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## **Running Head: Pregnancy Lead Exposure and Child IQ to Ten Years**

**Key words:** Child development, intelligence, lead, prenatal exposure delayed effects

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BPb – blood lead concentration

IQ – Intellectual Quotient

FSIQ – Full Scale Intellectual Quotient

SES – Socioeconomic status

µg/dL – microgram per deciliter

µmol/L – micromole per liter

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## **Abstract**

**Objective:** Low level postnatal lead exposure is associated with poor intellectual development in children, though effects of prenatal exposure are less well studied. We hypothesized that prenatal lead exposure would have a more powerful and lasting impact on child development than postnatal exposure.

**Design:** We used Generalized Linear Mixed Models with random intercept and slope to analyze pattern of lead effect of the cohort from pregnancy through 10 years of age on child IQ from 6-10 years. We statistically evaluated dose-response non-linearity.

**Participants:** A cohort of 175 children, 150 of whom had complete data for all included covariates, attended the National Institute of Perinatology in Mexico City from 1987-2002.

**Evaluations/Measurements:** Wechsler Intelligence Scale for Children-Revised Spanish measured IQ. Blood lead was measured by a reference laboratory of the Centers for Disease Control and Prevention quality assurance program for blood lead.

**Results:** Geometric mean blood lead during pregnancy was 8.0  $\mu\text{g}/\text{dL}$  (range: 1-33  $\mu\text{g}/\text{dL}$ ), from 1-5 years was 9.8  $\mu\text{g}/\text{dL}$  (2.8-36.4  $\mu\text{g}/\text{dL}$ ), and from 6-10 years was 6.2  $\mu\text{g}/\text{dL}$  (2.2-18.6  $\mu\text{g}/\text{dL}$ ). 6-10 year IQ decreased significantly only with increasing natural log third trimester blood lead ( $\beta = -3.90$ , 95% CI = -6.45, -1.36), controlling for other blood lead and covariates. The dose-response blood lead-IQ function was log-linear, not linear-linear.

**Conclusions:** Lead exposure around 28 weeks gestation is a critical period for later child intellectual development, with lasting and possibly permanent effects. There was no evidence of a threshold; the strongest lead effects on IQ occurred within the first few  $\mu\text{g}/\text{dL}$  of blood lead.

**Relevance to Clinical Practice:** Current CDC action limits for children applied to pregnant women permit a majority of lead-associated child IQ decrease measured over the studied blood lead range.

## **Introduction**

Prospective lead studies of child development from the 1980's to date show associations between low blood lead concentration (BPb) and poor neurobehavioral development (Baghurst et al. 1992; Bellinger et al. 1986, 1987, 1989, 1994; Bornschein et al. 1985; Dietrich et al. 1987, 1991a, 1991b, 1993a, 1993b; McMichael et al. 1988, 1992; Rothenberg et al. 1989; Schnaas et al. 2000; Wasserman et al. 1992, 1994, 1997, 2000a, 2000b), though the focus of most of these studies has been on postnatal exposure. Only some studies included measurement of maternal BPb during pregnancy or at delivery (Bornschein et al. 1985; Graziano et al. 1990; Rothenberg et al. 1994). The Yugoslavia study (Wasserman et al. 2000 a) used a repeated measures design and found that increased mid-pregnancy BPb (12-20 weeks) was significantly associated with decreased 3-7 year IQ regardless of pattern of postnatal exposure. The Cincinnati study (Ris et al 2004) showed lasting significant effects of BPb between 6 and 28 weeks on factor scores representing attention and visuoconstruction in adolescents when prenatal BPb was tested without simultaneously considering postnatal BPb exposure history.

Ideally, we would like to include the entire history of lead exposure in assessing lasting effects of lead on child development. When the study sample is exposed to relatively constant sources of environmental lead there is often substantial tracking of BPb over time (Tong et al. 1996; Wasserman et al. 2000a), producing high correlations among BPb between and within prenatal and postnatal periods. Collinearity among highly correlated BPb variables in the same linear model will produce biased estimates of lead effect with inflated standard errors. On the other hand, piecemeal analysis of lead effect, testing one period of lead exposure at a time, ignores potential effects of earlier or later exposure. Such omission could lead to residual confounding of tested lead effects.

The principal lead exposure sources in pregnant women and their children in the Mexico City Prospective Lead Study were air lead and lead from ceramic ware (Schnaas et al. 2004). Air lead decreased continually throughout the 15 year study period due to reduction and elimination of lead in gasoline. Individual exposure to leaded ceramic ware was both idiosyncratic and intermittent. Such variable individual lead exposure substantially reduced PbB tracking in this sample and allowed an analysis of the effect of lead exposure from 12 weeks of pregnancy through the first 10 years of life on child intelligence from six to ten years of age.

## **Methods**

### *Subjects*

The subjects belonged to a cohort of children born in Mexico City at the National Institute of Perinatology between 1987 and 1992, followed until 2002. The Ethics Committee of the National Institute of Perinatology approved the research protocol. Investigators met with parents, verbally explained the project, asked them to read the description in the informed consent, and to sign if they wished to participate with their child. We recruited women at 12 weeks of pregnancy and measured BPb every eight weeks to delivery. We also measured BPb from maternal and cord blood at delivery. 321 children born to these women met the following inclusion criteria: child born with at least 36 weeks of gestational age, 5-min Apgar score  $\geq 7$ , birth weight  $> 2000$  g, without major or minor congenital anomalies or being the product of multiple birth. We evaluated children with psychometric tests, anthropometric measurements, and BPb at six month intervals after birth. We collected data on demographic, socioeconomic, and other factors that might constitute potential confounders or important control variables modifying the relationship between lead and child development.

Of the 321 infants comprising the original sample, we successfully tested 175 children after five years of age.

### *Blood lead measurements*

Venous blood was drawn into purple-top Becton-Dickinson Vacutainers™ (Franklin Lakes, NJ, USA) with EDTA anti-coagulant. Environmental Science Associates Laboratories, Inc (Chelmsford, MA) determined BPb in duplicate analysis by anodic stripping voltammetry. Samples with mean duplicate values  $<5 \mu\text{g/dL}$  were reanalyzed via atomic absorption spectrometry. Quality control information is provided elsewhere (Rothenberg et al. 1994). The lab is a reference laboratory for the Centers for Disease Control and Prevention's Blood Lead Laboratory Reference System (Atlanta, GA, USA) and participates in the Commonwealth of Pennsylvania Department of Health Blood Lead Proficiency Testing Program (Exton, PA, USA). BPb during pregnancy was measured every eight weeks starting at week 12 of pregnancy. We used the geometric mean of lead at 12 and 20 weeks as the lead measure for the second trimester of pregnancy and the geometric mean of lead at 28 and 36 weeks as the lead measure for the third trimester of pregnancy. We calculated geometric mean BPb from biannual measurements from six months to five years and used BPb at each age from 6 to 10 years to measure lead exposure contemporaneous with each year's IQ measurement. In supplementary models we also used maternal blood lead at each prenatal measurement and postnatal geometric mean yearly blood lead from 1 to 5 years.

### *Developmental assessment*

We assessed child intelligence under standardized conditions with the Wechsler Intelligence Scale for Children-Revised (Spanish version of the WISC-R) (Wechsler 1981a) providing a Full Scale Intelligence Quotient (FSIQ). The WISC-R has 12 subtests, six of which are used to estimate a Verbal IQ and the remaining a Performance IQ. Three psychologists unaware of child BPb evaluated IQ. For each child evaluated by a psychologist the two other psychologists reviewed the test protocols and assigned scores given by the examiner for each test. An analysis of variance with post-hoc testing for mean IQ grouped by examining psychologist and child age was used to assess possible psychologist bias.

### *Covariates*

We measured maternal IQ with the Wechsler Adult Intelligence Scale (Spanish) (Wechsler 1981b). We constructed an index for socioeconomic status based on head of household education and occupation, and family income. We evaluated degree of stimulation and quality of caretaker-child interaction in the home environment using the HOME Scale (Home Inventory for Families of Infants and Toddlers) (Caldwell and Bradley 1984). All covariates used in statistical analyses were collected during pregnancy or in the first six postpartum months.

### *Data analyses*

We used Fisher exact tests, Pearson Chi-squared with exact probability or t-tests to contrast subjects included in the analysis, subjects lost to follow up in the first five postnatal years and subjects with incomplete post-five year data with the variables sex, socioeconomic stratum, BPb at different ages, maternal IQ and educational level, and postnatal developmental scores.

Descriptive statistics, identification of outliers, and appropriate transformations were performed prior to bivariate and multivariate analyses. BPb was converted to natural logarithms to eliminate heteroskedasticity and normalize skewed distributions of residuals, reduce the influence of outlying high lead values on regression coefficients, and adequately specify the functional relation of BPb on FSIQ. We examined associations between the FSIQ measured from 6 to 10 years of age and each measurement of lead exposure in panel regression analyses (Kennedy 2003) first without covariates and then controlling by child sex, SES, maternal IQ, HOME and birth weight, instead of bivariate regressions, to adjust the regressions for repeated measurements of IQ in each subject.

As the data are multilevel with BPb at each age nested within children, we used a Linear Mixed Model to analyze the pattern of lead effect on FSIQ evaluated from 6 to 10 years of age. The dependent variable was FSIQ at ages 6, 7, 8, 9 and 10, whereas the independent variables with fixed effects were: maternal IQ, child sex, SES, birth weight, geometric mean of BPb during the first five years of age, BPb at each age at which the FSIQ measurements were made, geometric mean of BPb during the second and third trimester of pregnancy and a dummy variable indicating the first FSIQ measurement of the child, allowing control for test learning between the first IQ measurement and the following ones. Some children had their first WISC test at 6 years; others were first tested at 7 or 8 years.

We included as random effects subject and BPb measured at each year of WISC FSIQ measurement of the child. We modelled the covariance matrix of the residual error by a first order autoregressive process. We used the likelihood ratio test to determine if the addition of random intercepts, random slopes, and autoregressive residual covariance matrix significantly improved model fit.

To examine the effect of simultaneous inclusion of all lead variables, we constructed several mixed models each with only one lead variable and statistically compared those lead coefficients with the

lead coefficients of the mixed model with all lead variables. We also constructed mixed models without the control variables to determine lead coefficients unadjusted for covariates.

The same analyses were performed for Verbal IQ (VIQ) and Performance IQ (PIQ).

We used Schwarz's Bayesian Information Criterion (Hardin 2001) to determine which model best fit the data. The information criterion includes a penalized function based on number of estimated parameters. If number of parameters increases without substantial model improvement the information criterion also increases, indicating a poorer data fit.

The two-level model had two different residuals: level 1 residuals, annual observations, calculated by subtracting the linear predictor from the FSIQ, and the empirical Bayes predictions, considered as higher level residuals, called here level-2 residuals.

To check the normality of the two residual types we generated kernel density plots with overlaid normal density functions and plotted quartiles of the residuals against quartiles of a normal distribution to emphasize possible non-normality near the tails. Shapiro-Wilk and Shapiro-Francia tests were also used to check residual normality. We divided level-2 residuals by the standard errors (from the posterior standard deviations) to detect outliers and plotted residuals against predictions to examine homoskedasticity.

In addition to calculating correlations among blood lead variables to assess potential for collinearity, we also ran an artificial multiple regression with the full mixed model variables to calculate the variance inflation factors (Hardin 1995) for the lead terms. As a final check on the possibility that

collinearity among lead variables significantly affected the pattern of results in the mixed model, we converted the group of lead variables to orthogonal variables and ran the model again.

We refit the mixed models with linear lead terms and used the J-Test (MacKinnon 1981) to determine if the logarithmic specification of the lead variables produced a better fit to the data than a linear lead specification.

## Results

From the sample of 175 children retained to 6 years of age, we studied 150 with complete data for all covariates included in the model. There were no significant differences in sex, socioeconomic stratum, birth weight, FSIQ of the child, maternal IQ, BPb at second trimester, and geometric mean BPb from age one to five between children included and not included in the analyses (table 1). BPb in the third trimester of pregnancy and at 9 and 10 years was significantly lower in the group with complete data.

More of the group dropping out before reaching 6 years tended to be in the lowest socioeconomic stratum, compared to the tested group with complete data. Bayley (Bayley 1969) and McCarthy (McCarthy 1972) developmental scores also tended to be lower for this group.

The Pearson correlation between the 12-20 week and 28-36 week prenatal natural log BPb = 0.48, between either of the prenatal and any of the postnatal BPb  $\leq 0.23$ , and between the 1-5 year and 6-10 year postnatal BPb = 0.70. Variance inflation factors (VIF) for all variables in the model were  $< 2.2$  (mean VIF = 1.45), where VIF  $\geq 10$  is considered significant (Chatterjee S. 2000). Models using orthogonal lead variables showed no change in model results. Collinearity among simultaneously included lead variables in the models was not a factor in the results presented below. Figure 1 shows the distribution of blood lead from the cohort followed to 6 to 10 years.

Fixed effects panel regression analyses, unadjusted for covariates, testing separate prenatal, perinatal and postnatal BPb with FSIQ of the child showed IQ reduction associated with BPb increase for all lead measurements (table 2). However, the only significant BPb effects were with BPb at third trimester of pregnancy and BPb measured simultaneously with IQ tests.

We performed panel analyses for FSIQ with each of the other covariates alone. All covariates were associated with IQ in the expected direction, but only maternal IQ ( $p < 0.001$ ), maternal educational level ( $p < 0.001$ ), socioeconomic stratum ( $p < 0.01$ ), and HOME score ( $p < 0.05$ ) showed positive significant effects on the FSIQ of the child (analyses not shown).

Using a linear mixed model with random intercept and random slope for 6-10 year BPb and adjusting for all covariates (table 3, model A), children whose mothers had higher BPb during 28-36 weeks of pregnancy had significantly lower FSIQ, children of the higher IQ mothers had higher FSIQ at all ages, and child FSIQ in the first evaluation was significantly lower than in subsequent evaluations. Most other remaining covariates were associated with child intelligence in the expected direction, but were not significant.

We developed additional models containing all prenatal and postnatal BPb with only the covariates that were significant in the full linear mixed model (maternal IQ and the dummy variable for the first FSIQ measurement of the child). Non-significant BPb variables were eliminated, resulting in the model including only significant covariates (table 3, model D). The third trimester BPb coefficients in all additional models with progressive deletion of non-significant variables (table 3, models B, C, and D) were not significantly different from the coefficient found in the full mixed model (table 3, model A), also suggesting minimal collinearity effects.

In the linear mixed model with VIQ as the dependent variable, higher 28-36 week BPb was associated with lower intellectual coefficient of the child ( $\beta = -3.15$ ,  $p = 0.007$ ) and children of higher IQ mothers

had better performance ( $\beta = 0.29$ ,  $p < 0.001$ ). There was no significant change in the VIQ from the first evaluation to subsequent evaluations.

In the linear mixed model with PIQ as the dependent variable, 28-36 BPb was inversely associated with child IQ ( $\beta = -4.37$ ,  $p = 0.004$ ), and children of the higher IQ mothers had better performance ( $\beta = 0.40$ ,  $p < 0.001$ ). We also observed significant PIQ improvement from first to subsequent tests ( $\beta = 7.2$ ,  $p < 0.001$ ).

To more precisely evaluate at which pregnancy stage maternal BPb was best associated with later reduction in child IQ, we constructed a linear mixed model adjusted by the same covariates used in the full linear mixed model (table 3, model A), but exchanged the averaged prenatal BPb variables for prenatal BPb at week 12, 20, 28 or 36 of pregnancy. BPb at week 28 of pregnancy was the only prenatal lead measure significantly predicting lower FSIQ ( $\beta = -4.13$   $p < 0.001$ ) (table 4).

To statistically test whether natural log BPb transformation fit the data significantly better than a linear BPb specification we used the J-Test to compare the two specifications of lead at the third trimester of pregnancy on FSIQ in the full model (table 3, model A). The logarithmic form of third trimester BPb fit the data significantly better than a linear functional form ( $t = 2.15$ ,  $p = 0.02$ ).

Figure 2 shows a partial residual plot of the effect of third trimester maternal BPb on FSIQ at eight years of age adjusted for the covariates and other BPb values in the full model (table 3, model A).

## **Discussion**

Increased maternal lead concentration at third trimester of pregnancy, especially around week 28, was associated with decreased intellectual child development, even after controlling for other prenatal and postnatal lead measurements. Other studies found significant adverse associations between postnatal BPb and IQ (Baghurst et al. 1992; Bellinger et al. 1992; Dietrich et al. 1993b; Wasserman et al. 1997). In our panel unadjusted regression analyses we noted a significant effect of 6-10 year BPb on child IQ as well, but this effect lost significance when other BPb and covariates were included in mixed model analysis. Collinearity between prenatal and 6-10 year BPb variables was not responsible for loss of explanatory power of 6-10 year BPb, as shown in the extensive diagnostic testing reported in Results. Given the modest sample size and relatively low power of this study, we do not claim that lead exposure from 6-10 years or any other developmental period has no effect on child IQ. More likely, third trimester lead exposure is a more powerful predictor of later child IQ and absorbed enough of the variation in IQ formerly attributed to 6-10 year BPb to render it insignificant in our model.

In contrast to other studies in which prenatal lead exposure biomarkers were umbilical cord BPb (Bellinger et al. 1992), one (Dietrich et al. 1993b; Wasserman et al. 1997, 2000 a; Ris et al. 2004) or at most two (Baghurst et al. 1992) maternal lead measurements during pregnancy, we measured prenatal lead exposure systematically (within an interval of plus or minus two weeks) during specific pregnancy stages (weeks 12, 20, 28 and 36 of pregnancy, at delivery and in umbilical cord). We note that 28 week fetal central nervous system development is distinctly different than development at either 12 weeks or at term. Neuroblast proliferation is essentially complete before 28 weeks while neuronal migration and aggregation continue through the first half of the third trimester. Myelination of tracts within the developing human fetal brain has just begun by 25 weeks (Herschkowitz 1988). Deeper cortical layers are poorly defined at 24 weeks, clearly developed at 28 weeks, and reach postnatal appearance by 34 weeks of pregnancy (Larsen 1997). Limiting the range of permitted weeks

of pregnancy for placing each maternal BPb in its nominal category probably enhanced our ability to detect pregnancy phase-specific PBb effects.

Other studies did not simultaneously include all lead measurements in their analyses, although one (Wasserman 2000a) included directional postnatal lead change indicators along with the single pregnancy blood lead variable. We were able to include the entire history of lead exposure in our analyses since collinearity among the lead measures was not a significant factor. In our analysis, simultaneous inclusion of 6-10 year BPb and the remaining BPb reduced the size of the 6-10 year lead coefficient without changing its variance, rendering it insignificant. With the increased power afforded by a larger sample size, 6-10 year BPb might well have retained its significance.

#### *Methodological considerations*

A frequent problem in cohort studies is high loss rate during extended follow-up. From an original sample of 321 children we tested 175 available children after five years of age, of which only 150 were included in mixed model analyses due to missing covariates. The smaller number of subjects reduced the possibility of detecting subtle effects and increased the possibility of instability of model coefficients. Nevertheless, despite the medium sample size, we found a highly significant effect of maternal third trimester BPb on child IQ at ages 6 to 10 with little evidence of selective drop out bias in the descriptive statistics.

In addition to longitudinal analyses, we carried out separate analyses of IQ at each age. The pattern of results was consistent in these analyses; 28-36 week BPb and maternal intellectual quotient were the variables significantly predicting child IQ.

Repeated use of the same test to evaluate child IQ at short intervals could lead to learning of test components across time and a familiarization with the test situation. We found a significant change (table 3) only between the first FSIQ measurement and the subsequent measurements, nearly all of which was due to increase in the Performance Scale. Repeated test application produced a significant adjusted increase of 7.2 Performance IQ points and 4.0 FSIQ points from first to subsequent test applications. This might be expected in children encountering performance tasks for the first time during the initial test application.

Studies in developmental toxicity have shown that subtle developmental alterations are easier to detect when subjects confront challenging or stressful situations (Cory-Slechta 1990; Rice 2000). Familiarity with the test situation and repetition of the same test should have reduced our ability to detect subtle developmental deficits associated with lead. We conclude that the lead effect described is robust.

Other studies found a substantial impact of sociodemographic variables on IQ. Several studies reported significant associations between lead and child development that disappear (Ernhart et al. 1989) or become evident (Wasserman et al. 1997) when HOME score was used as a covariate. We applied the 6 month HOME scale in our study but did not include it in full modeling as it did not appreciably or significantly change the estimated magnitude and significance of BPb and model fit improved according to Schwarz's Bayesian Information Criterion when this covariate was omitted (see Appendix for mixed models with HOME added). In contrast to our models, other studies found the HOME scale useful. The HOME scale is distinctly Euro-North American culture bound. For example, we found that many homes we visited did not have items such as educational toys, which were not readily available in the domestic market at that time, thus altering the HOME score of our

subjects. Furthermore, 6 month evaluations might be expected to play little role in development at 6 to 10 years.

If increased third trimester BPb were associated with decreased birth weight and low birth weight were associated with poor postnatal intellectual development, the modeled effect of third trimester lead on 6-10 year IQ could be mediated through lead effect on birth weight. Our subject inclusion criteria only accepted newborn infants into the study with birth weight >2000 g (the Mexican standard for low birth weight at the time of the study), thus excluding cases with the highest probability of showing later deficits due to low birth weight. Exploratory modeling showed that no prenatal BPb was significantly associated with birth weight. Finally, excluding or including birth weight in mixed model analyses changed the 28-36 week BPb coefficient by less than 0.03. There is no evidence in these data that third trimester BPb effect on 6-10 year old IQ was mediated by lead effect on weight.

Both the Spanish WISC-R for child IQ and the Spanish WAIS used for maternal IQ have since been superseded by updated, renormalized versions. The tests we used were the only Spanish language versions available during data collection. We note that the IQ scores measured in our sample were generally higher than those obtained in other prospective studies, perhaps as a result of using outdated tests. Though the current version of the WISC might reveal the bias in the absolute IQ associated with lead in these data, the covariation between lead and IQ was likely not affected by the specific test version used.

*Public health implications*

These data suggest that early third trimester of pregnancy may constitute a critical period for subsequent intellectual child development, during which lead exposure can produce lasting and possibly permanent effects. In addition, the data suggest there is no threshold for the adverse consequences of lead. On the contrary, the largest IQ changes in our sample are observed within first few micrograms per deciliter of BPb, that is, at lower BPb (figure 2). The relationship between BPb and child IQ is logarithmic, not linear, as shown by the significant ( $p = 0.02$ ) J test. Other studies have already reported larger IQ change with change of lead at lower concentrations than at higher concentrations (Canfield et al. 2003; Lanphear et al. 2000; Schwartz 1994). A recent reanalysis of a large ( $N = 1333$ ) pooled data analysis (Lanphear et al. 2005) of seven prospective lead studies, including this one, also confirms that the log-linear dose-response relationship between IQ around seven years of age and contemporary BPb is superior to a linear-linear dose-response relationship (Rothenberg and Rothenberg 2005).

We noted the same pattern of BPb change during pregnancy in this study (Rothenberg et al. 1994) observed in other studies in the US (Hertz-Picciotto et al. 2000; Schell et al. 2000). Postnatal BPb pattern with age has already been examined in detail in this cohort (Schnaas et al. 2004) and is similar to that from US and Australian prospective studies (Dietrich et al. 1991b; McMichael et al. 1988). Postnatal PBb peaks around two years of age and then decreases with increasing age (Fig. 1). As our cohort did not exhibit unusual blood lead change from 12 weeks of pregnancy through ten years of age, our results cannot be attributed to the cohort's unique history of lead exposure.

Across a range of BPb from 1 to 32  $\mu\text{g}/\text{dL}$ , these data show that half of the deleterious effects of lead on child IQ measured here occurred when third trimester BPb increased from 1 to 6  $\mu\text{g}/\text{dL}$ . When maternal BPb reached current Mexican and US action limits for children and pregnant women (10

µg/dL), a majority of the adverse consequences on later child IQ associated with lead in the measured range had already occurred. If we continue to accept the current action limit, we also accept that most of the “damage” to the IQ of children associated with third trimester lead exposure in our sample is permissible.

The fetal brain seems susceptible to lower lead concentrations than those established by the official Mexican standard and current CDC guidelines and the effects are obvious at least until 10 years of age. Though these findings should be replicated, our data suggest we should establish lower action limits for lead exposure of reproductively active women.

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APPENDIX

Table A. Linear mixed models with random intercept and random slope for concurrent lead for a cohort of 128 children<sup>a</sup>. Fixed effects estimations.

Variable	Model			
	A		B	
	HOME and SES		HOME without SES	
	$\beta \pm SE$ (95% CI)	p	$\beta \pm SE$ (95% CI)	p
Intercept	75.09 ±12.84 (49.80,100.38)	<.0001	75.18±12.76 (50.04,100.32)	<.0001
ln(lead) 12-20 weeks	0.90 ±1.640 (-2.34,4.12)	0.5864	0.88±1.63 (-2.33,4.09)	0.5892
ln(lead) 28-38 weeks	-4.15 ±1.34 (-6.79,-1.51)	0.0024	-4.14±1.33 (-6.76,-1.52)	0.0023
mean ln(lead) 1-5 years	0.56 ±2.22 (-3.81,4.93)	0.8013	0.61±2.14 (-3.61,4.83)	0.7746
ln(lead) 6-10 years	0.46 ±0.85 (-1.21,2.13)	0.5907	0.46±0.85 (-1.21,2.13)	0.5911
child sex	-0.64 ±1.83 (-4.25,2.97)	0.7270	-0.67±1.80 (-4.22,2.88)	0.7109
birth weight	0.00 ±0.02 (-0.004,0.004)	0.9070	0.00023±0.002 (-0.004,0.004)	0.9076
socioeconomic stratum	-0.10 ±0.86 (-2.59,0.79)	0.9170		

HOME Scale	-0.16 ±0.15 (-0.46,0.14)	0.3103	-0.16±0.15 (-0.46,0.14)	0.2686
maternal IQ	0.42 ± 0.08 (0.26,0.58)	<.0001	0.42±0.07 (0.28,0.56)	<.0001
first full scale IQ application indicator	-4.11±0.45 (3.20,5.02)	<.0001	-4.11±0.46 (-5.02,-3.20)	<.0001

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<sup>a</sup>Dependent variable is Full Scale IQ of children from 6 to 10 years of age

TABLE 1. Comparison among subjects included in the model and subjects with incomplete data, or not assessed beyond 5 years of age

Characteristics	Not assessed beyond 5 years of age			Subjects with incomplete data			Subjects included in the model			p <sup>b</sup> Value (2-tailed)	p <sup>c</sup> Value (2-tailed)
	N	%	Mean <sup>a</sup> (5%,95%)	N	%	Mean <sup>a</sup> (5%,95%)	N	%	Mean <sup>a</sup> (5%,95%)		
Sex											
Male	83	56.8		12	48.0		79	52.7		0.49 <sup>d</sup>	0.67 <sup>d</sup>
Female	63	43.2		13	52.0		71	47.3			
Socioeconomic stratum											
Lowest	60	42.9		3	12.0		20	13.3		<0.001 <sup>d</sup>	0.82 <sup>d</sup>
Medium	77	55.0		16	64.0		93	62.0			
Highest	3	2.1		6	24.0		37	24.7			
APGAR 5 minutes											
6	1	0.7		0	0.0		1	0.7		0.98 <sup>d</sup>	1.00 <sup>d</sup>
7	1	0.7		0	0.0		0	0.0			
8	8	5.6		1	4.0		9	6.0			
9	134	93.1		24	96.0		139	92.6			
10	0	0.0		0	0.0		1	0.7			
Birth Order											
1	62	42.8		11	44.0		73	48.7		0.42 <sup>d</sup>	0.87 <sup>d</sup>
2	49	33.8		9	36.0		48	32.0			
3	28	19.3		3	12.0		22	14.7			
4	4	2.8		2	8.0		7	4.7			
≥5	2	1.3		0	0.0		0	0.0			
Birth weight (g)	144		3194 (2503, 4000)	25		3148 (2569, 3818)	150		3218 (2450, 3911)	0.64	0.46
Maternal IQ	127		91(68,113)	25		96 (65,115)	150		93 (71, 112)	0.31	0.26
Prenatal Lead											
12-20 weeks	126		8.4 (7.6, 9.1)	10		8.2 (3.0,13.7)	150		8.2 (3.0, 20.7)	0.20	0.98
28-36 weeks	129		7.3 (1.5, 17.4)	11		13.0 (5.3, 27.0)	150		7.8 (2.5, 24.6)	0.49	0.02
Bayley Scales of Infant Development											
MDI at 6 months	122		115.0 (91, 140)	20		117.4 (98, 137)	135		115.3 (89, 144)	0.87	0.60
MDI at 12 months	103		114.1 (94, 134)	25		115.2 (86, 131)	137		115.7 (93, 134)	0.33	0.85
MDI at 18 months	87		104.3 (78, 128)	23		112.3 (102, 128)	139		107.9 (88, 128)	0.05	0.11
MDI at 24 months	69		103.5 (79, 132)	21		119.8 (94, 150)	135		109.5 (87, 132)	0.009	0.003
McCarthy Scale											
GCI at 36 months	37		97.6 (64, 117)	22		102.0 (89, 118)	133		100.8 (85, 116)	0.11	0.61
GCI at 42 months	25		98.7 (82, 118)	20		110.1 (101, 122)	133		105.1 (86, 121)	0.01	0.06
GCI at 48 months	30		93.8 (60, 130)	24		105.5 (85, 119)	137		102.3 (81, 122)	0.003	0.26
GCI at 54 months	18		95.8 (57, 129)	22		106.8 (88, 120)	124		104.1 (89, 119)	0.008	0.29
GCI at 60 months	15		98.9 (62, 127)	18		108.8 (82, 121)	126		104.8 (88, 119)	0.048	0.12
WISC Full Scale IQ 6 years				23		109 (91, 126)	140		105 (87, 123)		0.17

7 years			20	109 (88, 127)	140	109 (91, 127)		0.93
8 years			21	109 (90, 130)	127	108 (91, 126)		0.72
9 years			16	114 (98, 141)	120	109 (91, 128)		0.09
10 years			15	112 (94, 140)	115	109 (87, 130)		0.45
Postnatal Lead								
1 year of age	131	10.0 (3.2, 18.8)	23	11.6 (5.5, 19.8)	142	10.8 (4.0, 22.0)	0.40	0.54
2 years of age	93	12.0 (4.2, 25.2)	25	13.1 (5.8, 23.0)	142	12.8 (5.0, 25.8)	0.42	0.82
3 years of age	52	11.6 (5.0, 23.5)	25	12.2 (5.2, 19.8)	140	11.3 (4.7, 22.9)	0.74	0.52
4 years of age	38	8.9 (3.2, 18.5)	25	11.3 (4.8, 19.0)	142	10.3 (4.2, 20.5)	0.13	0.46
5 years of age	22	9.0 (3.5, 16.5)	22	10.6 (5.0, 19.2)	136	9.3 (3.8, 18.0)	0.78	0.26
6 years of age			21	9.3 (4.5, 20.8)	135	7.9 (3.2, 16.0)		0.14
7 years of age			21	8.9 (4.2, 17.0)	142	7.5 (3.0, 13.8)		0.13
8 years of age			20	7.5 (2.5, 14.6)	132	6.4 (2.8, 12.8)		0.17
9 years of age			21	7.7 (3.5, 12.5)	123	6.0 (2.8, 11.8)		0.025
10 years of age			15	7.8 (3.0, 19.2)	118	5.6 (2.5, 11.2)		0.008

<sup>a</sup> Blood lead geometric mean

<sup>b</sup> Subjects included in the model vs. subjects not assessed beyond 5 years of age.

<sup>c</sup> Subjects included in the model vs. subjects with incomplete data.

<sup>d</sup> Fisher's exact test of Pearson chi-square exact probability. Unmarked probabilities by t-test for independent samples.

TABLE 2. Non-adjusted and adjusted models of Full Scale IQ (panel regressions). Each lead variable tested alone.

Lead Variable ( $\mu\text{g/dL}$ )	Unadjusted				Adjusted <sup>a</sup>		
	N	$\beta$	95% CI	p Value (2-tailed)	$\beta_{\text{adj}}$	95% CI	p Value (2-tailed)
ln(lead) 12-20 weeks	150	-1.90	-4.79, 0.98	0.20	-1.45	-4.75, 2.00	0.42
ln(lead) 28-36 weeks	150	-3.84	-6.24, -1.44	0.002	-4.00	-6.37, -1.65	0.001
maternal ln(lead)delivery	112	-1.77	-5.12, 1.57	0.29	-1.29	-4.41, 1.83	0.41
umbilical cord ln(lead)	109	-0.69	-3.50, 2.11	0.63	-0.95	-3.65, 1.75	0.49
mean ln(lead) (1-5 years)	150	-2.41	-6.38, 1.57	0.23	0.49	-3.81, 4.81	0.82
ln(lead) at 1 year of age	142	-1.51	-4.96, 1.94	0.39	0.51	-3.19, 4.21	0.79
ln(lead) at 2 years of age	143	-1.10	-4.49, 2.29	0.39	0.91	-2.67, 4.49	0.62
ln(lead) at 3 years of age	140	-2.53	-6.22, 1.15	0.18	-0.58	-4.53, 3.37	0.78
ln(lead) at 4 years of age	142	-0.61	-4.34, 3.12	0.75	1.17	-2.67, 5.02	0.55
ln(lead) at 5 years of age	136	-2.96	-6.67, 0.75	0.12	-0.32	-4.26, 3.36	0.87
mean ln(lead) (1-2 years)	147	-1.78	-5.46, 1.90	0.34	0.60	-3.36, 4.57	0.76
mean ln(lead) (3-5 years)	150	-2.63	-6.47, 1.22	0.18	-0.08	-4.15, 3.98	0.96
mean ln(lead) (6-10 years)	150	-2.70	-4.23, -1.16	0.001	-2.45	-4.09, -0.81	0.003

<sup>a</sup> Adjusted by maternal IQ, SES, sex, birth weight, an indicator variable of first full scale IQ application at 6, 7 or 8 years.

TABLE 3. Linear mixed models of Full Scale IQ with random intercept and random slope for 6 to 10 year blood lead ( $\mu\text{g/dL}$ )

Fixed effects estimations.

Variable	Model A (full model)			Model B (without non-significant control variables)			Model C (Model B without non-significant lead before 6-10 years)			Model D (without any non-significant variables)		
	$\beta$	95% CI	p*	$\beta$	95% CI	p	$\beta$	95% CI	p	$\beta$	95% CI	p
Intercept	73.6	52.4, 94.6	<.0001	73.6	56.9, 90.4	<.0001	75.8	62.6, 88.0	<.0001	76.3	63.7, 88.9	<.0001
mean ln(lead) 12-20 weeks pregnancy ( $\mu\text{g/dL}$ )	1.02	-1.98, 4.03	0.50	0.89	-2.09, 3.88	0.56						
mean ln(lead) 28-36 weeks pregnancy ( $\mu\text{g/dL}$ )	-3.90	-6.45, -1.36	0.0029	-3.85	-6.36, -1.33	0.0029	-3.46	-5.64, -1.29	0.0020	-3.44	-5.61, -1.28	0.0020
mean ln(lead) 1-5 years ( $\mu\text{g/dL}$ )	0.10	-3.88, 4.06	0.96	0.35	-3.48, 4.18	0.86						
ln(lead) 6-10 years ( $\mu\text{g/dL}$ )	0.17	-1.41, 1.76	0.83	0.15	-1.44, 1.72	0.86	0.21	-1.30, 1.72	0.79			
child sex (female)	-1.51	-4.75, 1.73	0.36									
birth weight (grams)	0.001	-0.003, 0.004	0.61									
socioeconomic stratum (tertiles)	-0.38	-1.86, 1.10	0.61									
maternal IQ	0.40	0.26, 0.55	<.0001	0.39	0.26, 0.52	<.0001	0.39	0.26, 0.51	<.0001	0.38	0.26, 0.51	<.0001
first Full Scale IQ measurement	-4.00	-4.84, -3.16	<.0001	-4.00	-4.82, -3.15	<.0001	-4.00	-4.83, -3.16	<.0001	-4.00	-4.78, -3.16	<.0001

\*(2-tailed)

TABLE 4. Linear mixed model of Full Scale IQ with random intercept and random slope for concurrent lead (n=122) Test of prenatal lead concentration at week 28 of pregnancy. Fixed effects estimations.

Variable	$\beta$	95% CI	p (2-tailed)
Intercept	79.5	56.5, 102.5	<.0001
ln(lead) 28 weeks pregnancy ( $\mu\text{g/dL}$ )	-4.13	-6.45, -1.81	0.0006
mean ln(lead) 1-5 years ( $\mu\text{g/dL}$ )	-1.01	-5.54, 3.52	0.66
ln(lead) 6-10 years ( $\mu\text{g/dL}$ )	0.21	-1.46, 1.88	0.81
child sex (female)	-1.21	-4.87, 2.45	0.52
birth weight (grams)	0.001	-0.003, 0.005	0.61
socioeconomic stratum (tertiles)	-0.40	-1.27, 2.07	0.64
maternal IQ	0.38	0.22, 0.54	<.0001
first Full Scale IQ application	-3.52	-4.43, -2.61	<.0001

## Figure Legends

Figure 1. Box plots of blood lead concentration by age of the 150 children used in linear mixed model analyses. The lower and upper limits of the rectangular boxes indicate the 25<sup>th</sup>-75<sup>th</sup> percentile range and the horizontal line within the boxes is at the 50<sup>th</sup> percentile. The vertical lines extending from the bottom and top of the boxes represent lead values 1.5 times the interquartile range below and above the 25<sup>th</sup> and 75<sup>th</sup> percentile, respectively. Open circles represent lead values between 1.5 and 3.0 times the interquartile range below and above the 25<sup>th</sup> and 75<sup>th</sup> percentile, and crosses indicate lead values exceeding the 3.0 times the interquartile range limit. Plots for each age, with extreme high values, are typical for log distributions plotted on a linear scale. Conversion factor  $10 \mu\text{g/dL} = 0.483 \mu\text{mol/L}$ .

Figure 2. Partial residual plot of the effect of third trimester maternal blood lead (thin lines: 95 percent confidence interval) on Full Scale IQ at 8 years of age adjusted for maternal IQ, gender, birth weight, socioeconomic stratum, and blood lead levels at other prenatal and postnatal ages. The third trimester of pregnancy is a critical period for lasting effects of lead exposure on intellectual development. The log-linear association between lead and child intelligence indicates that two-thirds of the deleterious effects of lead on child IQ occur when third trimester lead concentrations rise from 1 to 10  $\mu\text{g}/\text{dL}$ , the current CDC blood lead level of concern. The log-linear dose-response curve of lead-IQ suggests that current national and international standards do not prevent most of the damaging effects of lead on child intellectual development. Conversion factor  $10 \mu\text{g}/\text{dL} = 0.483 \mu\text{mol}/\text{L}$

Figure 1

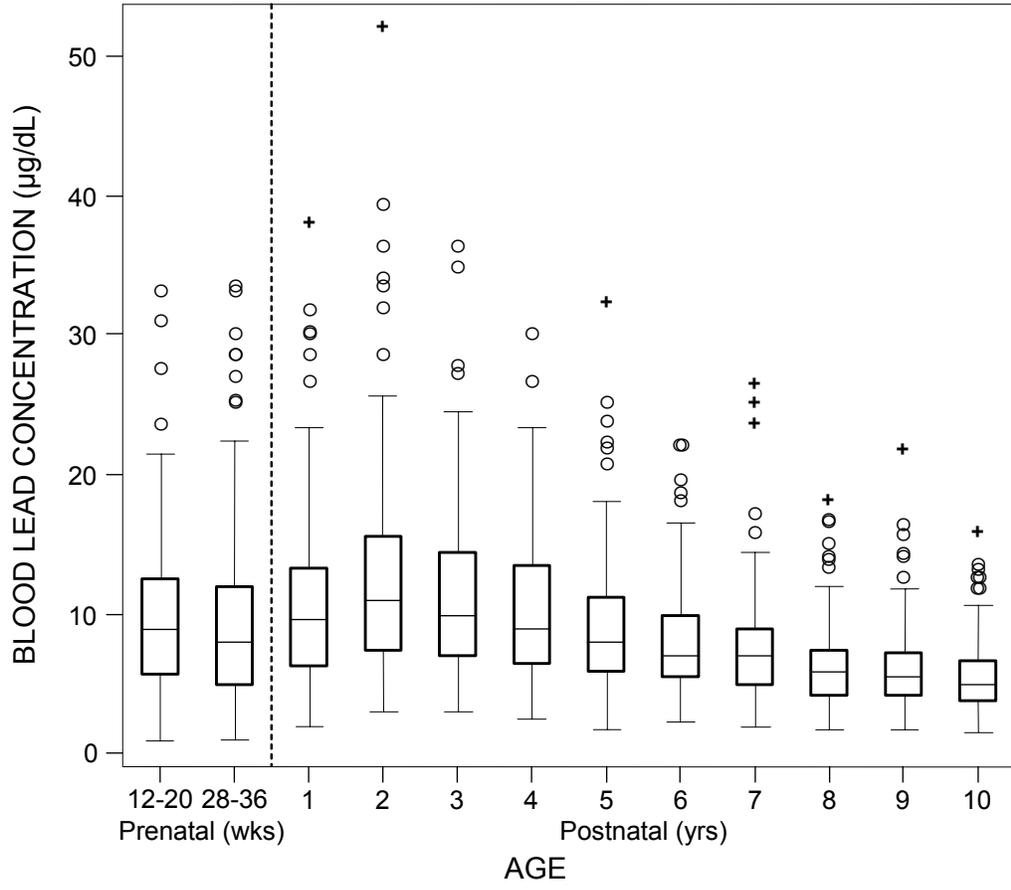


Figure 2

