Maternal Bone Lead as an Independent Risk Factor for Fetal Neurotoxicity: A Prospective Study

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ABSTRACT. *Objective.* **A number of prospective studies have examined lead levels in umbilical cord blood at birth as predictors of infant mental development. Although several have found significant inverse associations, others have not. Measurement of lead levels in maternal bone, now recognized as the source of much fetal exposure, has the potential to serve as a better or complementary predictor of lead's effect on the fetus. Our objective was to compare lead levels in umbilical cord blood and maternal bone as independent predictors of infant mental development using a prospective design.**

Methods. **We recruited women who were giving birth at 3 maternity hospitals in Mexico City that serve a homogeneous middle-class community. Umbilical cord blood lead levels were measured by graphite furnace atomic absorption spectroscopy, and maternal lead levels in cortical (tibial) and trabecular (patellar) bone were measured within 4 weeks of giving birth using a 109-Cd K-x-ray fluorescence instrument. At 24 months of age, each infant was assessed using the Bayley Scales of Infant Development-II (Spanish Version).**

Results. **A total of 197 mother-infant pairs completed this portion of the study and had data on all variables of interest. After adjustment for other well-known determinants of infant neurodevelopment, including maternal age, IQ, and education; paternal education; marital status; breastfeeding duration; infant gender; and infant illness, lead levels in umbilical cord blood and trabecular bone were significantly, independently, and inversely associated with the Mental Development Index (MDI) scores of the Bayley Scale. In relation to the lowest quartile of trabecular bone lead, the second, third, and fourth quartiles were associated with 5.4-, 7.2-, and 6.5-point decrements in adjusted MDI scores. A 2-fold increase in cord blood lead level (eg, from 5 to 10 μg/dL) was associated with a 3.1-point decrement in MDI score, which is comparable to the magnitude of effect seen in previous studies.**

Conclusion. **Higher maternal trabecular bone lead levels constitute an independent risk factor for impaired mental development in infants at 24 months of age. This effect is probably attributable to mobilization of maternal bone lead stores, a phenomenon that may constitute a significant public health problem in view of the long residence time of lead in bone.** *Pediatrics* **2002;110:110–118;** ***lead, bone, epidemiology, neurotoxins.***

ABBREVIATIONS. K-XRF, K-x-ray fluorescence; BSID, Bayley Scales of Infant Development; MDI, Mental Development Index; PDI, Psychomotor Development Index; SD, standard deviation.

The blood lead level considered to be toxic to children has been revised downward several times during the past 30 years.[1] The accumulated body of research that engendered this evolution in perspective has identified the central nervous system as particularly vulnerable to the harmful effects of lead. A key issue that remains to be clarified is the extent to which the fetal brain is susceptible to lead toxicity. Although much attention has been paid to public health efforts to reduce lead exposure in children between the ages of 6 months and 5 years, when environmental lead exposures tend to be greatest, less attention has been paid to understanding the transfer of lead from mother to fetus and its resulting health effects.[2]

A major obstacle in assessing the effects of prenatal lead exposures on neurobehavioral development is the measurement of fetal dose. A variety of biological markers of dose have been used or proposed, including umbilical cord blood lead level, maternal blood level at different times during pregnancy, amniotic fluid lead level, and the concentrations of lead in cord or placental tissues.[3] In 1 study, only modest correlations (−0.06–0.38) were found among the lead levels of such markers (maternal blood at 14–20 weeks' gestation, approximately 32 weeks' gestation, and delivery; umbilical cord blood; umbilical cord tissue; and placental tissue).[4] Because the kinetics of lead in the maternal-fetal unit are incompletely understood, these low correlations suggest that these various biological markers provide largely nonredundant information about fetal exposure. It is important, therefore, that the utility of such biomarkers be compared as predictors of fetal risk for adverse health outcomes.

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Most of the studies that have examined this topic used maternal venous or umbilical cord blood lead levels as indicators of fetal lead exposure. Although some studies reported a significant inverse association between fetal lead exposure using these indicators and infant scores on tests of cognitive development,[5–8] others did not.[9–11] This inconsistency in study findings is likely to be the result, at least in part, of differences in study populations and research methodologies.[12] An additional possibility is that lead levels in umbilical cord blood and maternal venous blood measured at 1 point of time are imprecise surrogates of cumulative fetal exposure, resulting in varying amounts of exposure misclassification in the different studies.

It is now recognized that mobilization of maternal bone lead stores constitutes a major source of fetal lead exposure. Recent isotopic speciation studies have demonstrated that the skeletal contribution to blood lead levels increases from 9% to 65% during pregnancy.[13] Maternal bone lead levels thus may serve as a useful biological marker of long-term fetal lead exposure over the course of pregnancy. With the development of K-x-ray fluorescence (K-XRF) instruments, it is now possible to make rapid, noninvasive in vivo measurements of lead in maternal bone.[14] In recent series of studies using this technique, our group demonstrated that levels of lead in maternal bone are more strongly associated than either maternal venous blood or umbilical cord blood lead levels with infant birth weight,[15] head circumference, and birth length[16] and velocity of infant weight gain.[17] To date, the association between maternal bone lead levels and infant neurobehavior has not been evaluated.

In this study, we compared umbilical cord blood lead levels and maternal bone lead levels with respect to their associations with neurodevelopment of children at 24 months of age. We also examined the association between children's neurodevelopment and their postnatal blood lead levels.

METHODS

Study Population

This study was conducted under an established interinstitutional collaboration among Harvard University, the Center for Population Health Research of the National Institute of Public Health in Mexico, The American British Cowdray Medical Center, and the National Institute of Perinatology of Mexico. The study cohort was recruited from 3 maternity hospitals in Mexico City that serve a low- to moderate-income population (Mexican Social Security Institute, Manuel Gea Gonzalez Hospital, and National Institute of Perinatology).

Baseline information on health status and on social and demographic characteristics was collected from all eligible participants at delivery and 1 month postpartum. Anthropometric data from the mother and newborn, and umbilical cord and maternal venous blood samples were gathered within 12 hours of delivery. Information on estimated gestational age, based on the date of last menstrual period, and characteristics of the birth and newborn period were extracted from the medical records. Interviewers explained the study to and obtained written consent from eligible women who were willing to participate.

Exclusion criteria included factors that could interfere with maternal calcium metabolism; medical conditions that could cause low birth weight; logistic reasons that would interfere with data collection, such as living in a household outside the metropolitan area; intention not to breastfeed; prematurity (<37 weeks) or an infant with Apgar score at 5 minutes of 6 or under, a condition requiring treatment in neonatal intensive care unit, birth weight <2000 g, or serious birth defects; a physician's diagnosis of multiple fetuses; preeclampsia, psychiatric, kidney, or cardiac diseases; gestational diabetes; history of repeated urinary infections; family or personal history of kidney stone formation; seizure disorder requiring daily medications; ingestion of corticosteroids or blood pressure >140 mmHg systolic or >90 mmHg diastolic; and single-parent households.

One month after delivery (±5 days), each mother-infant pair attended the research center for an evaluation that included measurement of maternal bone lead using a spot-source ^{109}Cd K-XRF instrument. Participating mother-infant pairs were subsequently assessed and interviewed when the infants were 12 and 24 months of age. At each assessment, attempts were made to collect infant venous blood for lead measurements and infant development was assessed using the Bayley Scales of Infant Development II (BSID-II; Spanish version; Bayley, N. Manual: Bayley Scales of Infant Development, 2nd Ed. San Antonio, TX: The Psychological Corporation, 1993). Transportation to and from our research center was provided or reimbursed; no other compensation was offered. Within 1 month after delivery, all participating mothers received a detailed explanation of the study and its procedures, as well as counseling on how to reduce environmental lead exposure. This research protocol was approved by the Human Subjects Committees of the National Institute of Public Health of Mexico, the participating hospitals, and the Harvard School of Public Health.

Blood Lead Measurements

Umbilical blood lead was collected in trace metal-free tubes at delivery. Infant blood samples for lead analyses were collected in capillary tubes after a thorough procedure for cleaning sites to be lanced. Blood samples were analyzed using an atomic absorption spectrometry instrument (Perkin-Elmer 3000, Chelmsford, MA) at the metals laboratory of the American British Cowdray Hospital in Mexico City. External blinded quality control samples provided throughout the study period by the Maternal and Child Health Bureau and the Wisconsin State Laboratory of Hygiene Cooperative Blood Lead Proficiency Testing Program were also analyzed. These analyses demonstrated good precision and accuracy with a correlation coefficient of 0.99 and a mean difference of 0.17 μg/dL.

Bone Lead Measurements

In vivo maternal bone lead measurements were taken within 4 weeks of delivery at 2 bone sites, the mid-tibial shaft (cortical bone) and the patella (trabecular bone). Although, theoretically, it would have been desirable to measure bone lead levels during pregnancy itself instead of right after pregnancy, Mexican law forbids nonemergency radiologic procedures in women during pregnancy. In addition, bone lead levels have been shown to change relatively little over 6 months of lactation,[18] a physiologic period accompanied by bone resorption that is at least as strong or stronger than that of pregnancy,[19] and there is no reason to believe that use of postpartum bone lead measurements would introduce bias into this study. Bone lead was measured noninvasively using a spot-source ^{109}Cd K-XRF instrument constructed at Harvard University and installed in a research facility in the American British Cowdray Medical Center. The physical principles, technical specifications, and validation of this and other similar K-XRF instruments have been described in detail elsewhere.[20,21] Briefly, this instrument uses a spot-source ^{109}Cd γ-ray source to provoke the emission of fluorescent photons from target tissue that are then detected, counted, and arrayed on a spectrum. The net signal is determined after subtraction of Compton background counts by a linear least-squares algorithm. The lead fluorescence signal is then normalized to the elastic or coherently scattered γ-ray signal, which arises predominantly from the calcium and phosphorous present in bone mineral. Because the instrument provides a continuous unbiased point estimate that oscillates around the true bone lead value, negative point estimates are sometimes produced when true bone lead level is close to 0. The instrument also provides an estimate of the uncertainty associated with each measurement, derived from a goodness-of-fit calculation of the spectrum curve that is equivalent to a single standard deviation. For this study, 30-minute measurements were taken at the midshaft of the left tibia and the left patella. Analysis of means and standard

deviations of phantom-calibrated measurements did not disclose any significant shift in accuracy or precision.

Measurements of Child Development and Potential Confounders

The BSID-II is a revision and restandardization of the BSID, the most widely used test of infant development. The revised scale can be used to assess the development of children between the ages of 1 and 42 months. Scores have been shown to be sensitive to a variety of prenatal, perinatal, and postnatal insults, including lead exposure.[5,7,22,23] The BSID-II has also been used in numerous cross-cultural studies of lead and child development .[4,6,8,22–25]

A Spanish version of the BSID-II was developed by our research group before this study. The team that administered the BSID-II Spanish Version was led and trained by our group (L.S. and D.B., respectively), with standardization and quality control checks conducted through reviews of videotaped interviews. Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores at 24 months of age were used as the primary child development endpoints in this study.

A database was collected on demographic, socioeconomic, and other factors that may constitute potential cofounders of the relationship between lead and child development. Maternal IQ was assessed using the Information, Comprehension, Similarities, and Block Design components of the Wechsler Adult Intelligence Score, which has been translated into Spanish and used in Mexico.

Data Analyses

All analyses were performed using the SAS 6.12 (SAS, Inc, Cary, NC). Descriptive statistics, appropriate transformations, and identification of outliers were performed before bivariate and multivariate analyses. Umbilical blood lead concentrations were converted to their natural logarithmic values to normalize the skewed distribution. K-XRF bone lead values with measurement uncertainties exceeding 10 and 15 for tibia and patella, respectively, were excluded from the analyses as part of an established quality control procedure,[15–17,26] as these values reflect inadequate sampling and are not correlated with the bone lead concentrations themselves.[27]

The associations between MDI scores at 24 months and various measurements of lead exposure and other covariates were first examined in bivariate analyses. The adjusted associations between MDI and biomarkers of lead were then assessed using multiple linear regression. An initial model was fitted and included maternal IQ, maternal age, child gender, maternal years of education, paternal years of education, marital status, duration of breastfeeding, and child hospitalization during the first 6 month of life.

Each of the lead biomarkers (umbilical blood lead, tibia bone lead, and patella bone lead) was then added separately to this model. A final model was selected using forward, backward, and stepwise methods to assess for the most stable and robust models. Variables significantly associated with MDI ($P < .1$) were retained for entry in forward, stepwise multiple regression with backward elimination (entry and elimination criteria were $P < .1$ and $P > .1$, respectively). Regression diagnostics were performed to assess the effects of multicollinearity and potentially influential data points.

The multivariate linear regression models were repeated: 1) after excluding potentially influential points, 2) using PDI at 24 months as the dependent variable, and 3) evaluating the interaction between umbilical cord and bone lead levels. We also examined the associations between child blood lead levels at 12 and 24 months instead of or in addition to umbilical cord or bone lead measurements in the multivariate models. Because bone lead levels do not have a reference range and do not therefore have an obvious interpretation, we also reran analyses treating bone lead as a categorical variable divided into quartiles.

RESULTS

Of 630 mother-infant pairs who were initially eligible for the study, 399 (63%) agreed to participate. The most common reason for nonparticipation was the inconvenience of making follow-up visits to the bone lead research unit. Of these, 278 (70%) attended the study evaluations through 24 months postpartum, with 197 meeting the study criteria and completing the study with data on all variables of interest. Of the 81 who attended the study evaluations but were excluded from subsequent analyses, specific reasons included birth weight <2000 g ($n = 3$), missing data for birth weight ($n = 1$), missing data for gender ($n = 2$), missing data for lactation ($n = 2$), missing data for maternal education ($n = 5$), missing data for paternal education (because of single mom or missing data; $n = 32$), missing data for patella bone lead ($n = 24$), missing data for tibia bone lead ($n = 9$), and missing data for maternal IQ ($n = 3$). A comparison of participants with nonparticipants or participants with missing data (Table 1) showed no meaningful differences with respect to maternal IQ, maternal age, gender of the child, mother's education, father's education, breastfeeding duration, and the percentage of children hospitalized during 6 months from delivery. Participants were composed of fewer parents who were living together (25%; as

TABLE 1. Characteristics of Nonparticipants and Participants in the Lead and Fetal Neurodevelopment Study

Characteristics	Eligible			Nonparticipants and Participants With Missing Data			Participants ($N = 197$)	
	N	%	Mean (SD)	*N*	%	Mean (SD)	%	Mean (SD)
Maternal IQ	458		85.4 (22.2)	261		84.6 (22.9)		86.5 (21.3)
Maternal age	630		24.6 (5.1)	433		24.3 (5.0)		25.1 (5.4)
Gender of the child								
Male	340	54		233	55		54	
Female	286	46		194	45		46	
Mother years of education	621		9.3 (3.1)	424		9.2 (3.0)		9.6 (3.1)
Father years of education	558		9.8 (3.4)	361		9.7 (3.5)		9.9 (3.2)
Marital status								
L	222	35		173	40		25	
M	408	65		260	60		75	
Breastfeeding duration								
<3 mo	53	10		36	12		9	
3–6 mo	170	32		95	31		34	
>6 mo	301	58		178	57		57	
Child was hospitalized in the first 6 mo								
Yes	69	11		51	12		10	
No	561	89		382	88		90	

L indicates living together; M, married.

opposed to married) compared with nonparticipants or participants with missing data (40%).

The levels of lead in umbilical cord blood demonstrated a mean (standard deviation [SD]) value of 6.7 (3.4) μg/dL and ranged from 1.2 to 21.6 μg/dL (Table 2). The peripartum levels of lead in maternal patella and tibia bones demonstrated mean (SD) values of 17.9 (15.2) and 11.5 (11.0) μg/g, respectively. The blood lead levels of the infants rose slightly as they grew older, with mean (SD) values of 7.2 (2.8) and 8.4 (4.6) μg/dL at age 12 and 24 months, respectively (Table 2). The peripartum levels of lead were intercorrelated to a modest degree, with Spearman correlation coefficients for lead levels in cord blood versus tibia bone, cord blood versus patella bone, and tibia bone versus patella bone of 0.13 ($P = .07$), 0.17 ($P = .02$), and 0.24 ($P < .001$), respectively.

In bivariate analyses of the nonlead covariates, only maternal IQ, maternal education, and paternal education were significantly ($P < .05$) associated with MDI scores (Table 3). Maternal age, duration of breastfeeding, and duration of child hospitalization were not significantly associated with MDI scores.

Infants who had higher cord blood lead levels and infants whose mothers had higher patella bone lead levels had lower MDI scores (Table 3). When patella bone lead levels were divided into 4 groups (quartiles), with the lowest group as the reference category, each of the higher 3 quartiles was associated with lower MDI scores (Table 3). Higher tibia lead levels were associated with lower MDI scores, but this association was not significant.

In the multivariate analyses (Tables 4 and 5), the directions of the associations were similar to those in the bivariate analyses. After adjustment for maternal IQ, maternal age, gender of the child, maternal and paternal years of education, marital status, breastfeeding duration, and child hospitalization status, higher umbilical cord blood levels were significantly associated with lower MDI scores. The adjusted association between cord blood lead and MDI was significant and similar in magnitude regardless of whether patella bone lead was included in the model, with P values of .02 and .05, respectively (Table 4, models B and E). Similarly, adjusted patella bone lead levels were significantly (or borderline significantly) associated with lower MDI score regardless of whether cord blood lead was included in the model (Table 4, models C and E). Using the lowest quartile of patella as the reference group, patella bone lead levels in the second, third, and fourth quartiles were associated with 5.1, 7.3, and 6.3 decrements in adjusted MDI scores, respectively (Fig 1).

Adjusted tibia bone lead levels were associated with lower MDI scores, but the relationship was not as strong as the one for patella bone lead (Table 4, model D). Forcing in marital status or excluding influential points from the analysis did not change appreciably the significance of the umbilical cord concentration or patella lead level terms. There were no apparent interactions among the different biological markers of lead exposure.

In the final backward elimination linear regression model, the only variables that were retained were maternal IQ, umbilical cord blood lead concentration, and patella lead level (Table 5). A 2-fold increase in umbilical cord blood lead concentration was associated with a decrease of 3.1 points in adjusted MDI scores, and an increase in patella bone lead concentration from the lowest to the highest 2 quartiles was associated with an additional decrease of 6.5 to 7.2 points in adjusted MDI scores.

The adjusted blood lead concentrations at child ages of 12 and 24 months were not significantly associated with MDI when added individually to model A (child blood lead levels at age 12 and 24 months were available only on 86 and 161 of the 197 participants, respectively). The β-coefficients and P values for blood lead at 24 months were -0.30 and .21, respectively, for the bivariate analyses, and -0.09 and $P = .72$ for the multivariate analysis, respectively. When forced into the final models of MDI scores, neither the 12- nor the 24-month blood lead values was associated with MDI score and the effect estimates associated with cord blood lead and maternal bone lead did not change at all.

When PDI scores at 24 months were used as the dependent variable instead of MDI scores, the bivariate and adjusted associations with biomarkers of lead exposure were not consistent or significant. In bivariate analyses, umbilical cord lead levels and patella bone lead levels were negatively associated with PDI scores but with P values of .24 and .74, respectively. Tibia bone lead was not associated with PDI scores ($P = .88$). In multivariate analyses, umbilical cord lead level was negatively associated with PDI scores, but the P value was .14. Tibia and patella lead levels were not associated with PDI score ($P = .59$ and .80, respectively).

TABLE 2. Blood and Bone Lead Levels in the Lead and Fetal Neurodevelopment Study

Peripartum Measurement ($N = 197$)	Mean (SD)	Range	N (%)
Umbilical cord blood lead (μ/dL)	6.7 (3.4)	1.2–21.6	
0–4.9			74 (37.6)
5.0–9.9			92 (46.7)
≥10			31 (15.7)
Maternal patella bone lead (μg/dL)	17.9 (15.2)	<1–76.6	
Maternal tibia bone lead (μg/dL)	11.5 (11.0)	<1–85.9	
Childhood Measurements*			
Blood lead at 12 mo	7.2 (2.8)	2.3–18.9	
Blood lead at 24 mo	8.4 (4.6)	2.5–38.6	

* $N = 86$ at 12 months; $N = 161$ at 24 months.

TABLE 3. Bivariate Analyses of MDI in Relation to Maternal Lead Biomarkers and Other Factors

	Coefficient	Standard Error	Test Statistics	*P* Value
Maternal IQ	0.18	0.05	3.74	<.01
Maternal age (y)	−0.22	0.19	−1.14	.26
Female gender	3.09	2.05	1.50	.13
Mother years of education	3.33	1.10	3.02	<.01
Father years of education	2.58	1.10	2.36	.02
Two-parent vs 1-parent household	3.18	2.37	1.34	.18
Duration of breastfeeding*				
3–6 mo	−4.67	3.91	−1.19	.23
>6 mo	−1.73	3.74	−0.46	.64
Child hospitalized in the first 6 mo	−0.11	3.57	−0.03	.98
Umbilical cord blood lead level (μg/dL)†	−4.52	2.12	−2.14	.03
Patella bone lead level (μg/g)	−0.19	0.07	−2.78	.01
Patella bone lead level[3]				
Second quartile	−5.51	2.85	−1.94	.06
Third quartile	−8.63	2.83	−3.04	<.01
Fourth quartile	−8.25	2.85	−2.90	<.01
Tibia bone lead level‡	−0.15	0.09	−0.60	.11
Tibia bone lead level				
Second quartile	−0.47	2.93	−0.16	.87
Third quartile	−0.19	2.91	−0.07	.95
Fourth quartile	−2.37	2.93	−0.81	.42

* In relation to <3 months.
† Log transformed.
‡ In relation to first (lowest) quartile.

DISCUSSION

The primary biomarker of prenatal lead exposure used in previous prospective studies of lead and child development has been the concentration of lead in whole blood, sampled either from the umbilical cord at the time of delivery or from maternal venous blood at various points during pregnancy. We also used this biomarker in the current study, and our findings replicate, in 4 major respects, those reported in some previous prospective studies that constitute this complex and sometimes confusing literature. First, as in the Boston[5] and Shanghai[8] studies, we found a significant inverse relationship between the concentration of lead in umbilical cord blood and covariate-adjusted MDI scores at 24 months of age on the BSID. In the Cleveland study,[11] cord blood lead level was inversely related to MDI at 6, 12, and 24 months of age but not significantly. Similarly, in the Yugoslavian study,[6] cord blood lead level was inversely but not significantly associated with MDI at 24 months. In contrast, the associations between cord or prenatal blood lead levels and MDI at 24 months were neither inverse nor significant in the Cincinnati[10] or Sydney[9] studies. In the Port Pirie Study,[7] average antenatal blood lead was inversely but not significantly associated with MDI at 24 months, whereas both maternal blood lead at delivery and cord blood lead were neither inversely nor significantly associated with MDI.

Second, the magnitude of the decline in MDI score with increasing cord blood level, 3.1 points for each doubling in blood lead level, is comparable to the decline seen in the studies reporting significant associations. In the Boston study, for instance, the differences between the mean scores of children in the low (<3 μg/dL) and high (>10 μg/dL) cord blood lead groups was 4 to 8 points in the 6- to 24-month period.[5] In the Chinese study of Shen et al,[8] children with cord blood lead levels between 10.7 and 17.5 μg/dL achieved MDI scores at 3, 6, and 12 months of age that were 3 to 6 points lower than children with cord blood lead levels below 7.4 μg/dL.

Third, we found a lack of association between children's postnatal blood lead levels and development within the first 2 years. The studies in which such associations have been reported are generally those in which the study cohorts have the highest average blood lead levels (eg, Yugoslavia, Port Pirie).

Finally, as in most other studies of infants, prenatal lead exposure was more strongly associated with cognitive development scores (MDI) than with motor development scores (PDI), although Ernhart et al[11] and Dietrich et al[10] did find significant associations between maternal blood lead level during pregnancy and PDI scores, in the latter study mediated by lead-associated reductions in birth weight and gestational age.

The striking similarities and dissimilarities between the findings of our study and those of others in this literature provide a context for interpreting the novel contribution of this study, namely, the demonstration of the importance of maternal bone lead level as a biomarker of prenatal lead exposure that provides information, independent of cord blood lead level, about a fetus's risk of reduced developmental performance in infancy.

In this study, increased levels of lead in maternal bone were associated with lower MDI scores even after controlling for cord blood lead level and other covariates. The inclusion of maternal bone lead increased the explanatory power of the model for mental development from 8.6% to 11.1% (as reflected by adjusted R^2 values); moreover, the inclusion of maternal bone lead reduced the effect estimate associated with umbilical cord blood lead by only 15% (−4.94 to −4.21). Although relatively modest, the

TABLE 4. Linear Regression of MDI in Relation to Maternal Lead Biomarkers and Other Factors

Variable	Model														
	A			B			C			D			E		
	β	SE	P	β	SE	P	β	SE	P	β	SE	P	β	SE	P
Mother IQ	0.15	0.06	.02	0.15	0.06	.02	0.12	0.06	.05	0.15	0.06	.02	0.13	0.06	.04
Maternal age (y)	−0.25	0.19	.19	−0.23	0.19	.22	−0.15	0.19	.44	−0.20	0.20	.32	−0.15	0.19	.43
Gender (female vs male)	3.16	2.05	.13	3.06	2.02	.13	2.76	2.03	.18	2.96	2.06	.15	2.74	2.02	.18
Total years in school mom	0.29	1.54	.85	0.47	1.52	.76	0.33	1.52	.83	0.29	1.54	.85	0.48	1.51	.75
Total years in school dad	1.06	1.24	.39	0.95	1.22	.44	1.36	1.23	.27	0.90	1.25	.47	1.21	1.23	.32
Two-parent vs 1-parent household	2.19	2.37	.36	2.25	2.35	.34	2.76	2.36	.25	2.18	2.37	.36	2.71	2.34	.25
Breastfeeding duration (mo)	0.79	1.57	.61	0.48	1.55	.76	0.58	1.55	.71	0.69	1.57	.66	0.35	1.54	.82
Child hospitalization in first 6 mo	−0.99	3.52	.78	−0.55	3.48	.87	0.10	3.51	.98	−0.78	3.52	.83	0.28	3.49	.94
Umbilical cord lead level (μg/dL)†				−4.94	2.0653	.0179							−4.21	2.09	.05
Maternal patellar lead (μg/g)							−0.16	0.07	.03				−0.13	0.07	.07
Maternal patellar lead*															
Second quartile							−5.25	2.81	.06				−5.05	2.78	.07
Third quartile							−7.66	2.85	.01				−7.32	2.83	.01
Fourth quartile							−7.20	2.88	.01				−6.33	2.88	.03
Maternal tibial lead (μg/g)															
Maternal tibial lead*										−0.10	0.10	.30			
Second quartile										−0.80	2.88	.78			
Third quartile										−0.18	2.89	.95			
Fourth quartile										−1.48	2.94	.62			

SE indicates standard error.
* In comparison to first (lowest) quartile.
† Log transformed.

TABLE 5. Final Model of MDI in Relation to Lead Biomarkers and Other Related Factors

	Coefficient	Standard Error	*T* Test Statistics	*P* Value
Intercept	89.86	5.52	16.27	<.01
Maternal IQ	0.17	0.05	3.65	<.01
Umbilical cord blood lead level*	−4.48	2.04	−2.20	.03
Patella bone lead level				
Second quartile	−5.36	2.75	−1.95	.05
Third quartile	−7.21	2.75	−2.62	.01
Fourth quartile	−6.48	2.79	−2.33	.02

Total model R^2 = 13.4%.
* Natural log of the umbilical cord blood lead concentration.

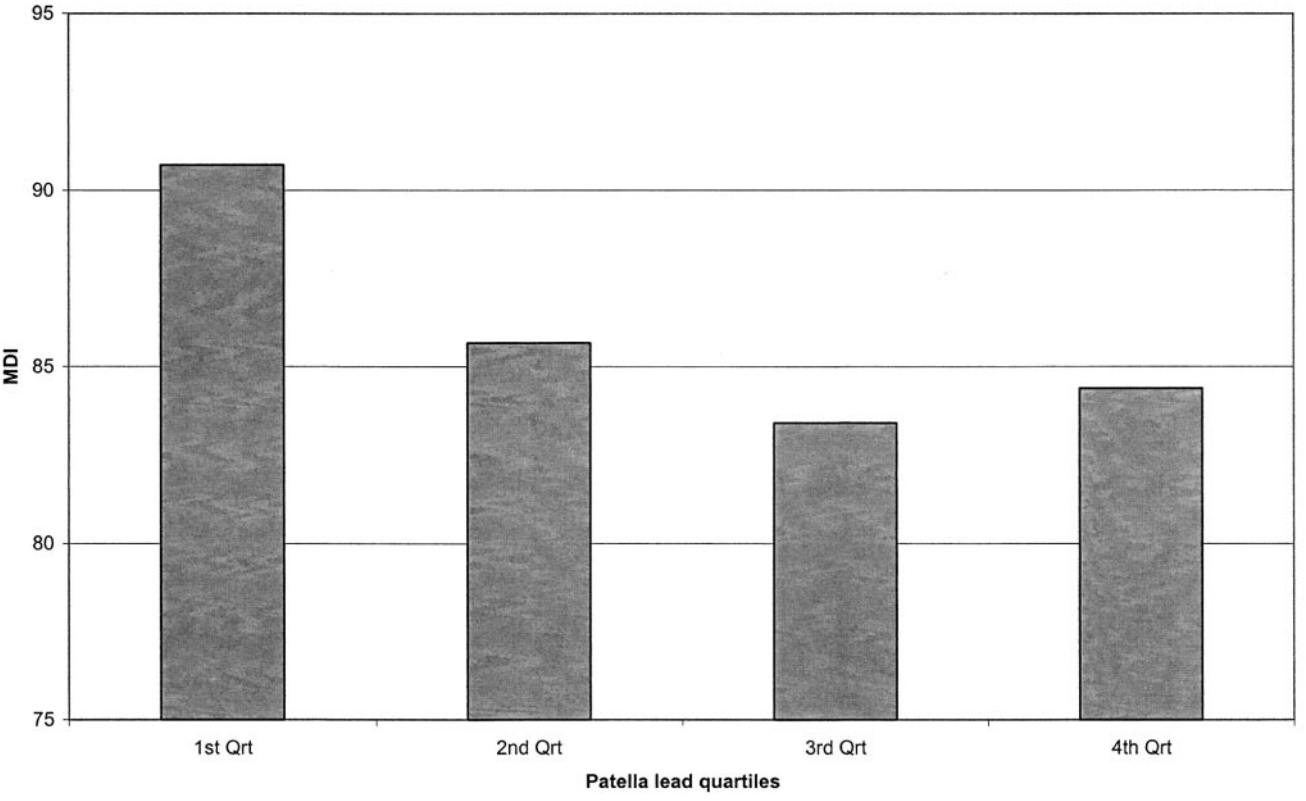

Fig 1. Maternal bone lead and MDI.

influence of bone lead is likely underestimated by this model because the bone lead measurements entail a substantial amount of random error, which tends to attenuate the apparent magnitude of effect.[28] In addition, as Gulson et al[13] pointed out, bone lead is a source of a substantial fraction of cord blood lead. Hence, some of the effect of bone lead is being captured by cord blood lead. Overall, this finding suggests that the general effect of fetal lead exposure on subsequent neurodevelopment has been underestimated by reliance on cord blood lead levels to reflect fetal lead exposure.

What does bone lead level that is not captured by measuring cord blood lead level signify? One possibility is that lead exposure fluctuates substantially during the course of pregnancy and bone lead levels capture some of the fetal lead exposure integrated over time that is not reflected by the cord lead levels. Multiple measurements of maternal venous blood lead during the course of pregnancy might capture the same parameter; this has not been tested, to our knowledge.

It is noteworthy that in comparison to levels of lead in the tibia bone, levels of lead in the maternal patella bone were more closely predictive of MDI scores. The histomorphometry of patella bone is mostly trabecular[14] and in comparison to cortical bones like the tibia, trabecular bone tends to be more heavily affected by pregnancy-associated bone resorption.[29] Maternal patella bone lead levels had been previously noted to be superior to tibia bone lead levels (as well as cord blood lead levels) in predicting lower infant birth weight[15] and lower growth velocity from birth to 1 month of age.[17]

The mean levels of lead that were found in tibia and patella bone in our population are approximately 2.5 times higher than those that have been found in middle- to high-income women who gave birth in Boston in the early 1990s[30] and approximately 1.5 times those found in low-income women

from Latin America who emigrated to the Los Angeles area as recently reported by Rothenberg et al.[31] Thus, they are high but well within the order of magnitude of levels being seen in women in this country.

Maternal bone lead stores are mobilized during lactation as well as during pregnancy, so it is possible that the mechanism by which bone lead levels predict neurobehavioral performance in offspring by 2 years of age is through mobilization into breast milk with subsequent ingestion and absorption. However, the postnatal infant blood lead levels in this study, which presumably would increase if a suckling infant were absorbing a significant amount of lead in breast milk, were not predictive of 24-month MDI, and forcing postnatal blood lead levels into our regression models of MDI score did not affect the effect estimates associated with either cord blood lead or maternal bone lead.

Among the most important limitations of our study are that we did not have measurements of maternal blood lead throughout pregnancy (which would have allowed us to compare maternal bone lead to a measure of blood lead that was integrated over pregnancy); we did not have a direct measure of family socioeconomic status or the caregiving environment (eg, the Home Observation for the Measurement of the Environment inventory), which constitute potential confounders of the lead exposure-mental development relationship; and our final sample size of 197 mother-infant pairs represented only 31% of the subjects who were initially eligible for this study. However, regarding the last 2 issues, maternal and paternal education have been found to parallel closely socioeconomic status among families in Mexico,[32] and the caregiving environment is likely to be similar across the homogeneous middle-income families that compose the patient population for this study. Finally, our comparison of final participants with nonparticipants and participants with missing data did not reveal substantial differences in our covariates, suggesting that the participants in this study were representative of the overall cohort.

CONCLUSION

Our study suggests that fetal development in women with low current lead exposures can still be at risk for lead toxicity from long-lived maternal bone lead stores acquired from previous lead exposures. This is likely to be of particular importance to women who grew up in heavily lead-contaminated environments or who worked in occupations associated with industrial lead exposure and provides additional impetus for the general movement in public health to decrease lead exposure in communities and workplaces. These results also suggest that there may be a need to consider potential secondary prevention strategies, ie, measures to prevent maternal bone lead mobilization during pregnancy. It is interesting that supplementation with calcium during pregnancy has been noted in some studies to decrease maternal bone demineralization,[33] and pooled results from a recent randomized crossover trial found that a nocturnal 1200-μg dietary calcium dose reduced urinary levels of n-telopeptide of type 1 collagen, a biological marker specific for bone resorption, by an average of 15% in pregnant women in the third trimester.[34] Given the relatively benign nature of calcium supplementation and the lack of a threshold that has been seen in the relationship between blood lead and IQ down to a blood lead of 1 μg/dL,[35] supplementation with calcium needs to be considered as a potential strategy for decreasing fetal lead exposure in women with a history of significant lead exposure. Additional research is needed to determine whether implementation of such interventions should be considered on a widespread basis and, if so, how women who would most benefit should be identified.

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"He who knows and knows that he knows is conceited; avoid him.
He who knows not and knows not that he knows not is a fool; instruct him.
He who knows and knows not that he knows is asleep; awaken him.
But he who knows not and knows that he knows not is a wise man; follow him."

—Arab Proverb

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