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Early Lead Exposure is Associated with Molar Hypomineralization

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Abstract

Purpose: To determine the association of prenatal and early life exposure to lead and the presence of Molar Hypomineralization (MH) in a group of Mexican children.

Methods: A subset of participants of the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENTS) cohort study was examined for the presence of Molar Hypomineralization using the European Academy of Pediatric Dentistry (EAPD) criteria. Prenatal lead exposure was assessed by K-ray fluorescence measurements of patella and tibia lead and by maternal blood lead levels by trimester and averaged over trimesters. Postnatal exposure was assessed by levels of maternal blood lead at delivery and child blood lead at 12 and 24 months.

Results: A subset of 506 subjects from the ELEMENT cohorts (9–18 years old) were examined for MH. 87 subjects (17.2%) had MH. Maternal blood lead levels in the third trimester [OR: 1.08; 95% CI: (1.02, 1.15)] and averaged over three trimesters [OR: 1.10; 95% CI: (1.02, 1.19)] were significantly associated with MH status. None of the maternal bone lead or the child's blood lead parameters was significantly associated with the presence of MH ($p > 0.05$).

Conclusions: The study documents a significant association between prenatal lead exposure especially in late pregnancy and the odds of Molar Hypomineralization.

Keywords

Molar hypomineralization; Lead; Prenatal; Enamel defects

Introduction

Molar hypomineralization (MH) is a common developmental enamel defect characterized by asymmetrical distribution of hypomineralized demarcated opacities of the permanent first molars (PFM) with or without involvement of the permanent incisors¹. Recent years have witnessed the growing efforts of oral health professionals to define the burden and the underlying determinants of these developmental defects. The MH global prevalence is estimated to be around 13%–14%, with the highest estimates of 18% from South America^{2,3}. However, reports from Mexico have estimated MH to be 16% among public elementary schoolchildren⁴ and as high as 35% in children with low socioeconomic background⁵, surpassing the MH global figures.

Systemic and environmental insults ensuing around and a few years after birth have been linked to disruption of amelogenesis of the permanent first molars with resultant soft porous hypomineralized enamel⁶. While acknowledging the regional disparities and the different factors that govern the individual's reaction to environmental toxicants, exposure to these toxicants, such as lead, remains a major public health concern for the pediatric population in Mexico⁷. Even in recent years, the lowest mean blood lead level in a Mexican birth cohort (2008–2015) was found to be more than double the mean reported among US children (NHANES 2013–2014)⁸.

The plausibility of Molar Hypomineralization (MH) being a multifactorial condition that involves the interaction of genetic susceptibility factors with environmental insults is now generally accepted^{9–15}. However, the identification of specific environmental risk factors remains under-studied. Demarcated hypomineralization opacities of PFMs have been linked to exposure to endocrine-disrupting chemicals (EDC) such as Bisphenol A^{16,17}, polychlorinated biophenyls (PCBs) and dioxins^{18–21} or combinations of these EDCs²². Other environmental toxicants, including lead (chemical symbol Pb), have been less studied in relation to demarcated hypomineralization opacities of the PFMs. There have been in vitro reports suggesting that the potential inhibitory effect of metal ions, including lead, on Metalloproteinase²³, a major enzyme group responsible for degradation of enamel matrix proteins during the enamel maturation process²⁴. Animal studies have confirmed that exposure to lead is associated with interfering with the mineralization of enamel²⁵ and can even potentially exacerbate the severity of fluorosis-induced enamel hypomineralization defects through a synergistic mechanism²⁶.

The potential role of lead in interfering with the enamel maturation process as well as lead's known ability to cross the placenta²⁷ justify the importance of the present study. Therefore, this study aimed to determine the association of prenatal and early life exposure to lead with the presence of MH in a group of Mexican children.

Methods

Ethical clearance

This study protocol was reviewed and approved by the Medical School Institutional Review Board of ethical, biosafety, and research committees of the National Institute of Public Health in Mexico and by the institutional review board of Indiana University, Indiana, USA. Subjects were selected from the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) cohort study.

Study population

Overall, the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) consists of three prospective cohorts (cohort 1, 2, and 3) recruited sequentially during the years 1994–2003²⁸. For this analysis, only subjects from cohorts 2 (1997–1999) and cohort 3 (2001–2003) were included. More details about the cohorts and recruitment stages are available elsewhere.²⁸

Study subjects who had their parents/guardians' signed consents and appropriate authorizations for the release of medical information for research purposes and had at least one previous visit as part of the ELEMENT study, with at least one collection of blood samples, were scheduled to receive a dental exam. Additionally, assents were also collected from participants who were 18 years or younger. Subjects who demonstrated inability to comply with or allow procedures, and those who had fixed orthodontic treatment were excluded from the study. Complete description of the study population is shown in figure 1.

Dental examinations

All dental examinations were performed by a single experienced pediatric dentist (J.L.U.). A trained dental assistant recorded all data on a paper format that were transferred into a dataset developed by the programmers of The National Institute of Public Health of Mexico using FoxPro System 2.6 (Fox Software Microsoft). All dental examinations were performed using portable headlight (Zeon™ Endeavour portable LED headlight system, Light intensity 34–68 lumens, Orascoptic, Wisconsin, USA) in a portable chair with No. 5 front surface mirrors and blunt dental explorers. Due to the nature of the investigation, cross infection guidelines procedures were followed. Prior to dental examination, each study participant was asked to thoroughly brush their teeth using regular toothpaste and toothbrush in order to eliminate dental plaque from the tooth surfaces. If large debris or plaque were still covering tooth surfaces, then the examiner used the subject toothbrush to remove debris and plaque. The presence of MH was the outcome variable. MH was diagnosed using the EAPD MH criteria. Any subject with demarcated opacity or the clinical consequence thereof (post-eruptive breakdown of enamel, atypical restoration, or extraction due to MH) of at least one PFM surface was considered a confirmed MH. A positive MH status was identified when subject had at least one PFM tooth surface with any of the EAPD MH criteria.

Exposure variables and their processing

Prenatal and postnatal whole blood lead data—Blood lead was measured for children's mothers at each trimester of the mother's pregnancy and in cord blood at delivery,

and for children at ages 12 and 24 months. T1, T2, and T3 refer to each trimester of pregnancy respectively. Prenatal maternal venous blood Pb data were available only from sub-cohort 2A PL and cohort 3 SF but not from sub-cohort 2B BI, because this cohort was recruited during delivery. Overall, 371 blood Pb samples taken at T1, 379 at T2, and 360 at T3 trimester visits were available for analysis. For postnatal blood Pb, 396 and 440 subjects had at least one venous blood Pb sample taken during any visit at 12 or 24 months of age respectively. Details on blood sample collection and storage using standardized protocols are described elsewhere²⁸.

Bone lead data—Given that the goal of this study was to fully understand the potential impact of prenatal lead exposure on MH status, the potential impact of maternal lead burden, as measured by the K-x-ray fluorescence was also examined. Bone lead was measured prenatally in patella and tibia bones and adjusted using uncertainty estimates provided by the K-x-ray fluorescence instrument, as described in detail elsewhere²⁹.

Calcium supplementation trial

The mobilization of maternal longstanding bone lead stores into the circulation is heightened during pregnancy and represents a sustained endogenous source of fetus/infant lead exposure via blood cord and/or breast milk. Calcium dietary supplements have been used as an effective prevention strategy during pregnancy to reduce lead levels in the mother's circulation and their unborn fetus/nursing infants³⁰. Cohort 3 subjects had participated in a randomized double-blind placebo-controlled trial of calcium supplements to reduce the mobilization of lead from maternal bone. They were randomly assigned to receive a daily supplement of 1,200 mg calcium (in the form of two-600 mg tablets calcium carbonate (Lederle, Inc.) at bedtime) or placebo. At three time points (baseline-1st trimester, and 6 (2nd) and 8 (3rd) months gestation), blood lead levels, dietary calcium intake, and reported use of lead-glazed ceramics were assessed. Compliance was assessed by pill count at each visit.

Statistical analysis

All statistical analyses were performed using R software (version 3.6). The association between acute (blood) and chronic (bone) lead exposures and MH status was estimated in participants in all cohorts through logistic models adjusting for sex, age, calcium treatment and cohort. The MH association with maternal blood levels were examined per trimester and averaged over three trimesters. Due to high correlations of lead, individual blood lead measurements as well as maternal blood lead (averaged over trimesters) and child blood lead (averaged over 24 months) were considered as exposures in the analysis, separately for each model. Due to the presence of negative bone lead measurements introduced by the K-x-ray fluorescence machine when adjusting for measurement uncertainty, the association between bone lead quartiles and MH was estimated.

Potential confounders and logistic regression model—Potential confounders examined were sex, age, smoking during pregnancy and maternal education in Table 2. Age was categorized into 9.5 to <12 years, 12 to <14 years, 14 to <16 years, and 16 to 18 years. Maternal education was obtained from questionnaires mothers completed

during the original enrollment visit and categorized as <9 years, 9 to <12 years, 12 years, or >12 years. For the purposes of evaluating the unadjusted association between lead and MH, lead was categorized into quartiles. Pairwise associations of MH status with sociodemographic and lifestyle characteristics and lead exposure were examined first to identify potential confounders. Maternal education was included as a confounder in the logistic regression models since it showed a suggestive association with MH status and, as a proxy for socioeconomic status, has been shown in the literature to be associated with lead exposure³¹. In addition, child's sex and continuous age at the dental visit were included as confounders since these are biologically relevant variables. Based on the established biological associations between plasma lead levels, calcium intake and fetus/infant exposure to lead via cord lead and breastmilk, cohort and calcium treatment were considered as confounders. Calcium treatment was coded as 1 for all participants with calcium supplementation in cohort 3SF and coded as 0 otherwise.

MH status was regressed on each lead biomarker – maternal blood lead by trimester and averaged over trimesters, maternal blood lead at delivery, child blood lead at the two time points (12 and 24 months) and averaged over the two time points, and maternal bone lead quartiles for patella and tibia – adjusting for the confounders.

Results

Descriptive results

A total of 506 subjects from the ELEMENT cohort study comprised the study population. A total of 87 subjects showed at least one PFM diagnosed with MH (17.2%). Maternal prenatal lead data were obtained from cohort 2A PL (n=123) and cohort 3 SF (n= 275). Umbilical cord and maternal blood and bone data were available from all three ELEMENT cohorts (PL, SF, BI). Table 1 shows the descriptive statistics and lead levels of the child- mother study pairs. Table 2 shows the unadjusted associations of confounders and lead levels by quartile with MH status.

MH and child and maternal lead

Table 3 and Table 4 show the logistic regression results for the associations between the presence of MH and the maternal bone and blood lead levels during the first, second, and third trimesters as well as the child's mean blood lead levels. Maternal blood lead averaged over three trimesters was significantly associated with MH status [OR: 1.10; 95% CI: (1.02, 1.19)]. This association is likely driven by the significant association between maternal blood lead in the third trimester and MH status [OR: 1.08; 95% CI: (1.02, 1.15)]. Adjusting for sex, age, calcium treatment, and cohort, a one standard deviation increase in mother's average blood lead was significantly associated with a 43% increase in the odds of MH, and a one standard deviation increase in mother's third trimester blood lead was significantly associated with a 38% increase in the odds of MH.

None of the maternal bone lead or the child's blood lead parameters was significantly associated with the presence of MH ($p>0.05$). This is consistent with the unadjusted results in table 2.

Discussion

Lead is a very common heavy metal toxicant and is one of the five heavy metals that are involved in endangering the health by its ability to provoke multiple organ damage, even at low level of exposure³². The impacts of exposure to lead are more conspicuous in children making the pediatric population the most vulnerable to lead³³. Moreover, evidence indicates that lead concentration in fetal cord blood and maternal blood are closely related suggesting that lead freely crosses the human placental barrier resulting in early fetal exposure to lead³⁴.

In this secondary data analysis from a Mexican cohort of children, a significant association was determined between molar hypomineralization and maternal blood lead during pregnancy, but not with the child's blood lead level up to two years after birth. The study population had a mean blood lead of 4.52 µg/dL, which is less than the geometric means of Mexican blood lead level (urban: 8.85 µg/dL, dropping to 5.36 µg/dL after the phasing out of leaded-gasoline in Mexico in 1997)⁷. The mean blood lead level of the study child participants' is also slightly less than the 5.0 µg/dL value identified by the CDC as the upper reference value of US children with elevated blood lead level³⁵.

Nevertheless, analyzing the range of blood lead levels of the study subjects reveals extremely variable values (some blood Pb reaching as high as 26.0 µg/dL). This offspring was born after 1997 where environmental exposure to lead in Mexico has been drastically reduced due to the secession of leaded gasoline. However, knowing that the study subjects belong to a population of low socioeconomic background, in addition to the variable demographic and maternal exposure factors might justify the reasons behind the remarkable variations of the blood lead levels.

Apart from this being the first study examining the correlation between MH and the early-life lead exposure, the study is also considered one of the very few that has employed biological blood sample monitoring as means to determine the level of exposure to environmental toxicants. Among the available published literature, only a single study has examined blood level as an exposure indicator in correlation to MH³⁶. However, the findings of this single study could not be compared to ours because of the inherent structural and metabolic dissimilarities between the two environmental toxicants investigated; lead and PCBs. The other human studies exploring the correlation between MH and exposure to environmental toxicants other than lead, such as dioxin¹⁸ and PCBs^{37 36} have been either affirmative or equivocal. Regardless of the putative environmental toxicant investigated, these studies have used exposure surrogates other than blood samples such as breast milk^{19 37}, soil samples²¹, food samples³⁷, placental samples²⁰, or maternal serum³⁷.

Reasonably agreeing with the findings of this study, the other available assenting evidence of the effect of lead on enamel maturation is mainly extracted from animal model studies. Gerlach et al., 2002 examined the effect of lead (0, 34, and 170 ppm lead in drinking water) on enamel development of rat incisors over the whole course of enamel formation²⁵. Consistent with the literature conclusions³⁸, the study findings suggested a significant altered protein contents of enamel in rats receiving lead when compared to those not

receiving lead, most likely due to the in-vitro alleged effect of heavy metals, including lead, on the activity of enamel proteinases²³. However, in contradiction to the confirmed reduction of mineral content of MH enamel³⁸, the same animal study was not able to reach similar outcomes when the enamel mineral density in lead and control animals was compared. Moreover, while the process of human enamel maturation³⁹ as well as the mechanism of action and molecular targets of lead⁴⁰ are somehow comparable in humans and animals, appraisal of lead absorption and excretion processes in humans and animals can be very complicated⁴¹.

Maternal bone lead levels are mobilized during pregnancy and constitute a source of fetal lead exposure that isn't fully captured by measuring maternal blood lead levels during pregnancy, in part because there is evidence that the lead mobilized from bone travels from plasma directly across the placenta without fully equilibrating with lead in red cells⁴². In this study, maternal blood lead in the calcium supplemented cohort were not different from the placebo non-calcium cohort. The potential interactions of lead exposure and cohort, and lead exposure and calcium treatment were evaluated, but none of the interaction terms were significant and all these models fit less well than those presented in this study. When scrutinizing the findings of this study, certain critical issues should be considered before drawing final conclusions. First of all, the permanent first molar mineralization takes place around birth and the immediate postnatal period up to three years and disturbances during the gestation might be less attributed to the interruption of mineralization of the permanent first molars. However, a recent meta-analysis of MH- related systemic influences has identified that children born to mothers with health problems during gestation has 40% higher odds of having MH than those born to healthy mothers during gestation¹³. While it remains unexplainable why the third-trimester high maternal blood lead levels were associated with MH, the postulation that gestational problems- in this case high maternal blood lead- are important determinants of enamel mineralization could not be excluded.

The other issue is that lead mobilization from maternal skeleton during pregnancy and lactation is a recognized manifestation⁴³ and that calcium supplementations have been associated with reduction in blood lead level during pregnancy and lactation⁴⁴, yet, this reduction is controlled by several dynamics such as maternal age and height⁴⁵, strict compliance with the intake of dietary calcium, and the initial pre-calcium maternal bone lead load⁴⁶.

Conclusions

- This study confirms a significant association between elevated maternal blood lead levels throughout pregnancy and the odds of Molar Hypomineralization.
- The finding of the study contributes to the quest of putative environmental risk factors and validates previous findings that optimal health including enamel health is associated with reduced lead exposure and that gestational health problems- in this case high maternal blood lead- are important determinants of enamel mineralization.

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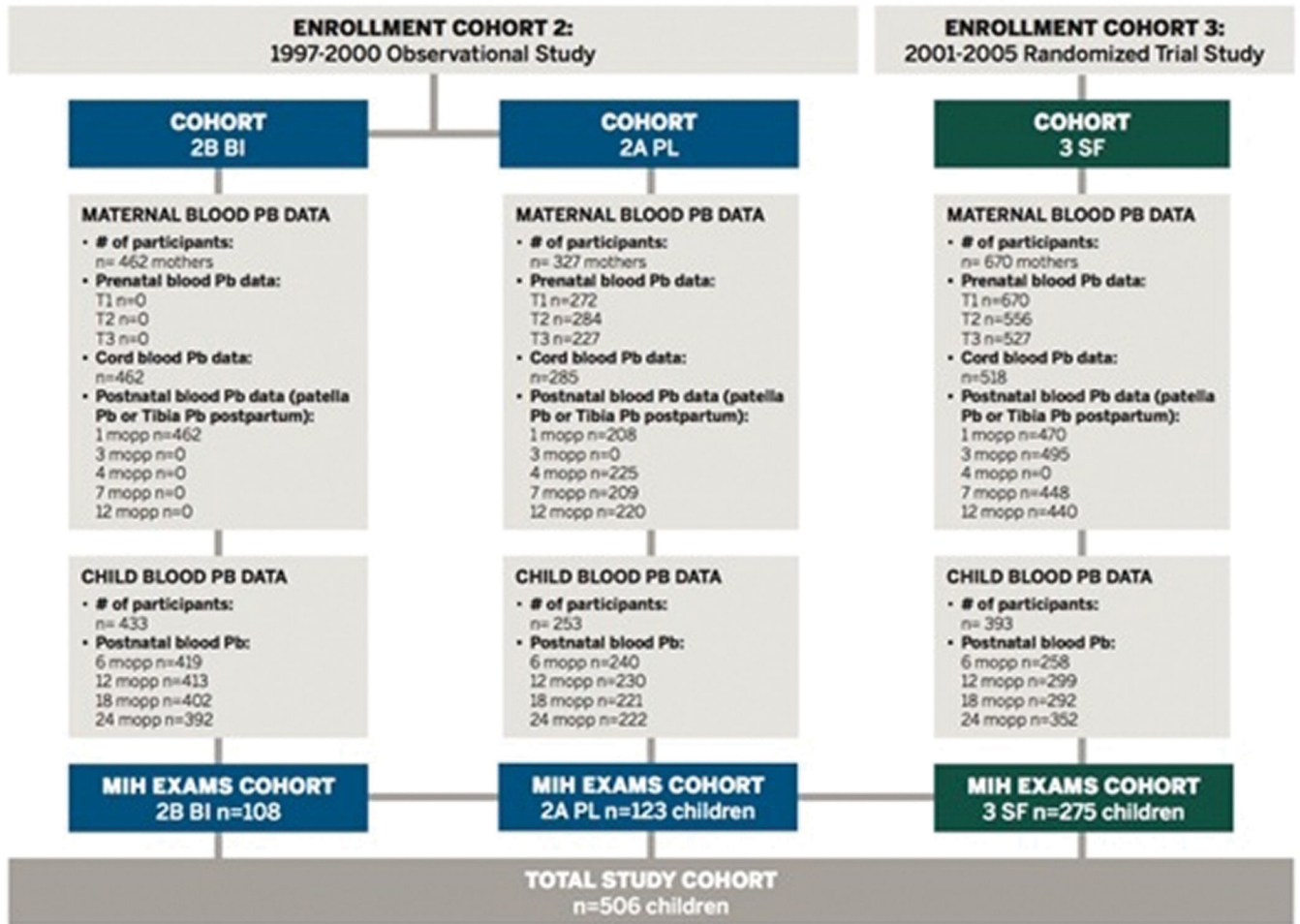


Figure 1:
Flowchart outlining the study population

Table 1.

Summary statistics of sociodemographic and lifestyle characteristics and lead exposure of the study subjects and their mothers

Sociodemographic and lifestyle characteristics	N	Summary Statistic	Range*
Sex (N, %)	501	Female (253, 50%)	0,1
MH status (N, %)	506	MH (87, 17.2%)	0,1
Age in years (Mean, SD)	506	14.3 (2.1)	9–18
Smoking during pregnancy (N, %)	501	No smoking (485, 96.8%)	yes, no
Mother's education in years (Mean, SD)	501	10.9 (2.9)	2–21
Mother's blood lead, first trimester** (Mean, SD)	371	5.7 (4.3)	0–36
Mother's blood lead, second trimester** (Mean, SD)	379	5.1 (4)	0–39
Mother's blood lead, third trimester** (Mean, SD)	360	5.5 (4.1)	0–39
Mother's blood lead, delivery** (Mean, SD)	117	7 (4.4)	0–33
Mother's bone lead, rotula** (Mean, SD)	422	8.7 (10.6)	–14–48
Mother's bone lead, tibia** (Mean, SD)	297	7.8 (10)	–16–38
Child's blood lead, 12 months** (Mean, SD)	396	4.5 (3.1)	0–21
Child's blood lead, 24 months** (Mean, SD)	440	4.7 (3.5)	0–37

Abbreviations used in this table: MH=Molar Hypomineralization, SD=Standard Deviation.

* Ranges of continuous variables are denoted by a dash “-”. Ranges of categorical variables are denoted by a comma “,”

** Lead measuring unit is µg/dL.

Table 2.

Association between lead exposure, sociodemographic and lifestyle characteristics and Molar Hypomineralization

Sociodemographic and lifestyle characteristics	N	MH status* p(q)**
Sex		
Male	248	0.17 (0.38)
Female	253	0.17 (0.38)
P value [†]		0.89
Age group, years (y)		
9.5 to <12 y	93	0.18 (0.39)
12 to <14 y	154	0.18 (0.38)
14 to <16 y	101	0.14 (0.35)
16 to 18 y	158	0.18 (0.39)
P, trend ^{††}		0.94
Smoking during pregnancy		
Yes	11	0.09 (0.3)
No	490	0.17 (0.38)
P value [†]		0.47
Education		
8 y or less (secondary or primary)	60	0.17 (0.38)
9 to 11 y (some high school)	198	0.22 (0.42)
12 y (completed high school)	171	0.13 (0.34)
>12 y	72	0.12 (0.33)
P, trend ^{††}		0.09
Mother's blood lead quartiles, first trimester		
0.8 to 2.9 µg/dL	92	0.18 (0.39)
2.9 to 4.7 µg/dL	94	0.12 (0.32)
4.7 to 7.25 µg/dL	92	0.18 (0.39)
7.25 to 35.8 µg/dL	93	0.16 (0.37)
P, trend ^{††}		0.99
Mother's blood lead quartiles, second trimester		
0.1 to 2.55 µg/dL	95	0.14 (0.35)
2.55 to 4 µg/dL	86	0.17 (0.38)
4 to 6.55 µg/dL	103	0.15 (0.35)
6.55 to 38.2 µg/dL	95	0.19 (0.39)
P, trend ^{††}		0.44
Mother's blood lead quartiles, third trimester		
0.9 to 2.9 µg/dL	88	0.15 (0.36)
2.9 to 4.6 µg/dL	101	0.14 (0.35)
4.6 to 6.72 µg/dL	81	0.15 (0.36)
6.72 to 38.1 µg/dL	90	0.22 (0.42)

Sociodemographic and lifestyle characteristics	N	MH status* p(q)**
P, trend ^{††}		0.17
Mother's blood lead quartiles, delivery		
0.9 to 4.3 µg/dL	27	0.26 (0.45)
4.3 to 6.1 µg/dL	34	0.09 (0.29)
6.1 to 8.4 µg/dL	27	0.19 (0.4)
8.4 to 32.4 µg/dL	29	0.28 (0.45)
P, trend ^{††}		0.58
Mother's bone lead quartiles, rotula		
-13.57 to 1.09 µg/dL	106	0.18 (0.39)
1.09 to 7.67 µg/dL	105	0.16 (0.37)
7.67 to 14.62 µg/dL	105	0.17 (0.38)
14.62 to 47.07 µg/dL	106	0.22 (0.41)
P, trend ^{††}		0.46
Mother's bone lead quartiles, tibia		
-15.57 to 1.19 µg/dL	74	0.23 (0.42)
1.19 to 7.27 µg/dL	75	0.17 (0.38)
7.27 to 14.71 µg/dL	73	0.18 (0.39)
14.71 to 37.28 µg/dL	75	0.15 (0.36)
P, trend ^{††}		0.22
Child's blood lead quartiles, 12 months		
0 to 2.5 µg/dL	98	0.16 (0.37)
2.5 to 3.7 µg/dL	98	0.14 (0.35)
3.7 to 5.7 µg/dL	105	0.22 (0.42)
5.7 to 20.4 µg/dL	95	0.18 (0.39)
P, trend ^{††}		0.46
Child's blood lead quartiles, 24 months		
0.8 to 2.7 µg/dL	105	0.19 (0.39)
2.7 to 3.8 µg/dL	122	0.18 (0.39)
3.8 to 5.5 µg/dL	100	0.16 (0.37)
5.5 to 36.8 µg/dL	113	0.19 (0.39)
P, trend ^{††}		0.85

Abbreviations used in this table: MH= Molar Hypomineralization.

* MH status defined as any subject with at least one permanent first molar with any of the EAPD diagnostic criteria.

** p is the proportion of subjects with MH, q is the standard deviation of the proportion (p), also expressed as $\sqrt{p(1-p)}$.

[†] For dichotomous characteristics, P values are from Wilcoxon tests.

^{††} For ordinal characteristics, P for trends are from logistic regression models with MH status as the dependent variable and a continuous variable representing ordinal categories of the sociodemographic or lifestyle predictor as the independent variable.

Table 3.

Association between Molar Hypomineralization child exposure

Lead exposure type	N	β (s.e.)	OR (95% C.I.)	P value*
Mother's blood lead, averaged over three trimesters	332	0.1 (0.04)	1.10 (1.02, 1.19)	0.01
Mother's blood lead, first trimester	371	0.06 (0.03)	1.06 (0.994, 1.13)	0.07
Mother's blood lead, second trimester	379	0.05 (0.03)	1.06 (0.992, 1.12)	0.09
Mother's blood lead, third trimester	360	0.08 (0.03)	1.08 (1.02, 1.15)	0.01
Mother's blood lead, delivery	117	0.03 (0.05)	1.03 (0.936, 1.14)	0.5
Child's blood lead, averaged	349	0.05 (0.05)	1.05 (0.964, 1.15)	0.25
Child's blood lead, 12 months	392	0.06 (0.04)	1.06 (0.979, 1.15)	0.15
Child's blood lead, 24 months	437	0.02 (0.03)	1.02 (0.953, 1.09)	0.58

Abbreviations: β "Beta" logistic regression coefficient is the log of the odds ratio that associates the predictor (lead level) to the outcome (having Molar Hypomineralization), s.e.: standard error, OR: odds ratio, C.I. Confidence interval, P value < 0.05

* From logistic regression models with MH status (separately for each lead exposure) as the outcome, continuous variable of lead as the predictor, adjusted for sex, age, calcium treatment and cohort.

Table 4.

Association between Molar Hypomineralization status and bone lead biomarkers of life course child exposure

Lead exposure type	N	Quartile	β (s.e.)	OR (95% C.I.)	P value*
Mother's bone lead, rotula	422	Quartile 2	-0.11 (0.37)	0.90 (0.433, 1.87)	0.77
		Quartile 3	-0.002 (0.37)	1.00 (0.484, 2.06)	1
		Quartile 4	0.29 (0.36)	1.34 (0.663, 2.69)	0.42
Mother's bone lead, tibia	297	Quartile 2	-0.38 (0.42)	0.68 (0.302, 1.55)	0.36
		Quartile 3	-0.36 (0.42)	0.70 (0.305, 1.61)	0.4
		Quartile 4	-0.47 (0.45)	0.63 (0.261, 1.51)	0.3

Abbreviations: β "Beta" logistic regression coefficient is the log of the odds ratio that associates the predictor (lead level) to the outcome (having Molar Hypomineralization), s.e.: standard error, OR: odds ratio, C.I. Confidence interval, P value < 0.05

* From logistic regression models with MH status (separately for each lead exposure) as the outcome, quartiles of lead as the predictor (with the first quartile as baseline), adjusted for sex, age, calcium treatment and cohort.