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Cognitive Deficits Associated with Blood Lead Concentrations <10 µg/dL in US Children and Adolescents

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SYNOPSIS

Objective. Lead is a confirmed neurotoxicant, but the lowest blood lead concentration associated with deficits in cognitive functioning and academic achievement is poorly defined. The purpose of the present study was to examine the relationship of relatively low blood lead concentrations—especially concentrations <10 micrograms per deciliter (µg/dL)—with performance on tests of cognitive functioning in a representative sample of US children and adolescents.

Methods. The authors used data from the Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994, to assess the relationship between blood lead concentration and performance on tests of arithmetic skills, reading skills, nonverbal reasoning, and short-term memory among 4,853 children ages 6–16 years.

Results. The geometric mean blood lead concentration for children in the study sample was 1.9 µg/dL; 172 (2.1%) had blood lead concentrations ≥10 µg/dL. After adjustment for gender, race/ethnicity, poverty, region of the country, parent or caregiver's educational level, parent or caregiver's marital status parent, serum ferritin level, and serum cotinine level, the data showed an inverse relationship between blood lead concentration and scores on four measures of cognitive functioning. For every 1 µg/dL increase in blood lead concentration, there was a 0.7-point decrement in mean arithmetic scores, an approximately 1-point decrement in mean reading scores, a 0.1-point decrement in mean scores on a measure of nonverbal reasoning, and a 0.5-point decrement in mean scores on a measure of short-term memory. An inverse relationship between blood lead concentration and arithmetic and reading scores was observed for children with blood lead concentrations lower than 5.0 µg/dL.

Conclusion. Deficits in cognitive and academic skills associated with lead exposure occur at blood lead concentrations lower than 5 µg/dL.

Subclinical lead toxicity, defined by a whole blood concentration greater than or equal to 10 micrograms per deciliter (μg/dL), affects an estimated 1 in 20 children in the United States.[1] The preponderance of experimental and human data indicates that there are deleterious and persistent effects of low-level lead exposure on brain function, such as lower intelligence, behavior problems, and poor school performance.[2–13] The lowest blood lead concentration associated with adverse effects on cognitive functioning or academic achievement has not been adequately defined.[14]

The current definition of an elevated blood lead concentration (often called blood lead level) for children and adolescents (≥10 μg/dL) was originally based on adverse outcomes associated with prenatal lead exposure. Children who had cord blood lead concentrations >10 μg/dL were found to be significantly delayed when assessed at 2 years of age, compared with those having lower cord blood lead concentrations.[15] Since then, most prospective studies have reported that the detrimental effects of prenatal lead exposure are attenuated in later childhood. However, persistent effects of a greater magnitude have been observed with postnatal lead exposure.[2,5,12]

The objective of the present study was to test for evidence of deficits in cognitive functioning or academic achievement associated with blood lead concentrations <10 μg/dL among a representative sample of US children and adolescents.

METHODS

The source of data for this study was the Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994. NHANES is a cross-sectional, random household survey of the civilian, noninstitutionalized population employing a complex, multistage probability sampling design.

NHANES III data collection procedures. Data were collected on children ages 6–16 participating in NHANES III through physical and dental examinations, laboratory testing, psychometric testing, and interviews with adult informants. Blood lead concentration was measured by graphite furnace atomic absorption spectrophotometry.[16] The detection limit was reported to be 0.5 μg/dL.[17] All lead assays were done on venous blood samples collected at mobile examination centers and shipped on dry ice to the NHANES laboratory.[17] The quality control and assurance procedures have been described elsewhere.[17]

All subjects ages 6–16 years were administered the Arithmetic and Reading subtests of the Wide Range Achievement Test–Revised (WRAT)[18] and the Block Design and Digit Span subtests of the Wechsler Intelligence Scale for Children, Revised (WISC–R).[19,20] These were the only measures of cognitive functioning or academic achievement included in NHANES III. WRAT Arithmetic and Reading scores were standardized to a mean of 100 (standard deviation [SD] = 15), while the WISC–R Block Design and Digit Span subtests were standardized to a mean of 10 (SD = 3).

The WRAT Arithmetic subtest includes oral and written problems ranging in level from simple addition to calculus, while the Reading subtest assesses letter recognition and word reading skills. In the Block Design subtest, the child replicates two-dimensional geometric patterns using a set of three-dimensional cubes; this subtest is a measure of nonverbal reasoning. Digit Span assesses short-term and working memory by asking the child to repeat a series of increasingly long number sequences forward and then backward. For the analyses reported in the present article, we used age-standardized scores on the four subtests.

The cognitive subtests were administered by trained interviewers in standardized environments, according to standardized procedures, during physical examinations of children 6 to 16 years of age.[20] Ninety-five percent of children ages 6–16 were tested in English, while the rest were tested in Spanish. An automated data recording system was used to improve adherence to the protocol, help assure accurate timing of the tasks, and streamline data collection. Quality control data showed consistent adherence to the protocol.[20]

Statistical analyses. We calculated geometric mean blood lead concentrations and mean scores on the four cognitive subtests for the 4,853 study subjects ages 6–16 years, by potential confounders. In addition, we calculated mean scores on the four subtests by blood lead concentration quartiles.

Multivariate analyses. To illustrate the effects of lead on cognitive functioning and academic achievement, we examined differences in performance on the four cognitive subtests by blood lead concentration quartiles in a multiple linear regression analysis, with blood lead concentration treated as a continuous independent variable. Although we were primarily interested in the relationship

Table 1. Mean blood lead concentrations for 4,853 children ages 6–16 years and percentages of children with blood lead concentrations ≥5 μg/dL, NHANES III (1988–1994), by potential confounding variables

Variable	*Geometric mean BLL (μg/dL)*	*SE*	*Percent with blood lead concentration ≥5 μg/dL*
Total (*N* = 4,853)	1.9	0.1	9.7
Gender			
Male	2.2[a]	0.1	11.5[a]
Female (reference)	1.7	0.1	7.6
Race/ethnicity			
African American	2.8[a]	0.1	21.6[a]
Hispanic	2.1[a]	0.1	13.0[a]
Other	1.9	0.2	11.2
White (reference)	1.7	0.1	6.2
Poverty Index Ratio			
Lowest tercile	2.7[a]	0.1	19.1[a]
Middle tercile	1.8[a]	0.1	7.1[a]
Highest tercile (reference)	1.4	0.1	2.6
Educational level of parent or caregiver			
< high school graduate	2.5[a]	0.1	18.0[a]
High school graduate	1.9[a]	0.1	8.9
> high school graduate (reference)	1.6	0.1	5.5
Serum ferritin level			
Lowest tercile (reference)	1.8	0.1	7.4
Middle tercile	2.0[a]	0.1	10.3[a]
Highest tercile	1.9	0.1	10.5[a]
Serum cotinine level			
Lowest tercile (reference)	1.5	0.1	3.9
Middle tercile	1.9[a]	0.1	9.5[a]
Highest tercile	2.4[a]	0.1	14.7[a]
Exposure to tobacco smoke[b]			
Prenatal and postnatal	2.5[a]	0.1	15.5[a]
Prenatal only	2.1	0.2	13.7
Postnatal only	2.5[a]	0.1	16.0[a]
None (reference)	1.9	0.1	9.4
Received care in NICU[b]			
Yes	2.3	0.2	12.3
No (reference)	2.1	0.1	12.0
Birthweight[b]			
< 2,500 g	2.6[a]	0.2	20.0[a]
≥2,500 g (reference)	2.1	0.1	11.0

[a]Comparison with reference group significant at $P < 0.05$
[b]Children ages 6–11 years only

μg/dL = micrograms per deciliter
SE = standard error
NICU = neonatal intensive care unit

of blood lead concentration and performance on measures of cognitive and academic skills, we included other variables to adjust for potential confounding, based on a review of the literature. These covariates, selected a priori, included: the child's gender; the child's "racial"/ethnic background as reported by the adult informant; the child's iron status (as measured by serum ferritin level), the child's serum cotinine level (cotinine, a metabolite of nicotine, is a biomarker of exposure to tobacco smoke); region of country as defined in NHANES; marital status, as reported by the adult informant, of the "family reference person," usually the head of household; educational level of the family reference person; and the Poverty Index Ratio (the ratio of total family income, as reported by the adult informant, to the federal poverty level for the year of the interview).

Other potential confounders were *in utero* and postnatal exposure to tobacco, birthweight, and admission to a neonatal intensive care unit (NICU). Data on these variables, as reported by adult informants, were available only for 6- to 11-year-old children. We conducted a secondary analysis of data on 6- to 11-year-old children to verify that inclusion of these three variables did not alter the findings of the analyses conducted using the larger sample. Although we used age-standardized scores on the four cognitive subtests in all analyses, we also examined the effect of age on the association between blood lead concentration and cognitive skills in secondary analyses.

Statistical analyses were performed on nontransformed blood lead values.

We used SUDAAN software to estimate confidence intervals that accounted for the complex, multi-stage sampling design of the survey.[21] Sample weights provided with the NHANES III data were used in order to adjust for the oversampling of young children, Mexican Americans, and African Americans in the survey.

Regression diagnostics were carried out by performing weighted regression analyses using a standard statistical package[22] to ensure that the results were not dependent on statistical outliers or influential points. All reported analyses were done with the three identified outliers excluded. We also conducted a comparison of the base model and the model with outliers included.

Deficits associated with blood lead concentration <10 µg/dL. We conducted a series of multiple linear regression analyses to examine the relationship of blood lead concentration with cognitive functioning for children with blood lead concentrations <10 µg/dL, <7.5 µg/dL, <5 µg/dL, or <2.5 µg/dL.

RESULTS

Of the 5,365 children and adolescents ages 6–16 years participating in NHANES III, 4,853 (91%) completed the four subtests measuring cognitive and academic skills and had blood lead concentration data available. These 4,853 children and adolescents, the subjects of the present study, did not differ significantly by gender, poverty status, educational level of the adult reference person, serum cotinine level, or serum ferritin level from those who were not included in the analysis due to missing data. However, the two groups did differ by race/ethnicity; 15% of the study subjects were African American, compared with 20% of those not tested ($P = 0.04$).

Unadjusted findings. The geometric mean blood lead concentration for the 4,853 subjects was 1.9 µg/dL (standard error [SE] = 0.1). Of these subjects, 2,386 (36.5%) had blood lead concentrations ≥2.5 µg/dL; 810 (9.7%) had blood lead concentrations ≥5.0 µg/dL; 327 (3.8%) had blood lead concentrations ≥7.5 µg/dL; and 172 (2.1%) had blood lead concentrations ≥10 µg/dL. Blood lead concentration varied by gender, race/ethnicity, Poverty Index Ratio, and the educational level of the adult reference person: mean blood lead concentration was higher for males than females, higher for African American subjects than white subjects, higher for Hispanic subjects than white subjects, and varied inversely with the Poverty Index Ratio and adult educational achievement. Postnatal exposure to tobacco smoke and lower birthweight were also associated with higher blood lead concentration in unadjusted analyses (Table 1).

Mean subtest scores for the four cognitive subtests were as follows: Arithmetic 93.5 (SE = 0.5), Reading 91.9 (SE = 0.5), Block Design 9.5 (SE = 0.1), and Digit Span 8.7 (SE = 0.1). In unadjusted analyses, significant differences were seen in subtest scores by gender, race/ethnicity, Poverty Index Ratio, educational level of the adult reference person, serum cotinine level, *in utero* and postnatal exposure to tobacco smoke, and birthweight. Females tended to score better than males on all subtests except Block Design (Table 2).

The unadjusted data also showed an inverse relationship between quartile of blood lead concentration and scores on the four cognitive subtests (Table 3). The unadjusted mean scores of children with values in the highest and lowest blood lead concentration quartiles differed by 10.8 points for Arithmetic, 12.0 for Reading, 1.2 for Block Design, and 1.7 for Digit Span.

Table 2. Unadjusted mean scores on cognitive/academic subtests for 4,853 children ages 6–16 years, NHANES III (1988–1994), by potential confounding variables

	Arithmetic		Reading		Block Design		Digit Span	
Variable	*Mean score*	*SE*	*Mean score*	*SE*	*Mean score*	*SE*	*Mean score*	*SE*
Total (*N* = 4,853)	93.5	0.5	91.9	0.5	9.5	0.1	8.7	0.1
Gender								
Male	92.8[a]	0.7	91.2[a]	0.6	9.8[a]	0.1	8.5[a]	0.1
Female (reference)	94.3	0.5	92.7	0.7	9.2	0.1	8.8	0.1
Race/ethnicity								
African American	86.1[a]	0.7	91.9[a]	0.5	7.2[a]	0.1	8.0[a]	0.1
Hispanic	86.9[a]	0.9	85.4[a]	0.9	8.8[a]	0.2	7.5[a]	0.2
Other	96.3	2.7	88.7	4.0	9.9	0.4	8.2[a]	0.3
White (reference)	96.4	0.7	95.1	0.7	10.2	0.1	9.1	0.1
Poverty Index Ratio								
Lowest tercile	86.9[a]	0.9	84.2[a]	0.7	8.3[a]	0.2	8.0[a]	0.1
Middle tercile.	93.1[a]	0.9	91.8[a]	0.6	9.4[a]	0.1	8.6[a]	0.1
Highest tercile (reference)	100.4	0.9	89.7	0.9	10.7	0.1	9.5	0.1
Education level of parent or caregiver								
< high school graduate	85.1[a]	0.8	83.4[a]	0.7	8.2[a]	0.2	7.7[a]	0.1
High school graduate	92.0[a]	0.7	90.9[a]	0.7	9.2[a]	0.1	8.5[a]	0.1
> high school graduate (reference)	89.7	0.8	97.6	0.8	10.5	0.1	9.4	0.1
Serum ferritin level								
Lowest tercile (reference)	93.9	1.0	92.0	0.7	9.6	0.2	8.8	0.1
Middle tercile.	94.2	0.8	92.4	0.7	9.7	0.1	8.7	0.1
Highest tercile	93.2	0.7	91.8	0.8	9.3	0.1	8.6	0.1
Serum cotinine level								
Lowest tercile (reference)	98.4	0.9	96.9	0.9	10.4	0.2	9.1	0.1
Middle tercile	94.1[a]	0.9	91.8[a]	1.0	9.4[a]	0.2	8.5[a]	0.1
Highest tercile	88.9[a]	0.7	87.7[a]	0.7	8.7[a]	0.1	8.4[a]	0.1
Exposure to tobacco smoke[b]								
Prenatal and postnatal	91.7[a]	1.3	87.5[a]	1.1	8.9[a]	0.2	8.6[a]	0.2
Prenatal only	92.6	2.6	91.8	3.1	9.9	0.5	8.5	0.4
Postnatal only.	91.5[a]	1.1	88.7[a]	1.0	9.2[a]	0.2	8.4[a]	0.2
None (reference)	96.1	0.7	92.4	0.8	10.2	0.2	9.1	0.1
Received care in NICU[b]								
Yes	91.7	2.1	88.5	1.7	9.8	0.4	8.5	0.3
No (reference)	94.5	0.7	91.1	0.6	9.7	0.1	8.9	0.1
Birthweight[b]								
< 2,500 g	87.9[a]	2.0	86.0[a]	2.0	8.3[a]	0.3	8.2[a]	0.3
>2,500 g (reference)	94.7	0.7	91.2	0.6	9.8	0.1	8.9	0.1

[a]Comparison with reference group significant at $P < 0.05$

[b]Children ages 6–11 years only

SE = standard error

NICU = neonatal intensive care unit

Multivariate analyses. In an analysis adjusted for potential confounders, we found inverse associations between performance on three of the four cognitive/academic measures and increasing quartiles of blood lead concentration, as shown in Table 3. The unadjusted mean scores of children with values in the highest and lowest quartiles differed by 4.4 points for Arithmetic, 6.3 for Reading, and 0.6 for Block Design. The 0.4-point difference between the highest and lowest quartiles for Digit Span was not significant.

As reported in Table 4, we found an inverse association between blood lead concentration and all subtest scores. A series of multiple linear regression analyses revealed a 0.70-point decrement in Arithmetic scores and an approximate 1-point (–0.99) decrement in Reading scores for each 1 µg/dL increase in blood lead concentration. The analyses also showed a 0.10-point decrement in Block Design and a 0.05-point decline in Digit Span for each 1 µg/dL increase in blood lead concentration (Table 4).

We next examined the adjusted relationship between performance on cognitive and academic subtests and blood lead concentration for children with blood lead concentrations <10 µg/dL, <7.5 µg/dL, <5 µg/dL, or <2.5 µg/dL (Table 4). We found an inverse relationship for Arithmetic and Reading with blood lead concentrations lower than 5.0 µg/dL. Block Design was inversely associated with blood lead concentrations lower than 7.5 µg/dL, while Digit Span was inversely associated with blood lead concentrations lower than 10 µg/dL.

Secondary analyses. We also examined the relationship between blood lead concentration and adjusted mean scores on the four cognitive subtests for children ages 6–11 years to detect any difference following adjustment for prenatal and postnatal exposure to tobacco smoke, low birthweight, and admission to NICUs. The magnitude of the associations between blood lead concentration and subtest performance (not shown) did not change appreciably. Similarly, there was little difference in the association of blood lead concentration with subtest performance after adjustment for age.

There was little change in the effect size or statistical significance of the association of blood lead concentration with adjusted mean scores on the four subtests (not shown) after the three outliers were removed from the model, with one exception. The independent association of Digit Span with blood lead concentration was not significant with outliers in the model (ß = –0.03, SE = 0.2, $P = 0.20$). When the three outliers were removed, Digit Span was inversely associated with blood lead concentration (ß = –0.05, SE = 0.2, $P = 0.04$).

DISCUSSION

Prior to 1970, lead poisoning was defined by a blood lead concentration ≥60 µg/dL, a level sometimes associated with acute symptomatic disease, such as abdominal colic, anemia, or encephalopathy, or with death.[23] Before the advent of chelation therapy, only 50% of children who were hospitalized with acute lead poisoning survived.[24] For those who survived, many were left with conspicuous sequelae, including mental retardation (40%), seizures (20%), cerebral palsy (2%), or optic atrophy (1%).[24]

Since then, the blood lead concentration defining unacceptable lead exposure in children and adolescents has gradually been reduced from 60 µg/dL in the 1960s, to 40 µg/dL in 1971, to 30 µg/dL in 1978, and then to 25 µg/dL in 1985.[23] In 1991, the Centers for Disease Control (now the Centers for Disease Control and Prevention [CDC]) reduced the acceptable level even further, so that blood lead concentrations ≥10 µg/dL were considered unacceptable.[23] This reduction was the result of evidence indicating that blood lead concentrations as low as 10 µg/dL were associated with adverse effects, such as lowered intelligence.[15]

The results of the present analyses suggest that cognitive deficits are associated with blood lead concentrations lower than 5 µg/dL. Although we did not conduct a formal threshold analysis, these data support the conclusion that there is, at present, no detectable threshold for the adverse effects of lead exposure on cognitive development or academic abilities. These data further suggest that more than 12.8 million US children and adolescents born from 1972 to 1988 were adversely affected by environmental lead exposure, as indicated by blood lead concentrations >2.5 µg/dL (based on weighting factors and Census data provided by NHANES).

Consistent with the findings of other studies,[6,13] we found that Reading scores were especially affected by lead exposure. Indeed, while the adverse effects of lead exposure on Reading scores were not significant for children with blood lead concentrations <2.5 µg/dL, the size of the effect and the borderline significance level (ß = –1.71, $P = 0.07$) suggest that the smaller sample size and the imprecision of the relationship of blood lead concentration with performance on the Reading subtest—as indicated by the large standard error—may be the reason we did not find a statistically significant association for children in that range. The adverse effects of lead exposure on reading and

Table 3. Unadjusted and adjusted[a] mean scores on cognitive/academic subtests for 4,853 children ages 6–16 years, NHANES III (1988 to 1994), by blood lead concentration quartile

Subtest	*Unadjusted mean score*	*SE*	*Adjusted mean score[a]*	*SE*
Arithmetic[b,c]				
≤1 μg/dL	98.0	1.2	95.8	1.2
1.1 μg/dL–1.9 μg/dL	95.1	0.9	94.0	0.9
2.0 μg/dL–3.0 μg/dL	94.3	0.9	94.7	0.8
>3.0 μg/dL	87.2	1.1	91.4	1.1
Reading[b,c]				
≤1 μg/dL	96.5	1.1	94.5	1.0
1.1 μg/dL–1.9 μg/dL	94.3	1.0	93.3	0.9
2.0 μg/dL–3.0 μg/dL	92.5	0.9	93.0	0.9
>3.0 μg/dL	84.5	0.9	88.2	1.0
Block Design[b,d]				
≤1 μg/dL	10.2	0.2	9.8	0.2
1.1 μg/dL–1.9 μg/dL	9.7	0.1	9.5	0.1
2.0 μg/dL–3.0 μg/dL	9.7	0.2	9.7	0.2
>3.0 μg/dL	8.5	0.1	9.2	0.1
Digit Span[b,e]				
≤1 μg/dL	9.2	0.1	8.9	0.2
1.1 μg/dL–1.9 μg/dL	8.8	0.2	8.6	0.2
2.0 μg/dL–3.0 μg/dL	8.7	0.1	8.8	0.1
>3.0 μg/dL	8.0	0.2	8.5	0.2

[a]Adjusted for gender, race/ethnicity, Poverty Index Ratio, educational level of reference adult, serum ferritin level, and serum cotinine level in a linear regression analysis

[b]Difference between quartiles in unadjusted scores significant at $P < 0.0001$

[c]Difference between quartiles in adjusted scores significant at $P < 0.0001$

[d]Difference between quartiles in adjusted scores not significant ($P < 0.09$)

[e]Difference between quartiles in adjusted scores not significant ($P < 0.36$)

SE = standard error
μ/dL = micrograms per deciliter
NICU = neonatal intensive care unit

other deficits in language-based abilities are of particular importance, because they are potent predictors of academic achievement and antisocial behavior.[25]

The relationship of blood lead concentration and cognitive skills was adjusted for numerous potential confounders in these analyses. However, we lacked a measure of the home environment, such as the HOME score, and of maternal intelligence; not adjusting for these variables may have resulted in underestimating or overestimating the detrimental effects of lead.[2,5,7,12] Other investigations have found an inverse relationship between blood lead concentration and IQ scores at blood lead concentrations <10 μg/dL after adjusting for maternal IQ and home environment.[13,26] In a reanalysis of the Boston Lead cohort, Schwartz reported that the effect of lead appeared to persist at concentrations <5 μg/dL.[26] Other adverse effects of lead exposure, such as hearing loss, have also been reported to occur at concentrations <10 μg/dL.[27] Thus, while the Poverty Index Ratio and the educational level of the reference adult may have acted as surrogates for maternal intelligence and home environment in our analyses, further research is needed to refine the relationship of blood lead concentration and cognitive/academic deficits in children at concentrations <5 μg/dL.

Table 4. Adjusted[a] coefficients representing the decrement in mean scores on cognitive/academic subtests associated with each 1 µg/dL increase in blood lead concentration, for 4,853 children ages 6–16 years, NHANES III (1988 to 1994), by blood lead concentration range

	Total N = *4,853*			*Blood lead concentration <10 µg/dL* n = *4,681*			*Blood lead concentration <7.5 µg/dL* n = *4,526*			*Blood lead concentration <5.0 µg/dL* n = *4,043*			*Blood lead concentration < 2.5 µg/dL* n = *2,467*		
Subtest	*Coefficient*	*SE*	*P*	*Coefficient*	*SE*	*P*	*Coefficient*	*SE*	*P*	*Coefficient*	*SE*	*P*	*Coefficient*	*SE*	*P*
Arithmetic	–0.70	0.17	<0.001	–0.89	0.32	0.008	–1.06	0.39	0.01	–1.06	0.48	0.03	–1.28	0.98	0.20
Reading	–0.99	0.19	<0.001	–1.44	0.30	<0.001	–1.53	0.31	<0.001	–1.66	0.36	<0.001	–1.71	0.93	0.07
Block Design . .	–0.10	0.04	0.009	–0.13	0.06	0.03	–0.11	0.06	0.04	–0.05	0.07	0.45	–0.08	0.22	0.72
Digit Span	–0.05	0.02	0.04	–0.08	0.04	0.03	–0.09	0.05	0.11	–0.09	0.07	0.20	–0.25	0.17	0.17

[a]Adjusted for gender, race/ethnicity, Poverty Index Ratio, educational level of reference adult, serum ferritin level, and serum cotinine level in multiple linear regression analyses

SE = standard error
µg/dL = micrograms per deciliter

The current definition of an elevated blood lead level, as recommended by both the CDC and the World Health Organization, is a value ≥10 µg/dL.[14,23] This cut-off was originally based on adverse outcomes associated with cord blood lead concentration for children assessed at 2 years of age.[15] Since then, prospective studies have reported that the detrimental effects of prenatal lead exposure on intelligence appear to be attenuated in later childhood, whereas postnatal lead exposure has been associated with persistent effects of greater magnitude.[2,5,7,12,28]

It is not clear whether the cognitive and academic deficits observed in the present analyses are due to lead exposure that occurred during early childhood or due to concurrent exposure. Critical neurodevelopmental processes occur in the human central nervous system during the first three years of life, including synaptogenesis, myelination, and programmed apoptosis. Studies of the effects of low-level lead exposure in animals suggest that these processes are vulnerable to lead toxicity, yet no single mechanism of lead toxicity has been described.[29–31] On the other hand, concurrent blood lead concentration was the best predictor of adverse neurobehavioral effects of lead exposure in all but one of the published prospective studies,[2,5,7,12,28] and blood lead concentration measured in early childhood track closely with subsequent blood lead concentration.

Although a "behavioral signature" for lead has been elusive,[4] existing data suggest that attention, executive functions, visual-motor reasoning skills, vestibular-proprioceptive control, and social behavior are especially affected by lead exposure.[30] Many of these effects of lead on central nervous system functioning are difficult to assess in infants or toddlers with the degree of reliability and precision that is possible in older children.[31] Moreover, neurobehavioral assessments in later childhood are more predictive of adult neurocognitive functioning, vocational success, and social adjustment than assessments of infants and toddlers. Thus the relationship of blood lead and cognitive and academic deficits in children 6 years of age and older may be the most cogent measure of the persistent and deleterious effects of subclinical lead toxicity.

Despite dramatic declines in the prevalence of children who have blood lead concentrations ≥10 µg/dL,[1] the present findings underscore the increasing importance of prevention as the consequences of lower blood lead concentrations are recognized. We observed inverse associations between blood lead concentration and deficits in cognitive functioning and academic achievement in children at levels below 5.0 µg/dL. Although blood lead concentrations up to 10 µg/dL are widely considered "normal" for children, contemporary levels of childhood lead exposure remain exceedingly high compared with those of pre-industrial humans,[32] providing further evidence that contemporary children are unduly exposed to lead.

Collectively, the results of the present analyses and other studies[13,26,27] argue for a reduction in blood lead levels that are considered "acceptable"—from 10 µg/dL to 5 µg/dL or lower. They also argue for a shift toward primary prevention of childhood lead exposure, which contrasts

sharply with current efforts that rely almost exclusively on management of children with elevated blood lead levels.[33]

This study was funded in part by the National Institute of Environmental Health Sciences (RO1-ES 08338) and by an Institutional National Research Service Award (#1T-32 PE-10027) from the Bureau of Health Professions, Health Resources and Services Administration, Department of Health and Human Services.

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