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Antecedents and Correlates of Improved Cognitive Performance in Children Exposed *in Utero* to Low Levels of Lead

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Up to 2 years of age, children with umbilical cord blood lead levels of 10 to 25 μg/dL achieve significantly lower scores on tests of cognitive development than do children with lower prenatal exposures. By age 5 years, however, they appear to have recovered from, or at least compensated for, this early insult. Change in performance between 24 and 57 months of age was examined in relation to level of postnatal lead exposure and various sociodemographic factors. Among children with high prenatal lead exposure, greater recovery of function was associated with lower blood level at 57 months, higher socioeconomic status, higher Home Observation for Measurement of the Environment scores, higher maternal IQ, and female gender. The difference between the scores at 57 months of children with optimal and less optimal values on these variables generally exceed ½ standard deviation. Higher prenatal lead exposure is associated with an increased risk of early cognitive deficit. Furthermore, the risk that a deficit will persist through the preschool years is increased among children with high prenatal exposure and either high postnatal exposure or less optimal sociodemographic characteristics.

Introduction

In our prospective study of lead and cognitive development, children with high umbilical cord blood lead levels (10–25 μg/dL) achieved significantly lower Mental Development Index scores through 2 years of age than did infants whose cord blood lead levels were low (<3 μg/dL) or medium (6–7 μg/dL) (*1*). In contrast to the results of the infant assessments, cord blood lead level was not significantly related to children's performance on the McCarthy Scales of Children's Abilities at age 57 months (*2*).

These data may be explained in several ways. First, between 24 and 57 months of age, children recover from, or at least compensate for, the insult represented by high prenatal lead exposure. A variant of this is that the extent of recovery or compensation varies among children. Such a contingency might be difficult to appreciate using analytical approaches that focus only on differences in the mean recovery of groups defined by prenatal exposure level.

Finding that the likelihood of recovery is systematically related to some characteristic or event would be particularly important from the standpoint of intervention.

Alternatively, persisting impact of prenatal exposure is obscured by variations among children in postnatal lead exposure. Finally, the apparent attenuation of the association between prenatal lead exposure and development is a measurement artifact attributable to differences in the mix of cognitive skills that contribute to a child's scores on the Bayley Scales and the McCarthy Scales. For instance, prenatal exposure may be associated with the skills assessed by the Bayley Scales but not with skills assessed by the McCarthy Scales.

To distinguish among these alternatives, experiences and characteristics that correlate with change in performance (both improvement and deterioration) need to be identified. In this report, we describe our search for these covariates.

Methods

Sample and Data Collected

Of the original cohort of 249 children (*3*), 204 completed the 24-month evaluation. No effort was made to assess at 57 months three children with serious medical problems identified in the earlier phase of the study, and five sets of twins. Of the 191 eligible children, we evaluated 170 (89.0%). The median age at assessment was 57.8 months.

Information on a range of potential covariates of lead exposure and cognitive function were obtained (*3*). These included demographics, reproductive history, exposures during and characteristics of the index pregnancy, labor and delivery, neonatal characteristics, and measures of child rearing environment and practices. The outcomes considered here are a child's Mental Development Index (MDI) score from the Bayley Scales of Infant Development (*4*) at 24 months and General Cognitive Index (GCI) score from the McCarthy Scales of Children's Abilities (*5*) at 57 months.

Capillary blood samples were collected when the children were 6, 12, 18, and 24 months old and venous samples when they were 57 months old. Analytical methods used

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to measure blood lead levels are described elsewhere (*6,7*). In statistical analyses, postnatal blood lead levels were treated as both continuously distributed and as categorical variables. The same cutoff values used to classify cord blood lead levels as low (<3 μg/dL) and high (≥10 μg/dL) were used to classify postnatal levels. Levels between 3 and 10 μg/dL were classified as medium.

Data Analysis

The null hypothesis is that changes in children's performance between 24 and 57 months on global tests of cognitive development are not related to prenatal lead exposure (cord blood lead level); postnatal lead exposures; or sociodemographic characteristics (family social class, Home Observation for Measurement of the Environment [HOME] score at 57 months, maternal IQ, gender, ethnicity, maternal age).

Using population estimates for the mean and standard deviation of MDI and GCI scores (100 and 16, respectively), we computed children's z scores for both indices. Additional analyses using sample-based estimates of mean and standard deviation (115.6 and 16.4 for MDI; 115.5 and 14.5 for GCI) produced nearly identical results. As an index of a child's developmental trajectory between 24 and 57 months, change in z score (Δz) was calculated as follows:

$$\Delta = z_{\text{GCI-57}} - z_{\text{MDI-24}}$$

Thus, a child with a positive Δz improved in performance between 24 and 57 months of age.

Z transformations are necessary in order to compare scores expressed on different scales. Because MDI and GCI have the same expected mean and standard deviation, the analyses reported could have been conducted on Δ scores derived by computing the difference between a child's MDI and GCI scores. The more general method is used to illustrate its usefulness in identifying correlates of performance change and because some additional analyses reported involve scores measured on different scales.

The correlation between Δz and MDI scores at 24 months was large and negative in the full sample (−0.55) and within each strata of cord blood lead (−0.62, −0.42, and −0.58 in the low, medium, and high groups, respectively). This association, due at least in part to regression to the mean, was not attributable to the disproportionate influence of outlying observations. The relationship between Δz and MDI at 24 months is linear with approximately equal Δz variance for different values of MDI. A linear relationship also held within each of the cord blood lead strata. Therefore, in regression analyses of Δz, MDI at 24 months, a measure of initial value, was included as a predictor. To assess the impact of adjusting Δz for MDI, we compared the coefficients assigned to variables in models without MDI to coefficients assigned in models that included the MDI term.

Because of potential problems due to multicollinearity, the association between Δz and each variable was adjusted for MDI using both a one-stage and a two-stage procedure. In the two-stage approach, Δz was regressed on MDI alone and the residuals regressed on the variable of interest. In the one-stage approach, Δz was regressed on both MDI and the variable. The two approaches yielded virtually identical results. (Tables are available from the authors.)

Analysis proceeded in two phases: *a*) The association between Δz and each variable was examined by multiple regression analysis in the complete sample. *b*) The extent to which the association between Δz and a variable differed according to cord blood lead stratum was examined by means of stratified analyses and by fitting regression models that included the appropriate interaction term to the data for the whole sample.

Table 1. Regression coefficients, standard errors (SE), and probability values for predictors of Δz in models with and without a term for MDI at 24 months.

	Unadjusted for MDI			Simultaneous adjustment for MDI		
Predictor	Coefficient	SE	*p*	Coefficient	SE	*p*
Blood lead						
Cord[a]	0.04	0.01	0.003	0.03	0.01	0.016
6 Months[b]	−0.02	0.08	0.81	0.00	0.07	0.96
12 Months	−0.03	0.08	0.75	−0.08	0.07	0.23
18 Months	−0.22	0.09	0.018	−0.21	0.08	0.007
24 Months	−0.23	0.09	0.012	−0.22	0.08	0.005
57 Months	−0.17	0.12	0.16	−0.23	0.10	0.028
Covariates						
HOME score	0.02	0.02	0.30	0.07	0.01	0.0001
Social class[c]	−0.05	0.07	0.50	−0.22	0.06	0.0002
Maternal IQ	0.00	0.00	0.72	0.01	0.00	0.003
Maternal age	0.03	0.02	0.045	0.04	0.01	0.003
Gender[d]	0.05	0.14	0.72	0.18	0.12	0.13
Ethnicity[e]	−0.41	0.31	0.18	0.15	0.27	0.57

[a]Measured cord blood lead level, not category.
[b]Natural log of measured postnatal blood lead levels.
[c]Hollingshead Two-Factor Index (lower scores represent higher social class).
[d]Male coded 0; female coded 1.
[e]Nonwhite coded 0; white coded 1.

Results

Complete Sample

Both intrauterine and recent postnatal lead exposures are associated with the amount and direction of change in children's cognitive performance between ages 24 and 57 months (Table 1). The sign of the regression coefficient for cord blood lead level (expressed as a continuous variable) is positive, meaning that children with higher prenatal exposures tended to have higher Δz scores (reflecting greater relative improvement). This is consistent with our previous finding of attenuation by 57 months of the association between prenatal exposure and cognitive development.

Using the regression coefficient of 0.03 assigned to cord blood lead level (i.e., the slope of the regression of Δz against cord blood lead level) and the mean cord blood lead levels of children in the low and high prenatal exposure groups (1.8 and 14.6 μg/dL, respectively), the mean changes in performance of children in these two groups can be estimated. Among low lead children, the mean change was $+0.05$ standard normal deviate units (0.03×1.8). On an index with a standard deviation of 16, this corresponds to $+0.9$ points (16×0.05). Among high lead children, the mean change was $+0.44$ standard normal deviate units (0.03×14.6) or $+7.0$ points. Thus, the net gain of the high lead children between 24 and 57 months was 6.1 points ($7.0 - 0.9$), a substantial percentage of their relative deficit (7.8 points) at age 24 months (*1*).

The negative signs of the coefficients for blood lead level at 18, 24, and 57 months indicate an inverse relationship between Δz scores and the children's lead levels at these ages.

Δz scores were also significantly related to various indicators of sociodemographic status. Children with higher HOME scores, higher social class, and more intelligent, older mothers tended to have higher Δz scores. Δz was not significantly associated with gender or ethnicity.

The impact of adjusting Δz for MDI score at 24 months is evident by comparing the coefficients in Table 1. Those variables significantly associated with Δz before adjustment for MDI remained so when MDI was included in the model (cord blood lead level, blood lead level at 18 and 24 months, maternal age). Although adjustment had relatively little impact on the magnitude of the coefficients, the standard errors were reduced. For several other variables (blood lead at 57 months, HOME score, social class, maternal IQ, and gender), adjustment for MDI produced substantial changes in the coefficient. Indeed, for all but gender, the coefficient became statistically significant. The variable ethnicity, expressed as a dichotomy (white/nonwhite), not only had the largest change in its coefficient, but the sign for whites changed from negative to positive.

Thus, these analyses confirm our previous finding that children with high cord blood levels showed substantial improvement in performance between 24 and 57 months and that development in this period was inversely related to postnatal lead exposure. In addition, performance change between 24 and 57 months bore the expected relationships with sociodemographic factors, with more optimal values associated with more positive change.

Stratification by Cord Blood Lead Group

For several variables (blood lead level at 57 months, social class, maternal IQ, gender), the coefficient was considerably larger among children with high cord blood lead level than among children in the other prenatal exposure groups (Table 2). The *p*-value for cord blood lead level was considerably more extreme among these children than among those in the other groups, but this appears to be due mostly to differences in the standard errors of the coefficients. The restricted range of prenatal exposures among children in

Table 2. Regression coefficients, standard errors (SE), and probability values for predictors of Δz in each cord blood lead stratum.

	Cord blood lead category								
	Low			Medium			High		
Predictor	Coefficient	SE	*p*	Coefficient	SE	*p*	Coefficient	SE	*p*
Blood lead									
Cord[a]	0.04	0.11	0.72	0.10	0.29	0.74	0.07	0.04	0.07
6 Months[b]	−0.01	0.10	0.94	0.02	0.12	0.88	0.01	0.13	0.95
12 Months	−0.18	0.09	0.063	0.03	0.13	0.84	−0.18	0.14	0.20
18 Months	−0.13	0.09	0.16	−0.34	0.15	0.028	−0.16	0.16	0.33
24 Months	−0.16	0.08	0.057	−0.31	0.16	0.065	−0.28	0.16	0.079
57 Months	−0.16	0.14	0.26	−0.14	0.22	0.52	−0.46	0.18	0.013
Covariates									
HOME score	0.03	0.02	0.26	0.13	0.04	0.001	0.07	0.02	0.002
Social class[c]	−0.16	0.08	0.039	−0.12	0.12	0.29	−0.30	0.10	0.004
Maternal IQ	0.00	0.00	0.42	0.01	0.01	0.17	0.02	0.01	0.011
Maternal age	0.04	0.02	0.058	0.03	0.02	0.24	0.05	0.03	0.061
Gender[d]	−0.04	0.16	0.81	0.02	0.23	0.94	0.55	0.22	0.017
Ethnicity[e]	0.04	0.27	0.88	0.37	0.60	0.54	−0.08	0.63	0.90

[a]Measured cord blood lead level, not category.
[b]Natural log of measured postnatal blood lead levels.
[c]Hollingshead Two-Factor Index (lower scores represent higher social class).
[d]Male coded 0; female coded 1.
[e]Nonwhite coded 0; white coded 1.

the low and medium cord blood lead groups may have contributed to differences across strata in the strength of the association between cord blood lead level and Δz.

The association between Δz and blood lead level at 24 months was comparable in the three cord blood lead groups. This reflects in part the fact that in the complete sample, 24-month blood lead level was more strongly associated with GCI than was any other lead term. In this cohort, performance at 57 months was related to level of lead exposure at 24 months, regardless of a child's level of prenatal exposure.

Gender is a particularly striking example of the dependence of Δz scores on level of prenatal exposure. The scores of girls and boys were almost identical among children with either low or medium exposures. Among children with high prenatal exposures, however, girls had appreciably higher Δz scores (Fig. 1).

Although the associations between Δz and other variables appear to depend on initial exposure status (i.e., cord blood lead level), interaction terms constructed to assess the differences were not statistically significant. The regression coefficients for many of the variables differed significantly from zero only within the high cord blood lead group, but these did not necessarily differ significantly from the corresponding coefficients in the other two cord blood lead strata. For instance, in each stratum, children above the median social class tended to have Δz scores higher than those of their peers below the median (Fig. 2). This social class advantage was greatest, however, among children who had high cord blood lead.

To understand in greater detail the correlates of performance change among children with high cord blood lead levels, we examined the least-squares mean Δz scores in different postnatal lead exposure and sociodemographic strata (Table 3). For lead levels at 24 and 57 months and all sociodemographic variables, children with more optimal values had more positive Δz scores than did children with less optimal values. The differences in GCI scores for children in different strata can be estimated using the tabled values of Δz. For instance, among children who had high cord blood lead but low blood lead at 57 months, the mean difference between GCI and MDI z scores was +0.42. Among children with high blood lead levels on both occasions, the mean difference was −0.15. Therefore, if two children with high cord blood lead achieved the same MDI score at 24 months, but one had a low blood lead level at 57 months while the other had a high level, the child with lower exposure would be expected to have a GCI score that is 0.57 standard normal deviate units higher (0.42 minus −0.15). Viewed in terms of a standard deviation of 16, this corresponds to a difference of 9.1 points.

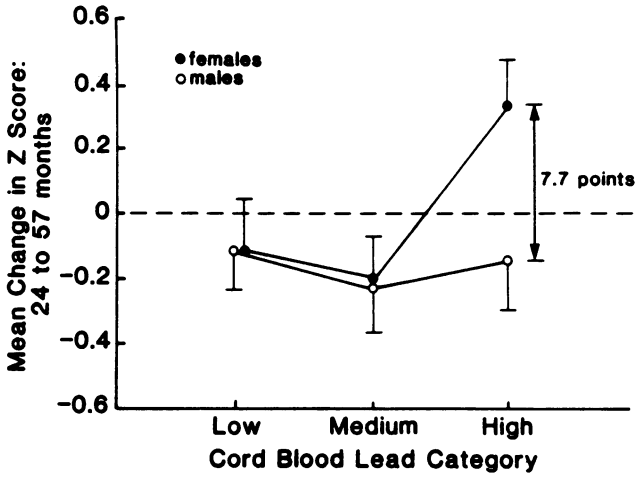

FIGURE 1. Least squares mean Δz scores for children stratified by cord blood lead category and gender. Error bars represent one SE (and for clarity are shown extending in one direction only). Means were obtained by modeling Δz score as a function of Mental Development Index score at 24 months of age, cord blood lead category (low, medium, high), child gender, and the interaction between cord blood lead category and child gender. The difference of 7.7 points between the scores of boys and girls with high cord blood lead levels was obtained by calculating the difference between the mean Δz scores of children in the two groups (0.48 standard normal deviate units) and expressing it in terms of performance on a test with an SD of 16.

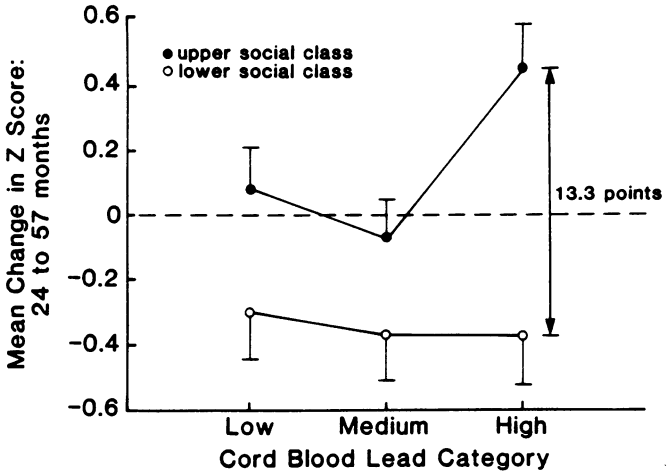

FIGURE 2. Least squares mean Δz scores for children stratified by cord blood lead category and family social class. Error bars represent one SE (and for clarity are shown extending in one direction only). Means were obtained by modeling Δz score as a function of Mental Development Index score at 24 months of age, cord blood lead category (low, medium, high), family social class (above/below median), and the interaction between cord blood lead category and social class. The difference of 13.3 points between the scores of lower class and upper class children with high cord blood lead levels was obtained by calculating the difference between the mean Δz scores of children in the two groups (0.83 standard normal deviate units) and expressing it in terms of performance on a test with a SD of 16.

Additional Analyses

We attempted to assess the extent to which the associations between Δz scores and blood lead and sociodemographic characteristics reflect differences in the skills measured by MDI and GCI scores rather than contingencies that govern the persistence and recovery of early lead-associated deficit. To make scores at 24 and 57 months more closely resemble repeated measurements, each child was assigned a nonverbal score based on his or her performance on a set of 22 items typically administered as part

Table 3. Means and standard errors (SE) of Δz scores of children with high cord blood lead: stratified by postnatal lead levels and sociodemographic variables.

Predictor		Postnatal exposure group: Low	Medium	High	Difference in GCI scores of low/high or optimal/less optimal groups
Blood lead					
57 Months[a]	Mean	0.42	0.15	−0.15	9.1
	SE	0.29	0.15	0.21	
24 Months	Mean	0.55	0.06	−0.08	10.0
	SE	0.22	0.13	0.23	
Covariates[b]		More optimal		Less optimal	
HOME score	Mean	0.49		−0.19	10.9
	SE	0.14		0.12	
Social class	Mean	0.46		−0.37	13.2
	SE	0.12		0.15	
Maternal IQ	Mean	0.39		−0.16	8.8
	SE	0.13		0.14	
Maternal age	Mean	0.25		0.01	4.2
	SE	0.14		0.15	
Gender	Mean	0.34		−0.14	7.7
	SE	0.14		0.15	

[a]Natural log of measured postnatal blood lead levels.
[b]"More optimal" defined as values above the median, as follows: HOME >52; social class, class 1 in the Hollingshead Two-Factor Index; maternal IQ >129; maternal age >30; gender, female is the optimal value.

of the Bayley Scales at age 24 months (#122–3, 125, 129, 131, 133–5, 137, 140, 142–3, 147, 151, 153–7, 159–61). Most of these assess a child's visual-motor coordination and integration skills (e.g., ability to copy block structures, speed and accuracy in completing formboards, perception of part-whole relationships). Sample-based estimates of mean and standard deviation were used to transform the total number of items passed to a z score. A Δz score was computed by subtracting this score from a sample-based z score transformation of a child's score on the perceptual-performance subscale of the McCarthy Scales. The set of analyses described above were applied to these Δz nonverbal scores.

Among children with high cord blood lead levels, optimal postnatal lead exposure and sociodemographic status were associated with higher Δz nonverbal scores (Table 4). In general, the antecedents and correlates of Δz nonverbal scores are very similar to those noted for Δz scores based on MDI and GCI (Table 3). Additional tables (analogous to Tables 1 and 2) are available from the authors.

These results with Δz nonverbal scores should not be viewed as a definitive test of the hypothesis that the pattern of results observed in the main body of analyses is due to differences in the mix of skills measured by the Bayley Scales and McCarthy Scales. To the extent that we can evaluate this hypothesis, however, the evidence suggests that the improvement with time is not an artifact of differences in testing instruments.

Discussion

An association between optimal sociodemographic characteristics and reduced likelihood of poor outcome has been demonstrated for many early nervous system insults, including low birthweight (*8,9*), prenatal infection (*10*), failure to thrive (*11*), and Down's Syndrome (*12*). A similar phenomenon has been observed with respect to lead exposure (*13–15*). In previous analyses of our cohort, we reported that in the second year of life, children from lower social classes expressed deficit at lower levels of prenatal lead exposure than did children from the highest social class (*16*).

These observations raise the question of whether children's sociodemographic characteristics are also related to the likelihood of recovery from a deficit already expressed. The data pertaining to this issue are limited to studies showing that at-risk infants who receive additional cognitive and/or psychosocial stimulation fare better developmentally than do children receiving only standard medical care (*17–19*).

Through the first 2 years of life, the children in our sample with high cord blood lead levels achieved significantly lower MDI scores than did children with lower prenatal exposures. The association between high prenatal exposure and lower performance persisted beyond age 2, although not as a main effect. Rather, the degree to which deficit persisted varies among subgroups of children with different sociodemographic characteristics and postnatal lead exposure profiles. The associations between performance trajectory between ages 24 and 57 months and several of these characteristics, including high social class, high HOME score, and high maternal IQ, are consistent with the hypothesis that environmental enrichment facilitates the rate and extent of recovery or compensation. The more positive developmental trajectories displayed by girls is consistent with previous suggestions that boys are at greater risk for many neuropsychiatric adversities (*20*). Differences between children with optimal and suboptimal covariate values tended to be greater among children with high prenatal exposure than among children with low or medium prenatal exposure. Children already stressed by sociodemographic disadvantages may be less able to weather the additional stress of high prenatal lead exposure.

Table 4. Means and standard errors (SE) of Δz nonverbal scores of children with high cord blood lead: stratified by postnatal lead levels and sociodemographic variables.

Predictor		Postnatal exposure group: Low	Medium	High	Difference in scores of low/high or optimal/less optimal groups[a]
Blood lead					
57 Months[b]	Mean	0.61	0.19	−0.37	8.5
	SE	0.33	0.17	0.25	
24 Months	Mean	0.93	−0.03	−0.20	9.8
	SE	0.26	0.15	0.28	
Sociodemographics[c]		More optimal		Less optimal	
HOME score	Mean	0.52		−0.28	7.0
	SE	0.16		0.15	
Social class	Mean	0.43		−0.40	7.2
	SE	0.15		0.19	
Maternal IQ	Mean	0.32		−0.14	4.0
	SE	0.16		0.18	
Maternal age	Mean	0.25		−0.06	2.7
	SE	0.17		0.19	
Gender	Mean	0.31		−0.17	4.2
	SE	0.17		0.18	

[a] Differences in scores on the perceptual-performance subscale of the McCarthy Scales of Children's Abilities at age 57 months, computed using sample-based estimate of 8.7 as the standard deviation.
[b] Natural log of measured postnatal blood levels.
[c] "More optimal" defined as values above the median, as follows: HOME >52; social class, class 1 in the Hollingshead Two-Factor Index; maternal IQ >129; maternal age >30; gender, female is the optimal value.

"Less optimal" is somewhat of a misnomer in our relatively advantaged cohort, referring only to values below the median (see footnotes of Table 3 for criteria). Most families classified as less optimal would probably be among the most advantaged families in other lead study cohorts (*15,21*). Our finding that children from families with the most optimal sociodemographic characteristics recover from the insult of high prenatal lead exposure may be less relevant to these other cohorts than is our finding that children with less optimal values may continue to express some degree of developmental deficit.

The rate of recovery may not be the same in different cognitive domains. For instance, following nutritional rehabilitation, severely malnourished children show slower gains in language than in visual-spatial skills (*17*). The association between family characteristics and a child's response to stress is not the same for all outcomes (*22*). We cannot determine from our observations how rate of recovery from early lead exposure may differ among cognitive and perceptual functions.

Summary

To date, we have observed the following associations between lead exposure and development in our cohort: High levels of prenatal lead exposure (>10 μg/dL in cord blood) are associated with less rapid cognitive development, at least through 24 months of age (*1*). A substantial percentage of children with high prenatal exposure contribute to this association (*23*). Children below the median in social class express deficit at lower levels of prenatal exposure than do children from more socioeconomically advantaged families (*16*).

At 57 months of age, the mean performance of children with high prenatal exposure is indistinguishable from the mean performance of children with lower prenatal exposure. Performance at this age is, however, inversely related to blood lead level measured at age 24 months (*2*). Children with high prenatal exposure who also experience higher levels of concurrent exposure or who have less favorable sociodemographic characteristics (e.g., lower social class, HOME score, or maternal IQ, male gender) do not improve in performance between 24 and 57 months to the same extent as children who have comparable levels of prenatal lead exposure but are free of these additional adversities.

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