric Mean	513	−0.10	(−0.20, −0.01)	0.01	0.03	−0.07	(−0.16, 0.02)	0.16	0.14
BlPb at 2nd Trimester Visit	487	−0.06	(−0.15, 0.03)	0.001	0.20	−0.04	(−0.13, 0.04)	0.16	0.32
BlPb at 3rd Trimester Visit	428	−0.14	(−0.23, −0.05)	0.02	0.003	−0.10	(−0.19, −0.01)	0.15	0.03
BlPb at Delivery	405	−0.07	(−0.16, 0.02)	0.003	0.13	−0.04	(−0.13, 0.05)	0.11	0.39

* Parameter (β) and 95% CIs estimated using linear regression model adjusted for mother's age, BMI (height when the outcome is HFA z-score), education, gestational age (weeks), primiparity, smoke exposure, delivery mode, breastfeeding, sex of the child, FFQ total dietary intake, LeadCare childhood blood lead, and child's age (when the outcome is PBF).

Table 5

Association between maternal patella and tibia lead concentration measured one month after pregnancy, and children's BMI z-score, percent body fat, weight for age z-score, and height for age z-score at follow-up visits aged 4–6 years.

Outcome		Unadjusted				Adjusted*			
Exposure	**N**	**β Coeff**	**(95% CI)**	**R^2-adj**	**p-value**	**β Coeff**	**(95% CI)**	**R^2-adj**	**p-value**
BMI z-score									
Patella Lead	424	0.001	(−0.01, 0.01)	−0.002	0.86	0.01	(0.01, 0.02)	0.05	0.31
Tibia Lead	430	0.002	(−0.01, 0.01)	−0.002	0.80	0.01	(−0.01, 0.02)	0.04	0.41
PBF									
Patella Lead	419	−0.0003	(−0.07, 0.07)	−0.002	0.99	0.01	(−0.06, 0.07)	0.07	0.88
Tibia Lead	425	−0.004	(−0.07, 0.06)	−0.002	0.92	0.01	(−0.06, 0.08)	0.07	0.72
WFA z-score									
Patella Lead	424	0.0002	(−0.01, 0.01)	−0.002	0.97	0.01	(−0.01, 0.02)	0.04	0.40
Tibia Lead	430	−0.003	(−0.01, 0.01)	−0.002	0.65	−0.0003	(−0.01, 0.01)	0.03	0.96
HFA z-score									
Patella Lead	424	−0.001	(−0.01, 0.01)	−0.002	0.81	0.01	(−0.003, 0.02)	0.14	0.17
Tibia Lead	430	−0.01	(−0.02, 0.004)	0.001	0.25	−0.003	(−0.01, 0.01)	0.15	0.54

*Parameter (β) and 95% Cls estimated using linear regression model adjusted for mother's age, BMI (height when the outcome is HFA z-score), education, gestational age (weeks), primiparity, smoke exposure, delivery mode, breastfeeding, sex of the child, FFQ total dietary intake, LeadCare childhood blood lead, and child's age (when the outcome is PBF).

Table 6

Analysis unadjusted for maternal height of the association of $\log_2$ transformed maternal pregnancy blood, patella, tibia, and cord blood lead concentrations with children's height for age z-score at the follow-up visit

Exposure	Adjusted*				
	N	β Coeff	(95% CI)	R^2-adj	p-value
Cord Blood Lead	282	−0.34	(−0.69, 0.01)	0.03	0.07
Blood Lead Geometric Mean	513	−0.12	(−0.22, −0.03)	0.03	0.01
Blood Lead at 2nd Trimester Visit	487	−0.08	(−0.17, 0.01)	0.03	0.09
Blood Lead at 3rd Trimester Visit	428	−0.16	(−0.25, −0.06)	0.04	0.001
Blood Lead at Delivery	405	−0.08	(−0.18, 0.01)	0.01	0.09
Patella Lead	424	0.002	(−0.01, 0.01)	0.01	0.78
Tibia Lead	430	−0.10	(−0.20, 0.01)	0.01	0.27

*Parameter (β) and 95% Cls estimated using linear regression model adjusted for mother's age, education, gestational age (weeks), primiparity, smoke exposure, delivery mode, breastfeeding, sex of the child, FFQ total dietary intake and LeadCare childhood blood lead.