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Early lead exposure and childhood adiposity in Mexico city

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ABSTRACT

Background: Prenatal and early childhood lead exposures have been associated with reduced weight in infants and young children, while studies that have examined such associations in children during peripubescence are rare.

Objectives: We investigated the associations of prenatal and early-life exposure to lead with indices of adiposity in peripubertal children living in Mexico City.

Methods: Maternal bone lead (as a proxy for cumulative fetal exposure) was assessed at 1 month postpartum. Blood samples were obtained from children annually from 1 to 4 years. Multivariable linear regression models were used to examine the association between each lead biomarker and BMI z-score, waist circumference, sum of skinfolds and body fat percentage in 248 children aged 8–16 years.

Results: After adjusting for covariates, maternal patella lead was associated with lower child BMI z-score ($\beta = -0.02$, 95% CI: 0.03, −0.01, $p = 0.004$), waist circumference ($\beta = -0.12$ cm, 95% CI: 0.22, −0.03, $p = 0.01$), sum of skinfolds ($\beta = -0.29$ mm, 95% CI: 0.50, −0.08, $p = 0.007$) and body fat percentage ($\beta = -0.09$%, 95% CI: 0.17, −0.01, $p = 0.03$). No significant associations were detected from the postnatal exposure period.

Conclusions: We observed a significant and inverse association of prenatal lead exposure with body composition in Mexican children, suggesting the potential role of early lead exposure in the fetal programming of child growth. Further research on the biological mechanisms underlying these associations is needed.

1. Introduction

It is widely recognized that lead, as a pervasive environmental toxicant, can impose a spectrum of adverse health effects, and children are particularly vulnerable to its toxicity (WHO, 2010). No safe threshold for lead exposure has been identified in children; however, 5.0 μg/dL was adopted by the Centers for Disease Control and Prevention (CDC) as a reference level for public health interventions (McClure et al., 2016). In Mexico, environmental lead levels have been reduced due to the complete phaseout of leaded gasoline by 1997; however, elevated blood levels of lead (≥5.0 μg/dL) in children continue to be reported due to its persistence in the environment and other sources of lead exposure (Caravanos et al., 2014; Clune et al., 2011). In particular, the extensive use of lead-glazed pottery has been associated with elevated blood lead levels in Mexican children (Caravanos et al., 2014). According to a review of blood lead concentrations in Mexico after 2000, the estimated geometric mean was 6.81 μg/dL in children and adolescents (Caravanos et al., 2014).

Developmental exposure to lead has been associated with preterm birth, decreased birth weight (Perkins et al., 2014; Taylor et al., 2015; Xie et al., 2013) and delayed child growth (Renzetti et al., 2017) in humans, as well as late onset of obesity in mice (Leasure et al., 2008).

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However, human studies of the association of prenatal and early postnatal exposure to lead with adiposity in children report inconsistent findings (Liu and Peterson, 2016). Previous studies have related maternal lead exposure during pregnancy to reduced weight in infancy (Hong et al., 2014; Sanin et al., 2001; Schell et al., 2009) and early childhood (Afeiche et al., 2011), while others found no associations (Gardner et al., 2013; Lamb et al., 2008; Renzetti et al., 2017). One study of early childhood lead exposure found that higher blood lead levels were associated with reduced measures of anthropometry in children aged 2–3 years (Cassidy-Bushrow et al., 2016) and girls aged 7–14 years (Deierlein et al., 2019), whereas two other studies reported no associations (Ballew et al., 1999; Gardner et al., 2013).

To date, published studies have focused on characterizing the association of prenatal or early postnatal exposure to lead with adiposity in infancy (Hong et al., 2014; Sanin et al., 2001; Schell et al., 2009), early childhood (up to 6 years of age) (Afeiche et al., 2011; Cassidy-Bushrow et al., 2016; Gardner et al., 2013; Renzetti et al., 2017) and middle childhood (up to 10 years of age) (Lamb et al., 2008), with only one investigation that included children in early adolescence (7–14 years) (Deierlein et al., 2019). In addition, the majority of these studies used indirect measures of body fat such as weight and BMI, with two studies that provided information on body composition using body fat percentage (Deierlein et al., 2019; Renzetti et al., 2017). Furthermore, given that the body composition of children changes dynamically during puberty, it is important to understand the association of developmental exposure to lead and child adiposity in adolescence (Hillman and Biro, 2010). In addition, body composition in adolescents strongly predicts adiposity and obesity-related health conditions in adults (Simmonds et al., 2015). Previously we reported inverse associations between prenatal lead exposure and child weight in children aged 0–5 years (Afeiche et al., 2011). In the present study, we investigated the association of prenatal and early-life lead, as measured by maternal bone lead and cumulative blood lead from 1 to 4 years with child BMI z-score, waist circumference, skinfold thickness and body fat percentage at age 8–16 years.

2. Materials and methods

2.1. Study population

Mother-child pairs in this study were identified from three sequentially-enrolled birth cohorts recruited in Mexico City between 1994 and 2003 that comprise the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project. Briefly, both cohort 1 and 3 were randomized control trials of calcium supplementation of pregnant women; the recruitment of pregnant women occurred in 1994–1995 and 2001–2003, respectively. Cohort 2 was an observational study; participants of cohort 2A were recruited between 1997 and 1999, and participants of cohort 2B were recruited between 1999 and 2001. Detailed information on the study cohorts has been published previously (Afeiche et al., 2011; Ettinger et al., 2009).

Pregnant women were recruited at three maternity hospitals (Manuel Gea Gonzalez Hospital, Mexican Social Security Institute and the National Institute of Perinatology), which serve low to moderate income population. Mothers were followed for 12 months post-partum and their children were followed up to 4 years of age. Mothers completed interview-based questionnaires and bone lead measurements at baseline. During the follow-up visit, each child completed self-reported questionnaires and anthropometric assessment. We originally recruited 827 mother-offspring pairs. For this study, we only included peripubertal children who had maternal bone lead measures and at least one measure of adiposity (n = 257). We further excluded children who had missing information on covariates of interest. A total of 248 children were included in the final analysis.

The research protocols were approved by the Institutional Review Boards at the University of Michigan School of Public Health and the Research Committees of Instituto Nacional de Salud Pública (INSP) in Mexico prior to enrollment.

2.2. Anthropometry

At the follow-up visit, child weight, height, waist circumference (WC) and skinfold thickness (biceps, subscapular and suprailiac) were measured by trained staff using established research protocols standardized by the Department of Nutrition in the Hospital de Perinatología Isidro Espinosa de Los Reyes, Mexico (Lohman et al., 1988). Children had their shoes off and wore hospital gowns during the anthropometric assessments. The weight of each child was measured using a digital scale (BAME Mod 420; Catálogo Médico) and read to the nearest 0.1 kg. The standing height was evaluated using a calibrated stadiometer (BAME Mod 420; Catálogo Médico) and read to the nearest 0.5 cm. BMI = kg/m^2 was calculated from weight and height. BMI z-score was calculated based on the World Health Organization (WHO) growth reference curves for children aged 5–19 years adjusting for children's age and sex (WHO, 2006). A non-stretchable measuring tape (QM 2000; QuickMedical) was used to obtain WC, which was read to the nearest 0.1 cm. Biceps, subscapular and suprailiac skinfold thicknesses were assessed with calibrated skin calipers (Lange; Beta Technology) to the nearest 0.1 mm. WC and skinfold measurements were carried out in triplicate, and the average of all observed values was taken (Yang et al., 2017). Finally, the sum of 3 skinfold thicknesses was obtained. Body fat percentage was estimated using air displacement plethysmograph by Bod Pod (Life Measurement Instruments, Concord, CA) (Fields et al., 2002). The Siri equation was used to calculate body fat percentage (Siri, 1993; Tucker et al., 2014). We performed all the measurements according to the instructions from manufacturer.

2.3. Lead measurements

Maternal tibia (cortical) and patella (trabecular) bone lead levels were assessed at 1 month postpartum to estimate the cumulative fetal exposure to lead. Bone lead was not measured during pregnancy due to restrictions on non-emergent radiation procedures in pregnant women according to Mexican law (Afeiche et al., 2011; Gomaa et al., 2002). Bone lead levels at the tibia and patella were measured using a non-invasive spot-source Cd K-shell X-ray fluorescence instrument constructed at Harvard University. Detailed information regarding the protocol, application, validation and quality control of using this system has been provided elsewhere (Gonzalez-Cossio et al., 1997). This instrument may produce negative values when the bone lead concentration of an individual is low (n = 42 children had maternal patella levels below the limit of detection (2 μg/g)) (Tellez-Rojo et al., 2004). However, the negative values should not be excluded due to the fact that they can better present the true distribution of lead exposure (Specht et al., 2016).

A blood sample was obtained from each child annually from 1 to 4 years. All blood samples were collected and stored in trace-metal-free tubes by trained staff using standardized protocols. Blood lead concentrations were measured using graphite-furnace atomic-absorption spectroscopy (model 3000; PerkinElmer, Chelmsford, MA, USA). The quality control tests have been described elsewhere (Afeiche et al., 2011; Gonzalez-Cossio et al., 1997). The detection limit was 1 μg/dL and all blood lead levels were above the limit of detection. We obtained the cumulative early-life lead levels by calculating the area under curve of repeated measures from 1 to 4 years.

2.4. Covariates

Maternal age, parity and education were collected from questionnaires at the pregnancy visit. For the sensitivity analyses, birth weight was obtained directly from the hospital personnel at delivery or from the medical reports provided by mothers. Hospital personnel

measured birth weight of nude newborns within 12 h of delivery by calibrated beam scales (Oken, Model TD16, Naucalpan, México). Pubertal stage was assessed in children using Tanner stage for pubic hair growth for both sexes (Liu et al., 2019), which was obtained from self-reported questionnaires administered at the follow-up study visit when children were 8–16 years of age. These self-reported pubertal assessments have been validated by comparing with physician-assessed pubertal stages and a panel of sex hormones in ELEMENT children as described previously (Chavarro et al., 2017). Maternal smoking history and gestational age were collected from questionnaires at the pregnancy visit.

2.5. Statistical analyses

The distributions of variables of interest were examined. Descriptive data are presented as mean ± standard deviations (SD) or proportions (%). Geometric mean and 95% confidence intervals (CI) are presented for non-normally distributed variables. Distribution of early-life blood lead was right-skewed and were natural log-transformed prior to analysis. Maternal bone leads were normally distributed. Spearman correlation coefficients were obtained for all the lead biomarkers. To compare the characteristics of included participants with excluded participants, the Wilcoxon signed-rank or Student's t-tests were used to examine differences between continuous variables, and Chi-square tests were adopted to examine the differences between categorical variables. We chose covariates *a priori* based on biological relevance as known predictors of body fat or potential confounders, including maternal age, parity, education (a proxy for socioeconomic status during pregnancy) and calcium treatment group, and children's age, sex and pubertal stage. Although diet is an important predictor of child growth and adiposity, we did not include diet in the models; lead may affect child adiposity by reducing food consumption, which makes diet a potential mediator.

Multivariable linear regression models were applied to examine the association of prenatal bone lead and cumulative early-life blood lead with each outcome (BMI z-score, waist circumference, sum of 3 skinfolds and body fat percentage) separately. Given that the effect of lead exposure on child body fat may be mediated by its influence on estrogen (Dearth et al., 2002; Iavicoli et al., 2004), which modulates growth hormones and subsequently affects child body composition (Juul, 2001; Leung et al., 2004), it is reasonable to evaluate the potential modifying effect of children's sex. In the present study, we included an interaction term between children's sex and each lead biomarker and found that none of the interaction terms were significant (p-interaction > 0.20). Therefore, we did not conduct analyses stratified by children's sex. In addition, we checked the potential nonlinear association between lead and each measure of child body composition using generalized additive models and found no evidence of nonlinearities in this study population (data not shown).

In sensitivity analyses, we evaluated the impact of adjusting maternal smoking history and children's height-for-age z-scores on the association between each lead biomarker and child adiposity. Given that low birthweight and preterm birth have been associated with child body weight and obesity (Vasylyeva et al., 2013; Woo Baidal et al., 2016), we repeated our analyses by excluding children born preterm (gestational age < 37 weeks) or low birthweight (< 2.5 kg) (total n = 26). To further assess the potential modifying effect of children's age (late childhood (< 12 years) vs. early adolescence (≥12 years)) and pubertal status (prepubertal vs. pubertal onset), we included interaction terms between each variable and lead biomarkers. We reran our models to examine the associations of early childhood lead exposure at each year (age 1, 2, 3 or 4) with each measure of child body composition. We repeated our analyses by excluding children who had maternal bone leads below the limit of detection at 2 μg/g. We performed all the analyses using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). We defined statistical significance as $p < 0.05$.

Table 1
Characteristics of included and excluded participants.[a]

Characteristics	Included (total n = 248)		Excluded (total n = 579)		p-value
	Mean (SD) or %	(min, max)	n	Mean (SD) or %	
Child age (years)	12.6 (2.5)	(8.0, 16.0)	578	12.0 (2.6)	0.15
Child female sex	49.5%		539	49.4%	0.88
Age at delivery (years)	25.6 (5.4)	(16.0, 42.0)	539	25.9 (5.4)	0.45
Number of siblings at birth	2.0 (1.0)	(0.0, 6.0)	539	2.0 (1.0)	0.46
Maternal education (years)	10.2 (2.9)	(1.0, 20.0)	537	10.8 (2.9)	0.01
Pubertal stage					
1	29.0%				
2	24.2%				
3	23.4%				
4	20.2%				
5	3.2%				

[a] Pubertal stage was not collected from excluded participants.

3. Results

In our study sample of 248 children, their mean age was 12.6 (SD: 2.5) years; 49.5% were girls (Table 1). On average, mothers were 25.6 (SD: 5.4) years old at delivery, and had two previous pregnancies. When comparing the characteristics between included and excluded participants, only maternal education of included children differed significantly from those who were excluded (mean: 10.2 vs. 10.8 years) (p = 0.01). No significant differences in other characteristics were observed. The distribution of children's BMI, waist circumference, sum of skinfolds and body fat percentage is shown in Table 2. In this study, the mean concentration of maternal patella and tibia lead was 12.3 (SD: 12.5) and 8.9 (SD: 10.0) μg/g, respectively (Table 3). Spearman correlation between maternal patella and tibia lead was moderate at 0.41 ($p < 0.0001$), while maternal bone lead (tibia or patella) and cumulative early-life blood lead were weakly correlated (r = 0.14–0.16) ($p < 0.05$).

We found that higher maternal patella lead was significantly associated with lower child BMI z-score (β = −0.02, 95% CI: 0.03, −0.01), waist circumference (β = −0.12 cm, 95% CI: 0.22, −0.03), sum of skinfolds (β = −0.29 mm, 95% CI: 0.50, −0.08) and body fat percentage (β = −0.09%, 95% CI: 0.17, −0.01) at age 8–16 years, adjusting for maternal age, parity, education and calcium treatment group, and children's age, sex and pubertal stage (Table 4). Maternal tibia lead concentration was not significantly associated with any measurements of adiposity in children. Similarly, no significant associations were detected from early childhood lead exposure.

Table 2
Distributions of BMI, waist circumference, sum of skinfolds and body fat percentage among 248 Mexican children.[a]

	Mean (SD) or %	(min, max)
BMI z-score	0.8 (1.2)	(-2.9, 3.5)
BMI		
< 5th	5.2%	
5th-85th	79.8%	
85th-95th	10.1%	
> 95th	4.8%	
Waist circumference (cm)	70.2 (10.7)	(49.5, 119.0)
Sum of skinfolds (mm)	53.1 (20.8)	(14.0, 105.0)
Body fat percentage (%)	29.0 (7.8)	(7.9, 49.5)

[a] Missing information: sum of skinfolds (n = 2); body fat percentage (n = 50).

Table 3
Distribution of lead concentrations in maternal bones and child blood among 248 Mexican children.[a]

Lead biomarkers	Mean	SD	Min	10%	25%	50%	75%	90%	Max
Maternal patella lead (μg/g)	12.3	12.5	−29.9	−1.5	4.6	10.6	19.7	28.8	50.1
Maternal tibia lead (μg/g)	8.9	10.0	−15.6	−5.2	3.4	8.3	15.2	21.5	38.6
Cumulative blood lead (1–4 years) (μg/dL)	19.6	8.6	6.4	10.5	13.7	17.7	23.5	31.6	55.0

[a] Missing information: maternal tibia lead (n = 23); cumulative blood lead (n = 11).

In sensitivity analyses, adjusting for maternal smoking history (Supplemental Table 1) or excluding children born preterm or low birthweight (Supplemental Table 2) or children's height-for-age z-scores (Supplemental Table 3) did not meaningfully change the observed associations of lead biomarkers with measures of child adiposity. We found that the magnitude, direction and significance of the associations between maternal patella lead and each measure of child adiposity were not altered. The associations of maternal tibia lead and cumulative lead exposure from 1 to 4 years with child adiposity remained insignificant. None of the interaction terms (between lead biomarkers and child age or pubertal status) were significant (p-interaction > 0.30), suggesting that neither pubertal stage (prepubertal vs. pubertal onset) nor child age (< 12 years vs. ≥12 years) modified the associations between lead exposure and child body composition in our study. We reran our analysis to examine the associations of early childhood exposure to lead at each year (age 1, 2, 3 or 4) with child body composition and found no significant associations (Supplemental Table 4), which is consistent with our findings with cumulative early childhood exposure. When excluding children who had maternal bone leads below limit of detection, our results did not change meaningfully, although the association between patella lead and sum of skinfolds became insignificant (β = −0.22, p = 0.15) (Supplemental Table 5).

4. Discussion

To our knowledge, this is the first epidemiological study that examines the prospective associations of both prenatal and early-life lead exposure (< 5 years of age) with body composition in peripubescence; the study extends our previous findings of inverse associations of prenatal lead levels with child weight up to 5 years of age (Afeiche et al., 2011). We provide evidence suggesting that prenatal exposure to lead but not cumulative lead exposure from age 1–4 years is inversely associated with multiple measures of adiposity in Mexican children. Additionally, the association between prenatal lead exposure and peripubertal adiposity did not change by further adjusting for maternal smoking history, child height-for-age z scores or excluding children born preterm or low birthweight.

We found that increasing concentration of maternal patella bone lead was associated with lower BMI z-score, waist circumference, sum of skinfolds and body fat percentage, while maternal tibia lead was not associated with child body fat. Our findings are somewhat consistent with previous investigations (Liu and Peterson, 2016). Two prospective cohort studies with similar lead exposure levels as ours found that higher maternal patella lead but not tibia lead was associated with reduced weight in 329 infants at 1 month (patella: mean = 15.3 μg/g, tibia: mean = 10.1 μg/g) (Sanin et al., 2001) and in 477 girls from 24 to 60 months from ELEMENT study (patella: mean = 10.4 μg/g, tibia: mean = 8.7 μg/g) (Afeiche et al., 2011); no associations were observed in boys. The mean level of patella lead was modestly higher than the concentration reported in Afeiche's study (mean (SD): Afeiche: 10.4 ± 11.8 μg/g vs. ours: 12.3 ± 12.5 μg/g). We only included a subset of Afeiche's study participants, which consists of a smaller percentage of participants from cohort 3 (ours: 6% vs. Afeiche's: 26%). As we described in the Study Population section, cohort 3 was a randomized trial of calcium supplementation during pregnancy and maternal patella lead may be higher in our study because fewer mothers had received calcium supplementation during pregnancy. Other cohort studies using maternal blood lead during pregnancy showed that prenatal low-level blood lead concentration (< 5 μg/dL) during mid- and late-pregnancy was associated with lower weight-for-age z-scores in 244 infants at 6 months from Albany, NY (Schell et al., 2009) and 298 infants at 2 years from South Korea (Hong et al., 2014).

In contrast, Gardner et al. found no association between urinary lead during pregnancy and child weight at age 5 (n = 1505) in rural Bangladesh (Gardner et al., 2013). Similarly, a study of 428 Mexican children aged 4–6 years by Renzetti et al. showed no association of mid- and late-pregnancy blood lead (mean = 3.7–3.9 μg/dL) with BMI z-score or body fat percentage (Renzetti et al., 2017). Another cohort study in Kosovo, Yugoslavia confirmed that blood lead concentration during mid-pregnancy (median = 5.60 μg/dL) was not correlated with BMI up to 10 years of age (Lamb et al., 2008). On the contrary, an animal study revealed that early lead exposure can induce weight gain following a dose-specific pattern (Faulk et al., 2013). The different study populations, age ranges, timing and measures of lead exposure and body composition may contribute to these inconsistent findings. For instance, the use of a single spot urine to estimate lead exposure in Gardner's study (Gardner et al., 2013) may have contributed to exposure misclassification, which may explain the inconsistent findings. The bioelectrical impedance analysis (BIA) used in Renzetti's study (Renzetti et al., 2017) to estimate body composition is more likely to produce larger predictive errors, and can be affected by illness, dehydration and physical activities (Duren et al., 2008). BIA is not as accurate as other criterion methods (e.g. dual-energy X-ray absorptiometry and air displacement plethysmography), especially in overweight and obese children (Duren et al., 2008); this study however did include children with high BMI z-score (Renzetti et al., 2017). Last, because the

Table 4
Adjusted associations of prenatal lead exposure with child adiposity among 248 Mexican children.[a]

	Patella lead		Tibia lead		Cumulative blood lead (1–4 years)[b]	p
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	
BMI z-score	−0.02 (−0.03, −0.01)	0.004	−0.00 (−0.02, 0.01)	0.65	0.02 (−0.40, 0.45)	0.92
Waist circumference (cm)	−0.12 (−0.22, −0.03)	0.01	−0.07 (−0.21, 0.07)	0.32	−0.38 (−3.74, 2.97)	0.82
Sum of skinfolds (mm)	−0.29 (−0.50, −0.08)	0.007	−0.10 (−0.38, 0.19)	0.51	−1.62 (−8.76, 5.52)	0.65
Body fat percentage (%)	−0.09 (−0.17, −0.01)	0.03	−0.01 (−0.13, 0.10)	0.81	2.08 (−0.98, 5.13)	0.18

Note: CI, confidence interval; all models adjusted for maternal age, parity, education and calcium treatment group, and children's age, sex and pubertal stage.
[a] Missing information: sum of skinfolds (n = 2); body fat percentage (n = 50); maternal tibia lead (n = 23); cumulative blood lead (n = 11).
[b] Log-transformed lead exposure.

sample size in the Kosovo study was relatively small when stratifying by residing towns (n = 83–127 for different age groups), the study was likely underpowered to detect significant associations. Unlike other countries, the authors found that high lead exposure was observed in children with higher socioeconomic status in Kosovo, Yugoslavia, which potentially lessened the adverse effect of lead exposure on child growth by the beneficial effects of diet (Lamb et al., 2008).

Maternal bone lead measured at postpartum can be considered a useful biomarker of cumulative fetal lead exposure over the course of pregnancy: first, the mobilization of maternal skeletal lead stores into plasma during pregnancy is the main route of fetal exposure to lead; secondly, maternal bone lead levels vary little during lactation (Gomaa et al., 2002; Gonzalez-Cossio et al., 1997). In our study, maternal patella lead level, but not tibia lead, was inversely associated with child adiposity. The different constitution of these two bone sites may explain this finding. Unlike the tibia bone that consists mostly of cortical bone, patella bone consists mostly of trabecular bone and has much greater rate of lead accumulation. Lead in patella may be more bioavailable for mobilization during pregnancy (Hu et al., 1989, 1998).

Bone lead represents cumulative lead exposure over years to decades, which accounts for about 94% of the body burden of lead in adults (Barbosa et al., 2005). Patella lead, reflecting both current bioavailable lead and cumulative exposure to lead, may serve as a better lead biomarker than both blood and tibia lead (Sanders et al., 2009). Blood lead has also been considered as a reliable measure of lead levels that represent recent lead exposure; it may also represent past exposures due to the fact that lead mobilizes from bone stores back to blood (Barbosa et al., 2005). Urinary lead, reflecting recent exposure, may not serve as a reliable marker of lead burden as compared with bone and blood lead. A spot urine is particularly not a reliable biomarker of lead exposure because it is subject to large biological variations, whereas a 24-h urine collection is a more reliable measure for evaluating lead levels in urine (Barbosa et al., 2005). A spot urine requires a urinary creatinine correction, which was not considered in Gardner's study (Gardner et al., 2013). Furthermore, the use of urinary lead level itself (regardless of a spot urine vs. 24-hours collection) can still be problematic. For instance, urate salts, likely to precipitate in urine during transit and storage, may result in inaccurate measures of lead levels in urine (Barbosa et al., 2005). In addition, it has been suggested that urinary lead levels with the adjustment of glomerular filtration rate may be considered as a proxy for blood lead levels. However, Gardner's study did not measure glomerular filtration rate that could further add to the inaccuracy of lead levels in urine, especially when the authors looked at children under age 5 who did not have fully developed kidney function (Sanders et al., 2009). Moreover, because only a few studies have examined associations of urinary lead with other reliable lead biomarkers (e.g. blood and bone lead), the validity of using urine measurements is largely unknown (Barbosa et al., 2005).

Cumulative early-life lead exposure from 1 to 4 years was not significantly associated with any measures of body fat in children aged 8–16 years. Similarly, a U.S. cross-sectional study of 4391 children aged 1–7 years found that blood lead concentration (mean = 3.6 μg/dL) was not associated with child weight or BMI (Ballew et al., 1999). On the contrary, a cross-sectional study showed that higher blood lead ($\geq$1 μg/dL) was associated with lower BMI in 299 young children aged 2–3 years in Detroit, Michigan (Cassidy-Bushrow et al., 2016). A logitudinal study of 683 U.S. girls found that blood lead concentrations at ages 6–10 years were associated with a decrease in body composition measured repeatedly in these girls from age 7 through 14 years (Deierlein et al., 2019). In our study, we used cumulative early-life exposure (ages 1–4 years) for measuing blood exposure in early childhood; therefore, it is not appropriate to make direct comparisons with other studies that evaluated the association between lead and adiposity using a single time point and cross-sectional design or at an older age. Futhermore, it is possible that the impact of early-life lead exposure is evident on the body fat during infancy and early childhood but not middle and late childhood.

According to our results, pregnancy is potentially a more sensitive period of the impact of lead on adiposity, as compared with early-life lead exposure. This is biologically plausible because lead can readily pass through the placenta into fetal circulation and accumulate in developing organs (Tellez-Rojo et al., 2004). Pregnancy stimulates bone turnover, which increases mobilization of lead from maternal bone stores to produce fetal bone (Tellez-Rojo et al., 2004). Even though environmental lead exposure has been reduced, the fetus can be at risk of lead toxicity because maternal bone lead stores can be retained for decades as a major source of fetal exposure (Hu and Hernandez-Avila, 2002). It has been shown that the third trimester when the fetus is undergoing rapid fetal growth and fat deposition can be a sensitive period for growth and fat development later in life (Rinaudo and Wang, 2012).

The biological mechanisms underlying the association between lead exposure and child adiposity are not clear, but various pathways are potentially involved in these associations. First, it is possible that maternal lead can disrupt the levels of thyroid hormones in pregnant women and restrict the availability of these hormones to fetus (Afeiche et al., 2011; Dundar et al., 2006; Luo and Hendryx, 2014). Second, animal studies found that lead can induce a reduction in body weight by downregulating the food-satiety signals, resulting in decreased food consumption (Hammond et al., 1990). Third, lead-induced body weight reduction can be mediated by the effects of gestational lead on the hypothalamic dopaminergic system. It has been found that obese rats had lower levels of dopamine and its metabolite dihydroxyphenylacetic acid (DOPAC) (Leasure et al., 2008). Finally, gestational lead exposure has been associated with lower serum insulin-like growth factor 1 (IGF-1) level in rats (Ronis et al., 1998).

Our study has some limitations. We did not examine the potential mediating effects of dopamine, thyroid or growth hormones on the association between lead and adiposity, which could potentially improve our understanding of the underlying mechanisms. However, our study has several strengths compared with earlier investigations. We were able to measure cumulative lead exposure during prenatal and early childhood periods. While the majority of earlier investigations relied on blood lead levels during pregnancy, we used bone lead as a more appropriate marker of cumulative prenatal lead exposure. Additionally, we included multiple measures of adiposity to extensively examine the association with lead exposure, and our findings are consistent with previous analyses. Finally, our study used air displacement plethysmograph by Bod Pod to assess body fat percentage, which provides accurate and reliable estimates.

5. Conclusions

We found that prenatal lead exposure was significantly associated with a decrease in child BMI z-score, waist circumference, sum of skinfolds and body fat percentage at age 8–16 years, while no significant associations were observed with early-life exposure. Future research examining the potential mediating effects of dopamine, thyroid or growth hormones are needed to elucidate the biological mechanism underlying these associations.

Conflicts of interest

Myriam C. Afeiche is currently at Nestlé Research, Lausanne, Switzerland and completed this work while at the Harvard School of Public Health.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.06.003.

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