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Low- Level Lead Exposure and Infant Development in the First Year[1]

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BELLINGER, D., A. LEVITON, H. L. NEEDLEMAN, C. WATERNAUX AND M. RABINOWITZ. Low level lead exposure and infant development in the first year. NEUROBEHAV TOXICOL TERATOL 8(2) 151-161. 1986.- The developmental impact of prenatal and early postnatal low-level lead exposure was assessed in a prospective study of 249 middle and upper-middle class infants with umbilical cord blood lead levels in the range currently considered "normal." Infants were classified into three exposure groups: "low" (‹3μg/dl), "mid" (6 to 7 μg/dl), and "high" (≥1μg/dl). At 6 and 12 months, the lead concentration of capillary blood was measured, and the Bayley Scales of Infant Development administered. At both ages, Mental Development Index scores. adjusted for confounding, were inversely related to infants' umbilical cord blood lead levels. The difference between the mean adjusted scores of the infants in the low and high cord blood lead groups was 5.8 points at 6 months and 7.3 points at 12 months. At neither age were scores significantly related to postnatal blood lead levels. Prenatal exposure to lead levels relatively common among urban populations appear 10 be associated with less favorable development through the first year of life.

Human studies Prenatal and postnatal lead studies Infant development

WE previously reported an inverse relationship between infants' umbilical cord blood lead concentrations and their scores at 6 months of age on the Mental Development Index (MDI) of the Bayley Scales of Infant Development [2,3]. This relationship was dose-dependent over 0 to 25 μg/dl, the range of lead levels observed in our sample. The difference between the adjusted MDI scores of the infants in the "low" (‹3 μg/dl) and" high" (≥. 10 μg/dl) exposure groups was approximately 6 points (0.4 SO).

Although this finding suggests that lead has adverse effects at blood concentrations prevalent among young children [12]. its implications for regulatory policy depend on the magnitude of the association and its stability over time. Among the relevant questions are the following. Do the performance differences between exposure groups persist beyond 6 months of age? Does the lower mean performance of infants with "high" cord blood lead levels reflect the enhanced susceptibility of a subgroup of these infants or does the effect extend to most of them? Does level of postnatal exposure alter the relationship between cord blood lead concentration and MDI? In this report we address these and related issues by including follow-up assessments of the infants at age 12 months in a re-examination of the association between pre- and postnatal lead exposure and performance on the Bayley Scales in the first year of life.

Sample Selection

The infants enrolled in this study were selected from a Population of 11,837 infants whose umbilical cord blood lead concentration was measured. These infants represent approximately 97% of the births at the Brigham and Women's Hospital in Boston. MA between April 1979 and April 1981. The mean cord blood lead level of this population was 6.6 μg/dl (SD=3.2, range=0-37) (16).

Our goal was to select three groups of infants for study: those with cord blood lead levels in the lowest tenth percentile for the population of births at this hospital (the "low" lead group), those with levels very close to the mean (the "mid" lead group), and those with levels exceeding the ninetieth percentile (the "high" lead group). The distribution of cord blood lead levels for the approximately 2,500 infants born in the first 4.5 months of blood sample collections was used to establish criteria for eligibility in these three groups (‹3,6 to 7, and ≥.10 μg/dl for the low, mid, and high lead groups, respectively). The study sample was chosen from the 9,489 infants born between August 10, 1979 and Apri130, 1981.

Not all eligible infants and families were invited to participate. Infants were excluded because of a serious medical condition evident at birth or in the early postnatal period (e.g Down's syndrome, gestational age less than 34 weeks. cleft palate). location of residence (greater than 12 miles from the Children's Hospital or in an area judged unsafe for home visitors), language barrier, failure to seek or obtain consent, an intention to relocate out of the immediate region, or our inability to locate them (Table I). Additional details about the sample selection process and ascertainment bias are presented elsewhere [3].

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TABLE 1

REASONS FOR EXCLUDING INFANTS WITH UMBILICAL CORD BLOOD LEAD LEVELS IN ONE OF THE TARGET RANGES

	Umbilical Lord Blood Lead Cataegory			
	Low	Mid	High	Total
No. infants provisionally	434	380	393	1207
No. excluded	349	292	317	958
Reason:				
no maternal consent	69	64	63	196
birth complication*	17	17	4	38
non-English speaking	23	18	24	65
location of residence †	150	107	108	365
refusal‡	52	54	61	167
moving	20	12	10	42
unreachable	18	20	47	85
No. infants enrolled	85	88	76	249

Some infants were not acceptable for inclusion for two or more off the following reasons: no maternal consent, birth complication, non-English glish speaking family, location of residence. For the purposes of classifying such infants, these reasons were ranked in the order listed above in terms of precedence. Therefore, except for "no maternal consent," the numbers in the table underestimate the incidence of the various reasons for exclusion

*Down's Syndrome, retinoblastoma, cleft palate, gestational age<34 weeks, etc.

†> 12 miles from Boston, inner-city area, specific housing projects.

‡ There were two opportunities for mothers to refuse participation.

While still in the hospital, all mothers were asked for permission to possibly be contacted in the future about participating in a follow up study. Some refused this request. Some who gave consent at this time refused when subsequently contacted.

A total of 249 infants were enrolled in the three exposure groups (Table 2). As planned, the means of the high and low groups fall at the extreme tails of the distribution of levels for births at this hospital. The highest cord blood lead level among enrolled infants was 24.9 -μg/dl.

Sample Characteristics

The selection criteria we applied and the self-selection exercised by the eligible families resulted in the recruitment of children at low-risk for developmental problems. In general, the enrolled families are intact, white, and middle- to upper-middle class. Cord blood lead grouping was not significantly related to any of the parental occupational or educational variables measured. The only demographic characteristics that differed significantly across groups were parental age and race. The low lead group had the lowest percentage of whites, and the mid lead group the highest percentage. The associations between cord blood lead level and several indicators of social disadvantage (e.g., receipt of public assistance, lower educational achievement, unmarried) seen in the more heterogeneous population from which this sample was drawn [17] were not seen in this highly selected subsample.

Infants of mothers who sought prenatal care earlier in pregnancy tended to have higher cord blood lead levels.

UMBILICAL CORD BLOOD LEAD LEVELS OF INFANTS ENROLLED IN THE THREE EXPOSURE GROUPS

Exposure Group	N	Mean (μg/dl)	Standard Deviation	Percentile of Mean"
low	85	1.8	0.6	2.5
mid	88	6.5	0.3	56.1
high	76	14.6	3.0	98.0

"Among the lead concentrations of the 11,837 umbilical cord blood samples collected at the Brigham and Women's Hospital (Boston) between April 1979 and April 1981.

Among the lead concentrations of the 11,837 umbilical cord blood samples collected at the Brigham and Women's Hospital (Boston) between April 1979 and April 1981.

Re-ported rates of alcohol and coffee consumption were highest among mothers delivering infants with high lead levels, though in neither case is the amount consumed thought to place a fetus at increased risk. Infants' cord blood lead levels increased with number of years of maternal cigarette smoking, although reported amounts of smoking during pregnancy did not differ across groups. A comparison of the three groups on a more extensive set of variables is presented elsewhere [3].

Data Collection

Developmental assessments. Visits with each enrolled family were conducted in the home when the index child was 1 and 6 months old, and at the Children's Hospital (Boston) when the infant was 12 months old. The types of information collected and the specific instruments used on the three occasions are listed in Table A of the Appendix. In this report we focus on the infants' scores on the Mental Development Index of the Bayley Scales of Infant Development [I] at 6 and 12 months of age. At the time of the 6 month assessment, the mean ages (in days) of the children in the low, mid, and high cord blood lead groups were 186.8 (SD=6.5), 187,5 (SD=5.4), and 186.3 (SD=4.3), respectively. The mean ages (in days) at the time of the 12 month assessment were 372.2 (SD=8.1), 372.5 (SD=6.6), and 371.3 (SD=8.6), respectively.

Five examiners blind to the infants' lead levels administered the Bayley Scales. Examiner reliability was assessed by correlating the scores assigned by two examiners observing a third examiner administer the Scales. The average inter-observer correlation was 0.97 (SD=0.02) for the 6 month administration, and 0.98 (SD=0.02) for the 12 month administration. At both ages, the correlation exceeded 0.945 for all pairs of examiners.

Blood samples. Five ml of umbilical cord blood were collected in heparinized Vacutainer tubes (B-D, Rutherford, NJ) at the time of delivery. These samples were analyzed in duplicate by anodic stripping voltammetry (Environmental Science Associates, Model 2014, Bedford, MA). To assess the extent of contamination during sample collection and handling, each batch of 30 samples was accompanied by 5 blank tubes. To assess inter-batch analytical stability, two biological standards (one containing 10 μg/dl, the other 20 μg/dl) were included in each batch. To assess inter laboratory reliability. we participated in quarterly blind

TABLE 3

BIVARIATE ASSOCIATIONS BETWEEN MENTAL DEVELOPMENT INDEX SCORES AT 6 AND t2 MONTHS AND BLOOD LEAD LEVELS AT BIRTH, 6, AND 12 MONTHS

Age at Measurement of Blood Lead Level	Age at Measurement of Mental Development Index Score: 6 Months				12 Months			
	N	Parameter estimate††	Standard. error	p-value	N	Parameter estimate††	Standard error	p-value
birth·*	216	-i,49	1.01	0.14	207	-2.04	1.11	0.07
6 months	205	0.65	0.94	0.49	196	-0.74	1.04	0.48
12 months†					198	-0.41	1.08	0.71

·Blood lead level at birth was categorized as "low," "mid," or "high" (coded 1,2, and 3, respectively).

†MDI score at 6 months was not regressed on blood lead level at 12 months of age because of its temporal priority.
††The parameter estimate for cord blood lead category represents the estimated difference in mean adjusted MDI scores of adjacent exposure groups (e.g., low and mid or mid and high). The sign indicates whether the score is higher (+) or lower (-) in the group with greater exposure. The parameter estimate should be multiplied by two to obtain the estimated difference between the scores of the low and high exposure groups.

TABLE 4

MULTIPLE REGRESSION MODELS OF MENTAL DEVELOPMENT INDEX SCORES AT6 MONTHS WITH AND WITHOUT CORD BLOOD LEAD CATEGORY AS A PREDICTOR·

Predictor Variables	Without Cord Blood Lead Category: Parameter estimate†	Standard error	p-value	With Cord Blood Lead Category: Parameter estimate†	Standard error	p-value
H.O.M.E. total score	0.69	0.21	0.0014	0.75	0.21	0.0004
length of gestation	2.60	0.43	0.0001	2.72	0.42	0.0001
cord blood lead category				-2.89	0.92	0.0019
Model R"		20.9			24.6	

·N =203 for both models.
†The parameter estimate for cord blood lead category represents the estimated difference in mean adjusted MDl scores of adjacent exposure groups (e.g., low and mid or mid and high). The sign indicates whether the score is higher (+) or lower (-) in the group with greater exposure. The parameter estimate should be multiplied by two to obtain the estimated difference between the scores of the low and high exposure groups.

TABLE 5

MULTIPLE REGRESSION MODELS OF MENTAL DEVELOPMENT INDEX SCORES AT 12 MONTHS WITH AND WITHOUT CORD BLOOD LEAD CATEGORY AS A PREDICTOR"

Predictor Variables Without Cord Blood Lead	Without Cord Blood Lead Category: Parameter estimate†	Standard error	p-value	With Cord Blood Lead Category: Parameter estimate†	Standard error	p-value
H.O.M.E. scale I		0.8	1	0.84	0,047	
length of gestation		6	0.0045	0.52	0.001	
cord blood lead category		0.5	1.68	1.12	3	
					0.001	
Model R^2		3	1.70 -	11.7	5	
		0.06	3.63			

·N = 185 for both models.

-3.63

†The parameter estimate for cord blood lead category represents the estimated difference in mean adjusted MDI scores of adjacent exposure groups (e.g., low and mid or mid and high). The sign indicates whether the score is higher (+) or lower (-) in the group with greater exposure. The parameter estimate should be multiplied by two to obtain the. essential difference between the scores of the low and high exposure groups.

TABLE 6

MEAN ADJUSTED MENTAL DEVELOPMENT INDEX SCORES OF INFANTS IN THE THREE CORD BLOOD LEAD GROUPS AT 6 AND 12 MONTHS

Cord Blood Lead Group	Adjusted Mental Development Index Score 6 months	 12 months
low	110.8 ± 1.2*	114.6 ±1.5
mid	107.1 ±1.3	114.0 ±1.6
high	105.0 ±1.4	107.3 ±1.6

*Mean ± standard error

TABLE 7

SCORES AT t2 MONTHS ON ITEM CLUSTERS FROM THE BAYLEY SCALES OF INFANT DEVELOPMENT

cluster (number of items)		Cord Blood Lead Category low	 mid	 high	p-value	items contributing to c1ustert
fine motor	(10)	4.3 ± 1.6·	4.3 ± 1.6	3.3 ± 1.7	0.0004	87,98,102,107,108,111 115,118,119,123
imitation	(6)	4.1 ± 1.0	4.1 ± 1.0	3.7 ± 1.2	0.011	92,95.99,104,105,125
object permanence	(4)	3.8 ± 0.5	3.8 ± 0.5	3.9 ± 0.4	0.74	86,88,91,96
language	(10)	4.6 :t *l.S*	4.9 ± 1.8	4.0 ± 1.2	0.018	89,93,101, 106.113,116 117,124,126,127
spatial	(3)	0.8 ± 0.8	0.6 ± 0.8	0.5 ± 0.8	0.064	110,120,121
goal-directed	(5)	2.4 ± 1.2	2.3 ± l.l	2.31.0	0.25	90,100,109,114,122

*Mean : ± standard deviation.

†Item numbers on the Bayley Scales of Infant Development.

comparisons organized by the Blood Reference Program of the Centers for Disease Control, and analyzed a bovine liver standard whose lead content was certified by the National Bureau of Standards. All intra- and inter-laboratory quality control checks were satisfactory. Additional details about the method used to analyze the cord blood samples are provided elsewhere (16].

Capillary blood samples were collected at age 6 months by a technician who visited the home during the week prior to the visit by the developmental assessment team. The technician also collected samples of air, water, house dust, paint, and milk. When children were 12 months of age, capillary blood samples were collected at the Children's Hospital immediately following the developmental assessment.

The concentration of lead in the capillary blood samples was measured in duplicate by anodic stripping voltammetry (Environmental Science Associates, Model 3010, Bedford, MA) using an exchange reagent. Aliquots of pooled standardized blood of known lead concentration were analyzed with each batch of samples. All values were calculated by comparison to amperage peaks from a gravimetrically prepared lead solution. The efficacy of these quality control procedures was assessed by participating in blind inter-laboratory comparisons conducted by West Allis Memorial Hospital (West Allis, WI) and the Centers for Disease Control. In 1982, when first made available by the CDC, we began measuring standardized blood samples with lead concentrations measured to three significant figures by isotope dilution mass spectrophotometry.

The infants' mean blood lead concentration at age 6 months was 6.2 $\mu g/dl$ (SD=7.I, median=4.I, range = 0-48.6). Mean (:±:SD) levels at this age for infants classified by cord blood lead category (low, mid, high) were 4.5 (:±:3.9), 6.9 (:±7.8, and 7.1 (:±:9.1)', respectively. At 12 months, the mean concentration was 7.7 $\mu g/dl$ (SD-6.5. median=5.9, range=0-30.6). Mean (:±:SD) levels at this age for infants classified by cord blood lead category (low, mid, high) were 5.8 (:±:5.I), 8.5 (:±:7.5), and 8.9 (:±:6.4), respectively. Infants' blood lead levels were not stable between birth and 12 months. The correlations among cord, 6, and 12 month values ranged from 0. 1 to 0.2 (15].

Levels of erythrocyte protoporphyrin (EP) (the zinc species) in the capillary blood samples were measured by hematofluorometry (Environmental Science Associates, Model 4000, Bedford, MA). Our laboratory participated in the monthly blind inter-laboratory comparisons sponsored by the Centers for Disease Control. The mean EP concentration at age 6 months was 20.3 $\mu g/dl$ (SD=I3.9, median = 18, range=0-128). At 12 months, the mean was 19.6 (SD= 20.4, median= 16, range =0-253). The hematocrit of the 6 and 12 month blood samples was also measured (Clay-Adams Microcrit).

LEAD EXPOSURE AND INFANT DEVELOPMENT TABLE

ON THE MENTAL DEVELOPMENT INDEX AT 6 AND 12 MONTHS

Performance Profile *	Cord Blood Lead Group Low	Mid	High	Total
(-, -)	8	14	24	46
	(l1.8)†	(23.3)	(42.1)	
(-,'I-)	22	15	16	53
	(32.3)	(:.>5.0)	(28.1)	
(+,-)	14	J0	9	33
	(20.6)	(16.7)	(15.8)	
(+,+)	24	21	8	53
	(35.3)	(35.0)	(14.0)	
Total	68	60	57	185

Infants with a (-, -) performance profile achieved lower MDI scores than expected at both 6 and 12 months. Infants with a (-,+) profile achieved a lower score than expected at 6 months and a higher score than expected at 12 months. The (+,-) and (+,+) performance profiles are interpreted in the same manner.

†Numbers in parenthesis are column percentages

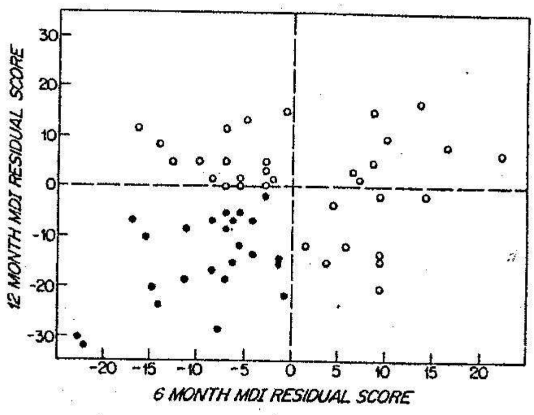

Fig.1. Plot of Mental Development Index (MDI) residual scores at 6 and 12 months for infants with "high" (≥10 μg/dl) umbilical cord blood lead levels. Residuals were calculated by subtracting an infant's expected MDI score from his or her observed score. Predictions of 6 month MDI scores were based on length of gestation and H.O.M.E. total score. Predictions of 12 month MDI scores were based on length of gestation and H.O.M.E. scale 1 score. Filled circles represent infants whose residual scores were negative at both ages. Open circles represent all others.

Sample Attrition

Seventeen children were lost-to-follow-up between the 1 and 6 month visits. Another seven were lost between the 6 and 12 month visits. The distribution of the cord blood lead levels of these 24 children did not differ significantly from the distribution for children who continued to participate. $X^2(2)=$ 1.29, p>0.50. By most indices. the socioeconomic standing of the families lost-to-follow-up was lower. The mothers in this group were more likely than participants to be unmarried. nonwhite, younger. and less well educated. In addition. boys and bottle-fed infants were overrepresented in .the group lost-to-follow-up. However. the two groups tended not to differ in terms of prenatal variables (e.g maternal alcohol. coffee. or drug consumption. pre-eclampsia or hypertension. weight gain, bleeding. length of gestation). labor and delivery events (e.g .presentation. duration of membrane rupture or the three stages of labor. type of delivery. anesthesia). or postnatal status (e.g.. birthweight. maturity. neonatal illness. jaundice. Apgar scores. colic). Despite the differences in sociodemographic characteristics. the groups tended not to differ on measures such as level of family stress. the Home Observation for Measurement of the Environment. and maternal perception of infant behavior and temperament

The Mental Development Index scores achieved at age 6 months by the infants subsequently lost-to-follow-up were higher than the scores of the infants who completed the 12 month appointment (I 12.8±17.6 versus 107.2:±12.7) although, because of the small number of dropouts between these two ages. this difference was not statistically significant.

Statistical Methods

Coding of lead levels. In most of the regression analyses reported, cord blood lead category was treated as an interval scale (I =low. 2=mid. 3=high), This is consistent with our sampling design., It does require the assumption that the differences in performance on the Bayley Scales between the low and mid groups and the mid and high groups are equivalent. For the purposes of comparison. the results obtained using alternative coding strategies are also reported. Because the 6 and 12 month blood lead distributions were positively skewed (i.e. toward large values). the measured values were transformed to (natural) log values.

Statistical modelling. Initially the association between the infants' blood lead levels and their Mental Development Index scores on the Bayley Scales were examined by means of simple bivariate regression analyses without adjustment for confounding. Five bivariate regression analyses are presented of the relationship between MDI score at two ages (6 and 12 months) and lead level at three ages (birth, 6 months, and 12 months) (Table 3). None of the crude associations between development in the first year and the levels of lead exposure experienced by the infants in this sample were statistically significant.

The procedures followed in constructing multivariate models of MDI scores are briefly described below. Because our goal was to achieve maximum precision in estimating the association between lead exposure and infant performance. we considered as potential confounders those variables most strongly related to MDI scores. This enabled us to assess the association between lead and MDI after adjusting for other important predictors of MDI [9]. Additional details about our modeling strategy are presented elsewhere [2.3].

Using Spearman rank-order correlation and analysis of variance, we measure the association between infants'MDI scores at 6 and 12 months and a large array of medical, perinatal, infant, and environmental factors. The rank-order method was used in these screening analyses to reduce the impact of skew in the distributions of some continuous variables. In order to identify the best joint predictors of MDI at each age, we performed separate stepwise (forward selection) regression analyses using the candidate predictors selected on the basis of the screening analyses. To minimize the incidence of Type 1 error, only those variables with parameter estimates significantly different from zero at p <0.0 1 were retained in the regression equations at this stage of the analyses [!O].

The infants' blood lead levels at different ages were then included in these regression equations. To reduce the likelihood of overlooking an important confounder, we examined the correlations between the residuals of the regression equations (both with and without lead measures) and each of the variables that were not included in the development of the equations because they were not significantly associated with MDI scores in the bivariate screening analyses. Our goals in these analyses were (I) to identify variables that contributed to the prediction of MDI scores only when other covariates were partialled out and (2) to assess the likelihood that any lead term that contributed significantly to the prediction was only a proxy for a third variable with which it correlated. Variables that correlated with the residuals of these models (p<0.05) were included in the subsequent regression analyses. The results of including measures of prenatal (umbilical) and postnatal (6 and 12 months) blood lead levels in these regression models are presented separately.

RESULTS

Prenatal Blood Lead Level

Infants' umbilical cord blood lead category was significantly related to MDI scores at both 6 and 12 months of age when adjustments were made for a small set of additional variables. For MDI scores at 6 months, these included length of gestation, total score on the Home Observation for Measurement of the Environment (H.O.M.E.), weight gain during pregnancy, maternal education, and gravidity. For MDI scores at 12 months, these variables included length of gestation, H.O.M.E. scale 1 score ("Emotional and Verbal Responsivity of Mother"), the amount of time an infant spent mouthing a standard set of toys during a 10 minute observation period, and maternal use of nausea medication during the first trimester of pregnancy. We trimmed these models one variable at a time, dropping any whose deletion did not substantially affect the magnitude or the precision (i.e., the standard error) of umbilical cord blood lead category's parameter estimate. Thus, our "final" models contain those variables responsible for the difference between the crude and adjusted estimates. These "final" models of MDI at 6 months (Table 4) and at 12 months (Table 5) are similar, differing only in whether adjustment is made for the total score or scale 1 score of the H.O.M.E. The modest impact of trimming on the estimate of cord blood lead category's association with MDI is evident from a comparison of these models and the full regression models for MDI at the two ages (Appendix: Table B).

Because of the way in which cord blood lead category is coded, the parameter estimate is interpreted as the estimated decrease in mean MDI between the high and mid lead groups, or between the mid and low lead groups. The 95% confidence intervals for the estimated effects at the two age:> are similar, -I..I to -4.7 (6 months) and -1.4 to -5.8 (12 months). The adjusted mean MDI scores of the low and high lead infants differed by 5.8 and 7.3 points at 6 and 12 months, respectively (Table 6).

The MDI provides little information about an infant's strengths and weaknesses. To suggest possible bases for the lower overall scores of the high lead infants, items from the Bayley Scales were grouped together to yield several "sub scale" scores. Using the clustering method of Yarrow *et al.* [23], we found that the. differences between groups at 6 months were greatest on items assessing fine motor function, visually-directed reaching, and social responsiveness [3]. Prior to data collection, we developed our own method for clustering the items typically administered to infants at 12 months of age. Regression analyses using the trimmed equation for MDI at this age indicated that the areas of greatest difference were fine motor function, language. and imitation (Table 7).

Postnatal Blood Lrad Levels

Infants' blood lead levels at 6 months were not significantly related to adjusted MDI scores at either 6 or 12 months, nor was blood lead level at 12 months significantly associated with adjusted MDI scores at 12 months.

To assess the overall association between lead level at 6 months of age and infants' MDI scores in the first year of life, we carried out a multivariate regression analysis. The dependent variables in this analysis were those portions of MDI at 6 and 12 months not "explained" by the covariates in the trimmed regression models. For each child, residual scores were, computed by adjusting MDI at 6 months for length of gestation and H.O.M.E. total score, and by adjusting MDI at 12 months for length of gestation and H.O.M.E. scale I score. Blood lead level at 6 months and cord blood lead category (coded' as a dummy variable) were the. independent variables in this analysis. (Blood lead level' at 12 months was not included because this would have involved predicting MDI scores at 6 months of age from blood lead levels measured 6 months later) This analysis identified no significant overall association between 6 month blood lead level and MDI scores, *F(2.180)=0.66,p=0.52.* However, as expected from the univariate regression analyses in which MDI scores at 6 and 12 months were treated separately, there was a significant overall effect of cord blood lead category, F(4,358)=4.52, p=0.OOI4.

In order to test whether integrating the measures of infants' prenatal and postnatal lead exposure reduced the amount of unexplained' variance in MDI scores, we evaluated the contributions of several interaction terms. In an additional multivariate regression analysis of MDI scores at 6 and 12 months, the interaction term, cord blood lead category (as a dummy variable) x 6 month blood lead level. was not significant, F(4,356)=0.22, *p=O.93.* Multiple regression analyses of 12 month MDI scores alone indicated that neither an interaction term combining all three blood lead measures or just cord blood lead category and 12 month blood lead level produced a significant improvement in the prediction of infants' scores. Thus, there was no evidence that pre- and postnatal lead exposure act synergistically on infant development·

Analyses of Residual Score's

Additional analyses of the joint distribution of the MDI

TABLE 9

PARAMETER ESTIMATES FOR CORD BLOOD LEAD LEVEL OBTAINED BY DIFFERENT ANALYTIC APPROACHES: MDI SCORES AT 6 MONTHS

Analytic Approach		Parameter estimate††	Standard error	p-value	95% (two-sided) confidence interval
I. stepwise/simultaneous regression·*		-2.89	0.92	0.002	-1.09 to -4.69
2. hierarchical regression		-2.83	0.91	0.002	-1.05 to -4.61
3. *a priori* selection of confounders†		-2.52	0.97	0.011	-0.62 to -4.42
4. alternative methods of coding cord blood lead level					
a. dummy variable .				0.007	
	low	5.75	1.84		2.I4.to 9.36
	mid	2.13	1.86		-1.52 to 5.78
	high	0			
b. measured value (natural log)		-3.09	1.02	0.003	-1.09 to -5.09

• Approach used to construct models presented in Table 4.

†Variables included in the regression equation were maternal education, intelligence, and age, race, family social class. sex of infant,. birth order, birth weight, length of gestation, H.O.M.E. total score, number of years of maternal cigarette smoking, and number of alcoholic drinks consumed.

ttFor lines 1-3. the parameter estimate for cord blood lead category represents the estimated difference in mean adjusted MDI scores of adjacent exposure groups (e.g., low and mid or mid and high). The sign indicates whether the score IS higher (+) or lower (-) in the group with greater exposure. The parameter estimate should be multiplied by two to obtain the estimated difference between the scores of the low and high exposure groups. For line 4b. the parameter estimates represent the estimated differences in the mean adjusted scores of the low and mid groups relative to the high lead or "reference" group. For line 4b, the parameter estimate represents the change in adjusted MDI score for each unit change (natural logarithm units) in cord blood lead level

residual scores were carried out to explore whether the association between cord blood lead category and MDI at 6 and 12 months can be attributed to consistently poor performance by a subset of the high lead children or to a reduction in the MDI scores (relative to expectation) of most infants with high prenatal lead exposure. Because the two residual scores are correlated (r=O.25), the 95% confidence region for their distribution is an ellipse. Therefore, a Mahalanobis distance metric, which takes into account the direction as well as the distance of an observation from the center of the distribution was calculated for each infant's pair of residual scores [5]. Using an empirical quantile-quantile plot, we confirmed that the sampling distributions of the 185 Mahalanobis distances were reasonably well approximated by a chi-square distribution with 2 degrees of freedom. Repetitions of the multivariate regression analyses excluding the 9 cases located outside the 95% confidence region produced essentially the same results as those reported above.

Children were classified into four groups based on whether they performed better or worse than expected on the Bayley Scales at the 2 ages (i.e., whether their MDI residual scores were positive or negative): those who achieved higher MDI scores than expected at both 6 and 12 months (+. +), lower scores than expected at both ages (-, -), or higher at one age, but lower at the other (either +.- or -,+). Children's group assignments were cross tabulated, separately, with blood lead category at birth, 6 and 12 months. (The criteria used to identify children with "high" and "low" cord blood lead levels were also used to identify children with "high" and "low" 6 and 12 month lead levels. Six and 12 month blood lead levels between 3 and 10 μg/dl were considered to be "midrange" values.) The distribution of children in the different cord blood lead categories among the four groups was not random, $X^2(6) = 18.79$, p=O.OO4 (Table 8). This was due principally to the higher number of high lead children who achieved lower scores than expected at both 6 and 12 months (-,-), and the lower number of high lead children than expected who achieved higher scores (+, +). The scores of the children with low cord blood lead levels followed the opposite pattern. Children's distribution among the groups was not related to 6 month blood lead category, $X^2(6)=8.44$, p=O.2I, or to 12 month blood lead category, $X^2(6)=2.04$, p=O.92.

If the overall association between cord blood lead category and MDI scores at6 and 12 months was due to the poor performance of only a subset of children who are particularly vulnerable to lead toxicity. then the high lead infants in the group that performed worse than expected at both ages (-, -) could be sorted into two discrete groups, one clustering near the origin and the other far away. Instead, these infants tend to be scattered throughout this quadrant (Fig. 1). Thus, the lower mean scores of these infants at 6 and 12 months reflect performance deficits of varying magnitude for most infants in this group and not just a subset.

Additional Analyses

The results of multiple regression analysis may vary with slight modifications in procedure. To explore the stability of cord blood lead's parameter estimate under different analytic conditions, we conducted a series of additional analyses of infants' MDIl scores at 6 months (Table 9) and 12 months (Table 10). These analyses involved three types of modifications.

(I) Hierarchical rather than stepwise or simultaneous regression. MDI scores were adjusted for length of gestation and H.O.M.E. score (total for MI;>I at 6 months, scale I

TABLE 10

PARAMETER ESTIMATES FOR CORD BLOOD LEAD LEVEL OBTAINED BY DIFFERENT ANALYTIC APPROACHES: MDI SCORES AT 12 MONTHS

Analytic Approach		Parameter estimate††	Standard error	p-value	95% (two-sided) confidence interval
I. stepwise/simultaneous regression·		-3.63	1.12	0.002	-1.43 to -5.83
2. hierarchical regression		-3.58	1.11	0.002	-1040 to -5.76
3. *a priori* selection of confounderst		-3.42	1.20	0.005	-1.07 to -5.77
4. alternative methods of coding cord blood lead level					
a. dummy variable				0.002	
	low	7.38	2.24	0.001	2.99 to II. 77
	mid	6.77	2.30	0.004	2.26 to 11.28
	high	0			
b. measured value (natural log)		-3.38	1.25	0.008	-0.93 to -5.83

• Approach used to construct models presented in Table 5.

tVariables included in the regression equation were maternal education, intelligence, and age, race, family social class, sex of infant, birth order, birthweight, length of gestation, H.O.M.E. total score, number of years of maternal cigarette smoking, and number of alcoholic drinks consumed per week in the third trimester of pregnancy.

ttFor lines 1-3, the parameter estimate for cord blood lead category represents the estimated difference in mean adjusted MOl scores of adjacent exposure groups (e.g., low and mid or mid and high). The sign indicates whether the score is higher (+) or lower (-) in the group with greater exposure. The parameter estimate should be multiplied by two to obtain the estimated difference between the scores of the low and high exposure groups. For line 4a. the parameter estimates represent the estimated differences in the mean adjusted scores of the low and mid groups relative to the high lead or "reference" group. For line 4b, the parameter estimate represents the change in adjusted MOl score for each unit change (natural logarithm units) in cord blood lead level.

score for MDI at 12 months) and the residuals regressed on cord blood lead category. Thus, the influence of both covariates on MDI scores was removed prior to assessing the influence of cord blood lead category. Using this more conservative adjustment strategy had little impact on cord blood lead category's estimate at either age.

(2) A priori rather than empirical selection of variables for which to adjust MDI scores. Twelve variables usually associated with infant development and thus potential confounders of an association between lead exposure and development were included in the regression equation whether or not they were significantly related to MDI in our sample. These included maternal age, education, and IQ. race, family social class, H.O.M.E. total score, infant sex, birthorder, birthweight, length of gestation, number of years of maternal cigarette smoking, and alcohol consumption in the third trimester. At both ages, the parameter estimate for cord blood lead category decreased by less than 15% when MDI scores were adjusted for this more extensive set of variables. Apart from length of gestation and H.O.M.E. score, the association between cord blood lead category and MDI appears to be relatively unaffected by these other factors.

(3) Alternative methods of expressing cord blood lead level.

(a) To avoid the assumptions required in treating cord blood lead level as an interval scale, we created two dummy variables, one coding membership in the low lead group. the second coding membership in the mid lead group. In contrast to the analysis in which lead level was treated as an interval scale, the performance of the infants in each group was compared individually to the performance of the high lead infants (the "reference" group). Thus, this strategy permitted the detection of any non-linear aspects of the relationship between cord MDI. At both ages, the greatest differences were between the adjusted scores of the infants in the low and high lead groups. However, the blood lead category and relative performance of the infants in the mid lead group differed at the two ages. At 6 months. their mean adjusted MDI score was approxil1J.ately midway between those of the other two groups. suggesting a slight effect of prenatal lead exposure on their performance. At 12 months, their mean adjusted score was indistinguishable from that of the low lead infants. indicating that only umbilical cord blood lead levels greater than 10 μg/dl are associated with relative performance deficit at this age.

(b) Despite the fact that the distribution of infants' cord blood lead levels deviated markedly from normal. these values (transformed to their natural logarithms) were included in the trimmed regression equations in place of the interval scale variable. Although the units of the parameter estimate yielded by the different coding strategies are not comparable. at both 6 and 12 months the p-values associated with the estimates are very similar to those associated with the estimates for the dummy variables and the interval scale.

To investigate the possibility that inter-examiner differences may have biased our estimate of the association between cord blood lead category and MDI scores. we created a set of dummy variables representing each of the:; Bayley Scales examiners and included them in the trimmed regression equation. The parameter estimate for cord blood lead category was -2.55 (standard error=0.91,p=0.006) for MDI ·scores at 6 months and - 3.18 (standard error= 1.08, p=O.OO4) for scores at 12 months. Thus, at neither age did examiner differences appear to account for the association.

DISCUSSION

Follow-up assessments at age 12 months indicate that the relative deficit we observed at age 6 months in the performance of infants with "high" prenatal lead exposure (umbilical cord blood lead concentrations ≥10 μg/dl) persists through the end of the first year of life. The differences between the mean adjusted Mental Development Index scores of these infants and those with "low" prenatal lead exposure (cord blood lead levels <3 μg/dl) were approximately equal at the two ages (5.8 and 7.3 points at 6 and 12 months, respectively). This was in spite of the fact that the 6 and 12 month blood lead levels of the infants with "high" prenatal exposure did not differ significantly from those of the infants in the other prenatal exposure groups (15]. Experimental studies with primates indicate that early lead-induced deficits may persist well after blood lead concentrations return to the normal range (4, II, 13, I8, 19).

Some aspects of the dose-response relationship between lead exposure and development are similar at 6 and 12 months while others differ,

Age related changes in vulnerability. At both ages, MDI scores were more strongly associated with umbilical cord blood lead levels than with the two measures of postnatal lead exposure (i.e., blood lead levels at 6 and 12 months). Furthermore, there was no evidence of synergy in the association between infants' MDI scores and their lead levels at the three ages,

Shape of the relationship. At 6 months, the mean adjusted MDI score of the infants with midrange cord blood lead con· centrations was intermediate to the scores of infants with low and high levels. At age 12 months, their mean adjusted score was almost identical to that of the low lead infants. For this group, either the lead-related developmental effects observed at 6 months diminished over the following 6 months, or the behaviors assessed by the Bayley Scales at 12 months of age are less sensitive to prenatal lead exposure than the behaviors assessed by the Scales at 6 months.

Pervasiveness of the relationship. The overall association between prenatal lead exposure and MDI scores at the two ages appeared to be due to a small but consistent deficit in the scores of infants in the high lead group. The distribution of the number of points by which the MDI scores of the high lead infants deviated from expectation was not markedly skewed or bi-modal, which would have suggested that the effect was limited to only a small group of children. Although the performance of these infants varied considerably, the percentage who achieved lower scores than expected at both 6 and 12 months was 2 to 4 times greater than it was among infants with low or midrange lead levels.

Functional target(s) of lead. At both 6 and 12 months, fine motor and interactional/linguistic skills were the aspects of infant behavior most strongly related to prenatal lead exposure. However, the number of items contributing to the different Bayley item clusters ranged from 2 to 17 at 6 months and 3 to 10 at 12 months, producing large discrepancies in the power of the group comparisons for the different areas of function. Therefore, these analyses should be considered exploratory.

The performance deficit of the infants with high prenatal exposure is modest by clinical standards. Moreover, at both 6 and 12 months, the scores of these infants were well above the mean of the infants in Bayley's standardization sample. On the other hand, the infants' blood lead levels spanned only 25 μg/dl. All children had a cord blood lead level less than 25 μg/dl, the current definition of an "elevated" level (14]. Under these circumstances, a mean difference in MDI scores of 0.4 to 0.5 standard deviations is surprisingly large.

The predictive validity of the Bayley Scales is limited (8). However, from a transactional perspective, these cognitive differences, or the differences in behavioral style, attention, or motivation which underlie them, may influence how a child reacts to his or her social and physical environment. These, rather than the slight deficits in MDI scores, may be the most important long-range effects of low-level lead exposure. Indeed, at both 6 and 12 months, the differences among the exposure groups on Bayley Item clusters suggested that the infants with high cord blood lead levels are less capable partners in their early social transactions. At 6 months, they scored lower in terms of social responsiveness. The items that contribute to the cluster include "likes frolic play" with the examiner, "smiles at own mirror. image," and makes a "playful response to mirror image." At 12 months, they scored lower on language skills ("jabbers expressively," "says 2 words," "uses gestures to make wants known") and imitation of the examiner's acts ("attempts to imitate scribble," "pushes car along," "dangles ring by string"). However, maternal ratings of infant temperament at 6 months of age (activity, rhythmicity, approachability, adaptability, intensity, mood, persistence, distractibility, threshold) did not differ across the three cord blood lead groups.

Typically, adjustment of outcome scores for variables known to influence development reduces the estimate of lead's association with the outcome [6, 7, 20, 22]. This was not the case in our analyses. The sociodemographic characteristics of our sample contrast with those of the samples usually selected to participate in lead research. As we discuss in detail elsewhere (2,3], the infants in the high lead group tended to have more optimal H.O.M.E. scores and longer gestations than did the infants in the other groups. We reduced the difficulty of distinguishing the adverse impact of lead from the adverse impact of correlated risk factors by selecting infants at low risk for developmental handicap. The impact of lead, however, may be most prominent among children whose developmental prospects are compromised by additional adversities (21]. The extent to which our findings can be generalized to infants less socioeconomically advantaged will be clarified by the results of several other longitudinal studies currently being conducted on samples of infants that differ widely from one another.

In summary, infants experiencing prenatal lead exposure sufficient to produce umbilical cord blood concentrations greater than 10 μg/dl achieved Mental Development Index scores that, at both 6 and 12 months, were significantly lower than those achieved by infants experiencing lower levels of prenatal exposure. This relative performance deficit persisted despite the fact that on the two occasions at which development was assessed, the mean blood lead levels of the infants experiencing a "high" level of prenatal exposure were below 10 μg/dl.

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APPENDIX TABLE A

DATA COLLECTED AT THE 1,6, AND 12 MONTH APPOINTMENTS

Type of Information		Instrument(s) or Method	Child Age (months)[a] 1	6	12
I.	pre- and perinatal history	maternal interview[b] and Hospital record review	X		
II.	postnatal history	maternal interview	X	X	X
III.	demographic characteristics				
	socio-economic status	Hollingshead's Four-Factor Index	X	X	X
	family structure	questionnaire	X	X	X
	day care arrangements	questionnaire	X	X	X
IV.	environmental process	Home Observation for Measurement of the Environment (H.O.M.E.)[c]		X	
V.	maternal characteristics				
	perception :of the child	Neonatal Perception Inventory[d]	X	X	
	life events/stress	Social Readjustment Rating Scale[e]	X	X	X
VI.	child characteristics				
	temperament	Infant Temperament Questionnaire[f]		X	
	pica (mouthing)	Infant Behavior Record[g]		X	X
		maternal judgment			X
		playroom observation[h]			X
	developmental status	Bayley Scales of Infant Development[g]		X	X
		Ordinal Scales of Psychological Development[i]			X

[a]"X" indicates that information in category collected at that age.
[b]Linn, S., S. Schoenbaum, R. Monson *et al. N Engl* J *Med* 306: 141-145, 1982.
[c]Caldwell, unpublished manual.
[d]Broussard. E. and M. Hanner. In: *Exceptiona Infant. vol2.* edited by 1. Hellmuth. New York: Brunner/ Mazel. 1971.
[e]Holmes, T. and R. Rahe. J *Psychosom Res* 11: 2!3-218, 1967.
[f]Carey, W. and S. McDevitt. *Pediatrics* 60: 621-624, 1977.
[g]Bayley, N. *The Bayley Scales of Infant Development.* New York: Psychological Corporation, 1969.
[h]A 10 minute observation session while infant played with a standard set of toys.
[i]Uzgiris, I. and J. Hunt. *Assessment in infancy: Ordinal Scales of Psychological Development.* Urbana: University of Illinois Press. 1975. Scales I and II only.

TABLE B

UNTRIMMED REGRESSION MODELS OF MDI SCORES AT 6 AND 12 MONTHS WITH AND WITHOUT CORD BLOOD LEAD CATEGORY AS A PREDICTOR

Predictor Variables	Without Cord Blood Lead Category Parameter' estimate	Standard error	*p*-value	With Cord Blood Lead Category Parameter 'estimate	Standard error	*p*-value
6 Months (N=191)						
H.O.M.E. total score	1.02	0.24	0.0001	1.06	0.23	0.0001
length of gestation	2.61	0.44	0.0001	2.74	0.43	0.0001
weight gain during pregnancy	0.20	0.07	0.0086	0.16	0.07	0.039
maternal education	-0.49	0.22	0.027	-0.51	0.21	0.019
gravidity	1.38	0.57	0.016	1.29	0.56	0.021
cord blood lead category				-2.52	0.92	0.006
12 Months (N=181)						
H.O.M.E. scale I score	2.06	0.80	0.0111	2.09	0.78	0.008
length of gestation	1.13	0.49	0.023	1.28	0.48	0.009
time spent mouthing toys	-0.16	0.03	0.0001	-0.15	0.03	0.0001
nausea medication: 1st trimester	-4.32	2.13	0.044	-4.81	2.08	0.022
cord blood lead category				-3.46	1.04	0.00 II

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