HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Environ Int. 2019 April ; 125: 445–451. doi:10.1016/j.envint.2019.02.021.

Early lead exposure and pubertal development in a Mexico City population

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Abstract

Background: Previous studies have examined the association between blood lead levels and pubertal timing in adolescent girls; however, the evidence is lacking on the role of lead exposure during sensitive developmental periods on sexual maturation.

Objectives: To examine the association of prenatal and early childhood lead exposure with pubertal stages among 264 boys and 283 girls aged 9.8-18.0 years in Mexico City.

Methods: We measured maternal bone lead (a proxy for cumulative fetal exposure to lead from maternal bone stores mobilized during pregnancy) at 1 month postpartum. Blood lead was measured annually from 1-4 years. Pubertal stage was assessed by a pediatrician. We examined the association between lead and pubertal stages of breast, pubic hair and genitalia using ordinal regression. Age at menarche was evaluated using Cox proportional-hazard models.

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Competing financial interests: Myriam C. Afeiche is currently working at Nestle Research, Lausanne, Switzerland and completed this work while at the Harvard School of Public Health. No other potential conflict of interest relevant to this article was reported.

Results: Multivariate models showed that maternal patella lead and early childhood blood lead were inversely associated with breast growth (patella OR=0.72, 95% CI: 0.51–1.00; blood OR=0.70, 95% CI: 0.53–0.93) in girls. Girls with maternal patella lead in the 3rd tertile and child blood lead in the 2nd tertile had a later age at menarche compared with girls in the 1st tertile (patella HR=0.60, 95% CI: 0.41–0.88; blood HR=0.65, 95% CI 0.46–0.91). Additionally, early childhood blood lead was negatively associated with pubic hair growth (OR=0.68, 95% CI: 0.51–0.90) in girls. No associations were found in boys.

Conclusions: These data suggest that higher prenatal and early childhood exposure to lead may be associated with delayed pubertal development in girls but not boys. Our findings are consistent with previous analyses and reinforce the reproductive effects of lead for girls.

Keywords

bone lead; blood lead; pregnancy; early childhood; puberty; age at menarche

1. Introduction

Lead, a ubiquitous environmental toxicant, is associated with a variety of adverse health effects (Bellinger 2011). Infants, children, and pregnant women are the most vulnerable to lead toxicity (National Research Council (U.S.). Committee on Measuring Lead in Critical Populations. et al. 1993). A growing body of research has shown that elevated blood lead levels *in utero* and during childhood are associated with impaired nervous, reproductive and cardiovascular systems (Silbergeld 1990; WHO 2010). Although blood lead levels have decreased over time, mainly due to the phase-out of leaded gasoline (Caravanos et al. 2014; Falk 2003), other routes of exposure still exist and pose a continued public health burden, especially in developing countries such as Mexico (Falk 2003; Schnur and John 2014) and many US inner cities and underserved areas (Bellinger 2016). Moreover, bone lead accumulated from years of exposure is known to both persist for many years and, in pregnant women, serve as a source of prenatal exposure due to the marked increase in bone turnover that is known to occur during pregnancy (Hu and Hernandez-Avila 2002).

Previous studies have shown that lead is readily transferred from mother to offspring by crossing the placental-fetal barrier during gestation and via breast milk during lactation (Koyashiki et al. 2010; WHO 2010). Many existing studies have investigated the association between early-life lead exposure and neurodevelopment in children (Bellinger et al. 1987; Sanders et al. 2009; Schnaas et al. 2006) with a few studies that have linked lead exposure to delayed pubertal timing. Animal studies found that prenatal and early-life exposure to lead resulted in delayed pubertal onset by decreasing serum hormones including estradiol, luteinizing hormone (LH) and insulinlike growth factor-1 (IGF-1) (Dearth et al. 2002; Dearth et al. 2004; Ronis et al. 1996). However, fewer analyses have characterized the potential role of lead in pubertal development across sensitive periods of exposure in human.

In girls, it has been shown that blood lead (3 μg/dL versus 1 μg/dL) was associated with a later age at menarche in African-Americans, delayed breast maturation and pubic hair growth in both African-Americans and Mexican-Americans (Selevan et al. 2003). Blood lead levels (> 2 μg/dL) were also found to be significantly associated with delayed female

pubic hair growth and attainment of menarche in another U.S. investigation (Wu et al. 2003). Blood lead concentration higher than 5 μg/dL has been related to a delay in pubertal development for breast maturation, pubic hair growth, and menarche in 13-year-old South African girls (Naicker et al. 2010). In contrast, two studies provide no evidence for the negative associations in U.S. girls at age 9 (Wolff et al. 2008), and in Polish girls at age 7–16 (Slawinska et al. 2012). The evidence on the role of lead exposure on pubertal development in boys is rare. Two Russian investigations revealed a delayed pubertal onset of genitalia in boys aged 8–9 years (Hauser et al. 2008) and testicular volume (>3mL) in a later follow-up study of the same boys (Williams et al. 2010).

In this study, we aimed at addressing research gaps including the lack of studies that characterize multiple sensitive periods of exposure using a longitudinal design and the studies in boys by examining the prospective association of prenatal and early-life lead exposure with secondary sexual characteristics in girls and boys at age 9.8–18.0 years in Mexico City.

2. Methods

2.1 Study population

Pregnant women were recruited at three public maternity hospitals (Manuel Gea Gonzalez Hospital, Mexican Social Security Institute and the National Institute of Perinatology) in Mexico City, which serve low-to-moderate income population. These mothers were followed for 12 months post-partum and their offspring were followed up to 4 years of age. Mothers completed interview-based questionnaires at baseline and a bone lead measurement. We collected blood samples from children every year from 12 to 48 months of age. We used the exclusion criteria applied to all birth cohorts, as described previously (Afeiche et al. 2011; Hu et al. 2006).

Children at age 9.8-18.0 years (n=550), who were likely to reach different stages of pubertal transition, were re-contacted and were asked to participate in the follow-up studies. The participants were selected if they had available maternal biological samples during pregnancy. Among these participants, 547 children had at least one measurement of maternal bone lead or childhood blood lead. During this visit, a blood sample and an interview-based questionnaire were collected from each child. Pubertal stages of breast, pubic hair and genitalia were evaluated by a trained pediatrician, as described elsewhere (Chavarro et al. 2017). Additionally, each girl was asked if and when she had initiated menses and each boy’s testicular volume was measured by a trained pediatrician using a Prader orchidometer.

Research protocols were reviewed and approved by the ethics committees of participating institutions including the University of Michigan and the Mexico National Institute of Public Health. Informed consent from mothers and informed assent from their offspring were obtained before participation in this study.

2.2 Lead biomarkers

Maternal bone lead at 1 month postpartum was measured at the mid-tibial shaft (cortical bone) and patella (trabecular bone), and was used for estimating cumulative lead exposure to

fetus. These 2 bone levels (separate measurements of tibia and patella) were determined using the X-ray fluorescence instrument, which is a non-intrusive approach and contains low radiation. Given that mobilization of maternal skeletal lead stores is a main route of fetal lead exposure, maternal bone lead can serve as an important biomarker of cumulative fetal lead exposure over the course of pregnancy independent of maternal blood or umbilical cord blood lead levels (Gomaa et al. 2002). The X-ray fluorescence instrument can sometime produce negative values when a person has low concentrations of bone lead (around zero). It is important to include these negative lead values because they can improve the presentation of the true distribution (Specht et al. 2016). Detailed information regarding the protocol, application, validation and quality control of using this system has been described elsewhere (Gonzalez-Cossio et al. 1997; Hu et al. 1989, 1991; Hu et al. 1995). In this study, we measured bone lead at 1 month postpartum, which has been used previously to study prenatal lead exposure and child health outcomes using the same cohort (Afeiche et al. 2011; Zhang et al. 2012).

Each child provided a blood sample (2mL), which was stored in trace-metal-free tubes by trained research assistants using standardized protocols. We evaluated the lead concentration in child blood using graphite furnace atomic absorption spectroscopy (GFAAS). The measurements were carried out at American British Cowdray Hospital and validated by the Maternal and Child Health Bureau and the Wisconsin State Laboratory of Hygiene Cooperative Blood Lead Proficiency Testing Program (Pilsner et al. 2009). The quality control tests were as described previously (Afeiche et al. 2011; Gonzalez-Cossio et al. 1997). All blood lead levels were above the limit of detection (<1 μg/dL). Cumulative early childhood lead exposure was obtained by calculating the area under the curve of repeated measures from 1-4 years.

2.3 Pubertal outcomes

In girls, the stages of pubertal development were defined by a pediatrician using Tanner staging scales for the breast maturation and pubic hair growth (Marshall and Tanner 1969). For breast growth, stage 1 represents having elevation of papilla only. Stage 2 represents the initiation of puberty. The breast tissues further enlarge at stage 3 and 4 and reach full growth at adult level at stage 5 (Marshall and Tanner 1969). For pubic hair growth, stage 1 represents pre-pubertal with no pubic hair. Stage 2 represents initiation of puberty. The pubic hair grows darker and coarser at stage 3 and 4 and reaches adult level at stage 5 (Marshall and Tanner 1969, 1970). Menarche was measured via a self-reported questionnaire. In boys, the stage of sexual maturation was defined by the pediatrician using Tanner staging scales for the development of genitalia and pubic hair. For genital development, stage 1 represents pre-puberty. Stage 2 represents the onset of puberty with enlargement of scrotum and testes. The penis continues to enlarge and further grow at stage 3 and 4 and reaches adult genitalia at stage 5 (Marshall and Tanner 1970). The volume of the testis was used as another indicator of puberty for boys. Right and left testicular volume was determined using an orchidometer ranging from 1 to 25 mL. In our analysis, the larger volume of the right and left testicles was used. A cutoff of 20 mL was applied to represent adult level (≥20 mL) (Burns et al. 2016).

2.4 Statistical analysis

Descriptive statistics were conducted. The distributions of lead measurements were examined. Patella and tibia lead were normally distributed, while early-life lead was skewed to the right. Since normality on independent variable is not required for logistic or Cox proportional-hazard regression models, we elected not to transform the non-normal variable in this study. We calculated Spearman correlation coefficients among all the lead biomarkers. Variables likely to be potential confounders of the association between lead and pubertal development based on biological plausibility or covariates considered to be predictors of outcomes of pubertal measures were included; these included maternal education, marital status, number of siblings at birth and child age. Maternal education and marital status at birth have been shown to be associated with age at menarche (Deardorff et al. 2014; Ramezani Tehrani et al. 2014) and lead levels (Choi et al. 2016; Kim et al. 2018). The number of siblings has been associated with increased menarcheal age (Morris et al. 2010).

Multivariate ordinal regression models were used to examine the association of bone lead at 1 month postpartum and cumulative blood lead from 1-4 years with each of the Tanner stages separately. The dependent variables in this analysis were Tanner staging for pubic hair and breast development (stage 1-stage 5) in girls. In boys, the dependent variables were Tanner staging for pubic hair and genitalia (stage 1-stage 5). We used multivariate logistic regression to examine the association with the attainment of matured testicular volume (≥20mL).

Time-to-event methods were used to analyze the association between lead concentration and age at menarche in girls, which appropriately account for censored data (Kleinbaum et al. 2012). Cox proportional-hazard regression models were applied to estimate hazards ratios (HRs) and 95% confidence intervals (CIs). Time to event (i.e. menarche) was based on the menarcheal age (years) reported by participants or right-censored observations using the age at the assessment of pubertal stages. For this analysis, we treated each lead biomarker as a continuous variable and also as a categorical variable by tertiles. We defined statistical significance as $p < 0.05$. We used SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) to analyze the data.

2.5 Sensitivity Analyses

In the sensitivity analyses, we further adjusted for variables that are possible confounders. To address the potential confounding effect of child growth and body size, we included height and BMI z-score in our models. BMI was calculated and converted to an age and sex-specific z-score based on the World Health Organization (WHO) standard curves for children and adolescents. We also examined the potential confounding effect of early-life lead exposure levels on the association between maternal bone lead and each indicator of pubertal development.

3. Results

Our final analysis included 547 mother-offspring pairs with a total of 283 girls and 264 boys (Table 1). The mean age was 14.5 years, ranging from 9.8 to 18.0 years. In the total sample, the interquartile range (IQR) for maternal patella and tibia and cumulative early-childhood lead was 13.57 μg/g, 13.3 μg/g and 7.66 μg/dL, respectively. Maternal bone lead concentration in the patella at 1 month postpartum was appreciably higher than in the tibia among girls, but not boys (female: median patella 8.2 μg/g; tibia 7.6 μg/g). The median of cumulative early-childhood blood lead was 14.3 μg/dL and 13.8 for boys and girls, respectively. The 3 lead biomarkers were correlated ($p < 0.0001$) (Supplemental Table 1). The Spearman correlation between maternal patella and tibia lead was moderate at 0.48; the correlation was 0.18-0.19 between maternal bone lead (tibia or patella) and cumulative early-childhood blood lead.

Among 264 male participants, 19.1% were at stage 1 (pre-pubertal) and 21.1% were at stage 5 (adult level) for pubic hair growth; 5.6% and 22.7% were at stage 1 and 5 for genitalia, respectively (Table 2). There were 176 boys (70.1%) who had matured testicular volume (≥ 20mL). Among 285 female participants, 7.3% were at stage 1 and 19.6% were at stage 5 for pubic hair growth; 4.3% and 23.3% were at stage 1 and 5 for breast maturation, respectively. Among 238 girls (84.4%) who had attained menarche, the mean (SD) age at menarche was 11.6 (SD=1.2).

We report the associations between one-IQR higher prenatal and early-life lead concentrations and pubertal development in boys (Table 3) and girls (Table 4) using separate models. No significant associations were found in boys between any given lead biomarker and puberty estimated by Tanner stage or testicular volume (Figure 1). In girls, maternal bone lead and early childhood blood lead were negatively associated with puberty. In the fully adjusted models, the odds of reaching a high stage of breast maturation versus combined low and middle stages decreased by 28% (OR: 0.72, 95% CI: 0.51, 1.00, p=0.048) per IQR increase in patella bone lead, and decreased by 30% (OR: 0.70, 95% CI: 0.53, 0.93, p=0.013) per IQR increase in cumulative 1-4 years blood lead (Figure 2). The cumulative early-life blood lead was also negatively associated with pubic hair growth with an OR=0.68 (95% CI: 0.51, 0.90, p=0.006). Maternal tibia lead level was not associated with any indicator of pubertal development in girls.

In addition, after controlling for number of siblings at birth, maternal education and marital status, we found that girls with maternal patella lead in the 3rd tertile (range: 13.0-45.3 μg/g) had a later age at menarche compared with girls in the 1st tertile (<3.9 μg/g) (HR=0.60, 95% CI: 0.41–0.88, p=0.008) (Table 5; Figure 3). In the adjusted models, girls with cumulative 1-4 years blood lead level in the 2nd tertile (range: 12.1-16.1 μg/dL) had a later age at menarche compared with girls in the 1st tertile (<12 μg/dL) (HR=0.65, 95% CI: 0.46–0.91, p=0.013).

In sensitivity analyses, additional adjustment for BMI z-score and height did not significantly change the association of pubertal development with any lead biomarker (Supplemental Table 2-4). The change of the magnitude of these associations ranged from

0% to 7.7% in girls, and from 3% to 17.2% in boys; the associations of puberty with maternal patella and cumulative early-life lead remained significant, although the association between maternal patella and breast maturation became marginally significant ($p = 0.09$). All the associations of lead biomarkers with puberty remained non-significant in boys. Further adjustment for cumulative early-life lead, we found that the parameter estimates of maternal patella lead in all the models were not appreciably changed (Supplemental Table 2 and 4).

4. Discussion

This is the first epidemiological study to investigate the prospective associations of cumulative prenatal (as measured by maternal bone lead at 1 month postpartum) and cumulative early-life lead exposure (as measured by cumulative blood lead 1-4 years) with physical markers of pubertal development in Mexican boys and girls aged 9.8-18.0 years. In the present analysis, higher prenatal and early-life lead exposure were associated with a significant delay in pubertal development among girls. No associations were observed among boys. In the sensitivity analyses, further adjustment for additional potential confounders (e.g. child growth and body size) did not alter these associations.

Our findings are consistent with previous animal studies on female rats measuring the effects of early life lead exposure on pubertal development (Dearth et al. 2002; Dearth et al. 2004; Ronis et al. 1996) and a few cross-sectional analyses performed in girls similarly suggesting a negative association between childhood lead exposure and pubertal development (Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003). However, in the present analysis, no association between a given lead marker and any physical markers of puberty was found in boys, which is inconsistent with previous findings among Russian boys (Hauser et al. 2008; Williams et al. 2010). The use of different study populations, exposure periods, pubertal stages and statistical analyses may contribute to these inconsistencies. For example, the 2 Russian studies in boys examined the onset of puberty (Tanner stage>1) and testicular volume > 3mL in much younger boys (at age 8-12 years), while our study evaluated the pubertal development from stage 1-5 (majority of the boys had Tanner stage>2) and testicular volume ≥ 20mL in older boys aged 10-17 years. The Russian investigations examined lead exposure levels in middle childhood, while we examined much earlier developmental periods during pregnancy and early-life. Furthermore, the significant associations between middle childhood lead exposure and pubertal onset were only observed in the high blood lead group (≥5μg/dL) (Hauser et al. 2008; Williams et al. 2010); the significance disappeared when treating blood lead levels as continuous variables. Therefore, it is possible that the effect of lead is more profound on pubertal onset compared with advanced pubertal stages in boys or male pubertal stages or sex hormones (e.g. testosterone) can only be affected by high lead exposure (≥5μg/dL). In addition, previous studies have found that the concentrations of pubertal hormones (follicle stimulating hormone (FSH) and LH) were much higher in female fetuses than in male fetuses at mid-pregnancy (Debieve et al. 2000). It is possible that the effect of prenatal exposure to lead on sex hormones is more obvious in girls than boys, which eventually advances pubertal development in girls. Further studies evaluating all the sensitive periods are needed to confirm the inconsistent findings.

Furthermore, only patella lead was significantly associated with delayed pubertal development while tibia lead was not. It is possible that these findings are due to the smaller sample size of tibia versus patella measurements, or the difference may be caused by the structure of the two bone sites with the patella, which is made mostly of trabecular bone (versus tibia, which is made mostly of cortical bone) being more vascularized, reflecting more recent lead exposure; in other words, the accumulation of lead is slower in the tibia, and the lead in the patella may also be more bioavailable for mobilization during pregnancy (Afeiche et al. 2011; Hu et al. 1989; Hu et al. 1998).

The negative associations of pubertal development with prenatal and early-life lead exposure in girls in our study are biologically plausible. It has been suggested that early lead exposure can cause decreased pubertal hormones, which subsequently lead to delayed pubertal development (Dearth et al. 2002; Dearth et al. 2004; Ronis et al. 1996). Specifically, early lead exposure can reduce the concentrations of estradiol, LH, and IGF-1 in serum, and then cause a delay in the timing of vaginal opening and the attainment of first estrus in rodents (Dearth et al. 2002; Dearth et al. 2004; Ronis et al. 1996). In addition to animal studies, a cross-sectional analysis of U.S. girls found that blood lead levels (≥ 5 μg/dL versus < 1 μg/dL) were associated with lower serum inhibin-B levels, which was used as an indicator of follicular development (Gollenberg et al. 2010). Since inhibin B is produced from the granulosa cells in the ovaries, it is possible that lead may also have a direct effect on ovaries (Gollenberg et al. 2010). Both developmental stages (prenatal and early-life) can be considered as sensitive periods for pubertal development. It has been found that the hypothalamic-pituitary-gonadal (HPG) axis is active in mid-gestation and early infancy (Liu 2017). In the 2nd trimester, with the increased activity of HPG axis, the concentrations of FSH and LH rise to the amount that is contributing to development of ovaries (Mueller 2013). In early infancy, FSH and LH further increase and reach the peak concentrations. During this period, sex hormones (e.g. estradiol) reach levels that are comparable to the levels at early-middle puberty, which is defined as “mini-puberty of infancy” (Kurtoglu and Bastug 2014). Hence, lead may have an impact on the development of ovaries and sex hormones in pregnancy and early-life, respectively, which may independently affect female pubertal development in later life.

This study was somewhat limited by the sample size for modeling ordinal outcomes. In addition, the mediating effects of serum sex and growth hormones were not evaluated. Given that our study sample represents low-to-middle class among Mexican children, the results may not be generalizable to other socioeconomic populations or populations with different ethnic composition. As with any investigations that report previous events, our study is subject to bias in recall due to the use of self-reported age at menarche. However, previous analyses have shown that the actual age at menarche was highly correlated with self-reported menarcheal age within 5 years of follow-up in peripubertal girls (Koprowski et al. 2001) and 30 years in middle-aged women with baseline age at 7-9 years (Must et al. 2002). The strengths of this study include the ability to examine the impact of lead at multiple life stages on pubertal development, the use of physician-assessed pubertal stages, the measurement of testicular volume as an additional pubertal marker, which has barely been used in previous studies, and the use of maternal bone lead representing cumulative measure of prenatal lead exposure. Given that lead can accumulate in bones with a long half-life

ranging from 10 to 30 years, lead exposure can persist for long periods after external exposure sources have ceased (Hu 1998; Zhang et al. 2012). Mobilization of cumulative bone lead stores during pregnancy into fetal circulation contributes significantly to the fetal exposure to lead (Hu et al. 1998; Tellez-Rojo et al. 2004; Zhang et al. 2012). Therefore, maternal bone lead may be more reflective of lead exposure during sensitive periods, which have been associated with disrupted development of fetus and infants (Tellez-Rojo et al. 2004).

5. Conclusions

We found that higher prenatal and early-life exposure to lead were associated with delayed breast maturation, pubic hair growth and later age at menarche in girls. Future research including mediators such as serum hormonal markers is needed to confirm our results and to deepen our understanding of the mechanism involved in the association between lead exposure during sensitive periods and the neuroendocrine system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the mothers and children who participated in this study and the American British Cowdray Hospital for providing facilities for this research. The study was supported by the grants R01ES021446, R01ES007821, P42ES05947, and P30ES017885 from the U.S. National Institute of Environmental Health Sciences (NIEHS), and the grants P20ES018171/RD83480019 and P01ES022844/RD83543601 from NIEHS/the U.S. Environmental Protection Agency, and by the National Institute of Public Health/Ministry of Health of Mexico.

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Highlights

- Lead is a ubiquitous environmental toxicant, which is associated with a variety of adverse health effects.
- Infants, children, and pregnant women are the most vulnerable to lead toxicity.
- Animal studies found a delay in pubertal onset as a result of prenatal and postnatal lead exposure, but it remains unclear in humans.
- We examined that association of secondary sexual characteristics with prenatal and cumulative lead exposure from 1-4 years of age in children.
- Higher prenatal and early childhood exposure to lead are associated with delayed pubertal development in girls.

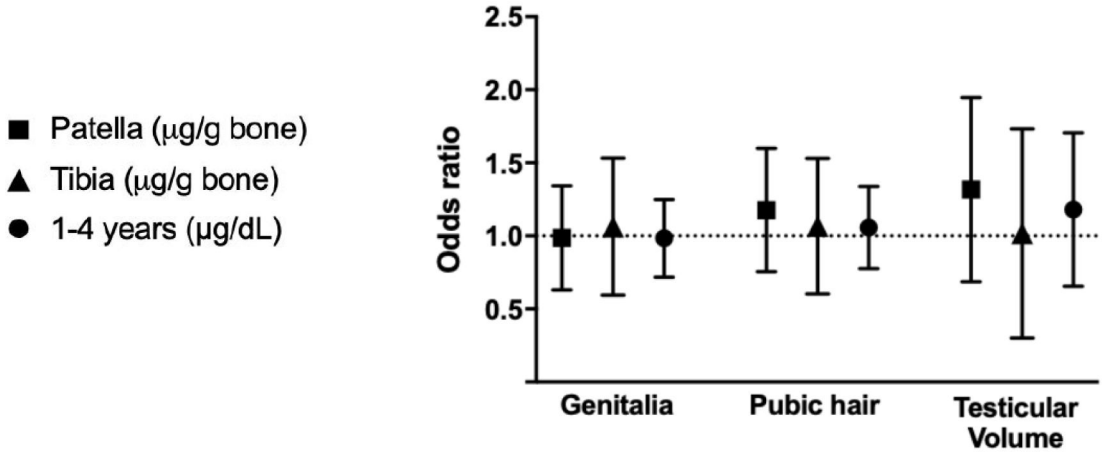

Figure 1.

Odds ratio (95% confidence interval) of physician-assessed pubertal development per IQR increase in maternal bone and early childhood blood lead concentrations in boys. Results adjusted for child age at visit, maternal education and marital status, and number of siblings at birth.

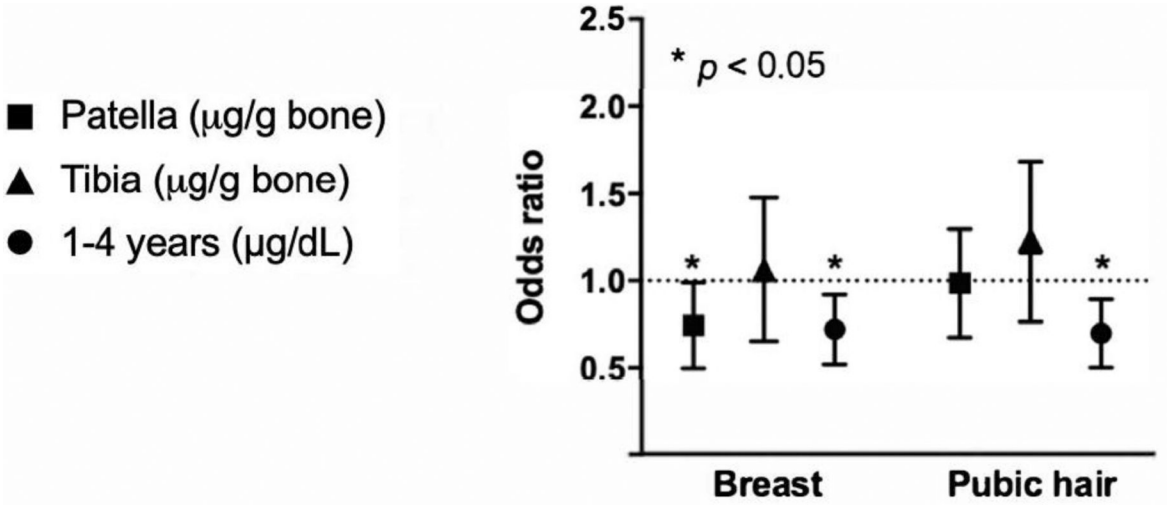

Figure 2.

Odds ratio (95% confidence interval) of physician-assessed pubertal development per IQR increase in maternal bone and early childhood blood lead concentrations in girls. Results adjusted for child age at visit, maternal education and marital status, and number of siblings at birth.

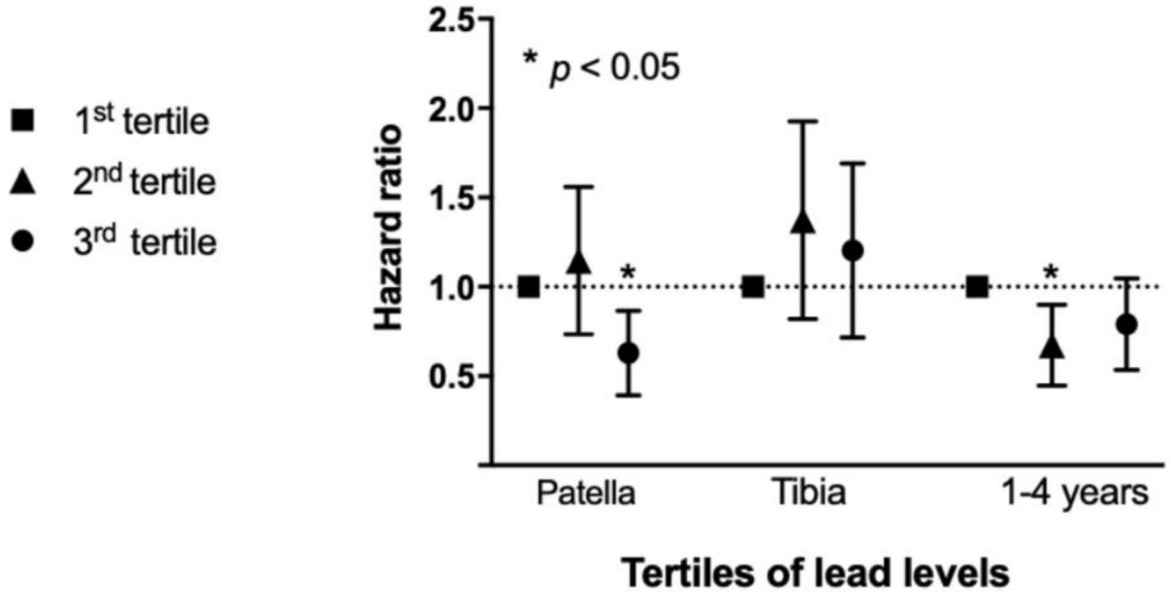

Figure 3.

Hazard ratio (95% confidence interval) of self-reported menarche according to maternal bone lead concentrations and early childhood blood lead concentrations in girls. Results adjusted for number of siblings at birth, maternal education and marital status.

Table 1.

Characteristics of 547 mother-offspring pairs[a]

	Boys		Girls	
	N	**Mean (SD) or %**	**N**	**Mean (SD) or %**
Demoaranhics				
Child age (years)	264	14.5 (2.1)	283	14.5 (2.2)
Number of siblings at birth	263	2.0 (1.0)	280	2.0 (1.0)
Maternal education (years)	263	11.1 (2.8)	280	10.8 (3.0)
Marital status				
Married	191	72.6%	194	69.8%
Not married	72	27.4%	84	30.2%
Lead Biomarkers				
Maternal patella lead (μg/g bone)[b]	230	7.44 (1.05, 14.56)	229	8.20 (1.88, 15.45)
Maternal tibia lead (μg/g bone)[b]	157	7.10 (0.94, 15.93)	177	7.63 (1.68, 13.80)
Cumulative blood lead 1-4 yrs (μg/dL)	255	14.33 (11.60, 18.90)	277	13.83 (10.82, 18.76)

[a] Included children at age 9.8-18.0 years

[b] K-XRF at 1 month postpartum

Values are median (25th and 75th percentile) for lead biomarkers.

Table 2.

Distribution of physician-assessed secondary sex characteristics among children

Measure	Stage	N (%)
Boys		
Pubic hair	1	48 (19.1)
	2	32 (12.8)
	3	63 (25.1)
	4	55 (21.9)
	5	53 (21.1)
Genitalia	1	14 (5.6)
	2	33 (13.2)
	3	44 (17.5)
	4	103 (41.0)
	5	57 (22.7)
Testicular volume	Yes (>=20ml)	176 (70.1)
	No	75 (29.9)
Girls		
Pubic hair	1	20 (7.3)
	2	66 (24.0)
	3	62 (22.5)
	4	73 (26.6)
	5	54 (19.6)
Breast	1	12 (4.3)
	2	28 (10.2)
	3	69 (25.1)
	4	102 (37.1)
	5	64 (23.3)
Menarche	Yes	238 (84.4)
	No	44 (15.6)

Table 3.

Odds ratio (95% confidence interval) of physician-assessed pubertal development per IQR increase in maternal bone and early childhood blood lead concentrations in boys

	Model 1[a]			Model 2[b]		
	n	**OR (95% CI)**	**p - value**	**n**	**OR (95% CI)**	**p - value**
Genitalia						
Maternal patella lead	218	0.95 (0.67, 1.34)	0.776	218	0.95 (0.65, 1.36)	0.748
Maternal tibia lead	148	1.04 (0.67, 1.62)	0.867	148	1.00 (0.63, 1.56)	0.993
Cumulative blood lead 1-4 yrs	241	0.92 (0.70, 1.20)	0.544	241	0.96 (0.73, 1.26)	0.788
Pubic hair						
Maternal patella lead	218	1.00 (0.71, 1.42)	0.975	218	1.13 (0.78, 1.62)	0.539
Maternal tibia lead	148	1.00 (0.64, 1.54)	0.980	148	1.00 (0.64, 1.56)	0.999
Cumulative blood lead 1-4 yrs	241	0.97 (0.74, 1.26)	0.829	241	1.03 (0.79, 1.35)	0.836
Testicular volume						
Maternal patella lead	218	1.11 (0.70, 1.77)	0.642	218	1.22 (0.74, 1.99)	0.436
Maternal tibia lead	148	0.83 (0.40, 1.71)	0.611	148	0.85 (0.40, 1.80)	0.666
Cumulative blood lead 1-4 yrs	241	1.05 (0.68, 1.63)	0.838	241	1.10(0.70, 1.74)	0.662

Note: OR, odds ratio; CI, confidence interval; IQR, interquartile range; IQR maternal patella lead =13.57 μg/g; IQR maternal tibia lead =13.3 μg/g; IQR cumulative blood lead 1-4 yrs = 7.66 μg/dL.

[a]For genitalia and pubic hair, all estimates are from ordinal regression models. For testicular volume, all estimates are from logistic regression models. All models adjusted for child age at visit.

[b]For genitalia and pubic hair, all estimates are from ordinal regression models. For testicular volume, all estimates are from logistic regression models. All models adjusted for child age at visit, maternal education and marital status, and number of siblings at birth.

Table 4.

Odds ratio (95% confidence interval) of physician-assessed pubertal development per IQR increase in maternal bone and early childhood blood lead concentrations in girls

	Model 1[a]			Model 2[b]		
	n	OR (95% CI)	p - value	n	OR (95% CI)	p - value
Breast						
Maternal patella lead	223	0.71 (0.51, 0.99)	0.042	223	0.72 (0.51, 1.00)	0.048
Maternal tibia lead	172	0.97 (0.66, 1.43)	0.873	172	1.01 (0.68, 1.50)	0.966
Cumulative blood lead 1-4 yrs	269	0.73 (0.55, 0.95)	0.022	269	0.70 (0.53, 0.93)	0.013
Pubic hair						
Maternal patella lead	223	0.96 (0.71, 1.33)	0.824	223	0.95 (0.69, 1.31)	0.752
Maternal tibia lead	172	1.13 (0.77, 1.64)	0.544	172	1.16(0.80, 1.71)	0.444
Cumulative blood lead 1-4 yrs	269	0.70 (0.53, 0.92)	0.009	269	0.68 (0.51, 0.90)	0.006

Note: OR, odds ratio; CI, confidence interval; IQR, interquartile range; IQR maternal patella lead =13.57 μg/g; IQR maternal tibia lead =13.3 μg/g; IQR cumulative blood lead 1-4 yrs = 7.66 μg/dL.

[a] All estimates are from ordinal regression models adjusted for child age at visit.

[b] All estimates are from ordinal regression models adjusted for child age at visit, maternal education and marital status, and number of siblings at birth.

Table 5.

Hazard ratio (95% confidence interval) of self-reported menarche according to maternal bone and early childhood blood lead concentrations in girls

	Model 1[a]			Model 2[b]		
	n	**HR (95% CI)**	**p - value**	**n**	**HR (95% CI)**	**p - value**
Menarche						
Maternal patella lead (μg/g bone)						
Continuous lead	229	0.83 (0.68, 1.00)	0.049	229	0.83 (0.68, 1.00)	0.056
1st tertile (<3.9)	76	Reference	-	76	Reference	-
2nd tertile (4.0-12.9)	77	1.10 (0.77, 1.57)	0.602	77	1.10 (0.76, 1.58)	0.611
3rd tertile (13.0-45.3)	76	0.59 (0.41, 0.85)	0.005	76	0.60 (0.41, 0.88)	0.008
Maternal tibia lead (μg/g bone)						
Continuous lead	177	1.03 (0.82, 1.27)	0.854	177	1.01(0.82, 1.27)	0.890
1st tertile (<4.6)	59	Reference	-	59	Reference	-
2nd tertile (4.7-11.3)	59	1.20 (0.80, 1.81)	0.373	59	1.30 (0.86, 1.96)	0.222
3rd tertile (11.4-37.3)	59	1.16 (0.77, 1.74)	0.478	59	1.14(0.75, 1.72)	0.537
Cumulative blood lead 1-4 yrs (μg/dL)						
Continuous lead	277	0.93 (0.79, 1.10)	0.377	277	0.91(0.77, 1.09)	0.300
1st tertile (<12.0)	92	Reference	-	92	Reference	-
2nd tertile (12.1-16.1)	93	0.66 (0.47, 0.92)	0.013	93	0.65 (0.46, 0.91)	0.013
3rd tertile (16.2-51.5)	92	0.77 (0.56, 1.07)	0.119	92	0.76 (0.55, 1.06)	0.109

Note: HR, hazard ratio; CI, confidence interval.

[a] All crude estimates are from Cox proportional-hazard models.

[b] All estimates are from Cox proportional-hazard models adjusted for number of siblings at birth, maternal education and marital status.