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Deficits in cognitive function and achievement in Mexican first-graders with low blood lead concentrations ☆

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Abstract

Elevated blood lead levels in children are associated with lower scores on tests of cognitive functioning. Recent studies have reported inverse relations between lifetime exposure and intellectual functioning at blood lead concentrations below 10 μg/dL, the Centers for Disease Control and Prevention's (CDC) level of concern. We report associations between blood lead and cognitive performance for first-grade Mexican children living near a metal foundry. Using a cross-sectional design, we examined the relation between children's concurrent blood lead concentrations (mean (SD) 11.4 μg/dL (6.1)) and their performance on 14 tests of global or specific cognitive functions. The blood lead–cognition relations were modeled using both linear and nonlinear methods. After adjustment for covariates, a higher blood lead level was associated with poorer cognitive performance on several cognitive tests. Segmented linear regressions revealed significant effects of lead but only for the segments defined by a concurrent blood lead concentration below 10–14 μg/dL. One implication of these findings is that at the age of 7 years, even in the absence of information on lead exposure in infancy and early childhood, a test result with blood lead <10 μg/dL should not be considered safe. Together with other recent findings, these results add to the empirical base of support available for evaluating the adequacy of current screening guidelines and for motivating efforts at primary prevention of childhood lead exposure.

Keywords: Child; School age; Cognition; Cut-off; Lead exposure

1. Introduction

It is well known that lead exposure is associated with children's scores on tests of academic achievement and intelligence (Bellinger et al., 1992; Needleman and Gatsonis, 1990; Stiles and Bellinger, 1993). However, little is known about the possible adverse effects at very low blood lead concentrations (PbBs). A level of concern set by the Centers for Disease Control and Prevention (CDC) to guide screening and prevention efforts has been repeatedly lowered since the 1970s. The current level of concern is based on a series of prospective and cross-sectional assessments showing adverse effects of lead concentrations below 25 μg/dL and as low as 10 μg/dL on children's mental development and IQ (CDC, 1991).

☆This study was approved by committees on research involving human subjects at the Johns Hopkins University Bloomberg School of Public Health and the National Institute of Medical Sciences and Nutrition in Mexico. All the work was conducted in accordance with guidelines for the protection of human subjects.

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Children with blood lead $<10\,\mu g/dL$ are not considered lead-poisoned and are usually not given medical attention. This practice is due partly to cognitive or developmental deficits not having been conclusively demonstrated at such low levels, and partly to lack of resources and effective treatment options for children with low PbBs (Barnard, 2003).

Recent studies, however, raise serious questions about the safety of PbBs less than $10\,\mu g/dL$. Using data from NHANES III, Lanphear et al. (2000) examined measures of nonverbal reasoning, memory, and achievement in relation to concurrent PbBs in children aged 6–16 years. When the sample was restricted to children with PbBs $<10\,\mu g/dL$, significant inverse associations were found for Block Design and Digit Span from the Wechsler Intelligence Scales for Children—Revised (WISC-R) and for the Arithmetic and Reading tasks from the Wide Range Achievement Test—Revised (WRAT). Remarkably, PbB was significantly and inversely related to Reading and Arithmetic scores even with the sample restricted to PbBs $<5\,\mu g/dL$.

A longitudinal study conducted in Rochester, NY provided more complete information about children's exposure history and also measured a broader range of potential confounders (Canfield et al., 2003). PbBs were assessed for 172 children at seven time points from 6 to 60 months of age and IQ tests were administered at ages 3 and 5 years. When estimated using covariate-adjusted semiparametric regression, an increase in lifetime average PbB was associated with a decline of 7.4 points on the Stanford–Binet intelligence test. Considering only those children whose *peak* PbB (the highest PbB measured at any time) was $<10\,\mu g/dL$, the inverse relation between PbB and IQ remained significant. There was also a nonlinear relation between PbB and IQ, with a steeper slope at lower rather than higher PbBs. A given increment in blood lead was associated with a greater decline in IQ for children with peak PbBs $<10\,\mu g/dL$ than $>10\,\mu g/dL$.

The populations studied in Lanphear et al. (2000) and Canfield et al. (2003) were US-based, with exposure derived primarily from lead-based paint and contaminated dust. In these circumstances, children's PbBs typically peak during the first 3 years of age. In developing countries, where environmental contamination is a serious public health problem (Tong et al., 2000), evidence of adverse lead effects is also strong. Because studies of childhood lead exposure are necessarily observational in design, there is a need to provide information from other cultures that may exhibit unique patterns of exposure and confounding. Several reports have described adverse cognitive functioning in lead-exposed children from Pristina and Mitrovica, Yugoslavia and Port Pirie, Australia (Baghurst et al., 1992; Tong et al., 1996; Wasserman et al., 1994), both with smelters as sources of lead exposure. More recently, studies of children from the Middle East and South Asia have also shown negative associations between lead exposure and cognitive performance in school children. The strengths of the individual studies include a large, representative sample (Al-Saleh et al., 2001; Wang et al., 2002) and a wide range of lead exposures with over 80% of children with PbB $\geqslant 10\,\mu g/dL$ and 20% $>20\,\mu g/dL$ (Rahman et al., 2002). In a Mexican study using standardized cognitive measures, lead exposure in children 6–9 years of age was not associated with concurrent PbB in the range 4–26 $\mu g/dL$ (Calderón et al., 2001). However, the small sample size and exposure to another toxin, arsenic, may have attenuated the lead–cognition association.

Each of these studies provides unique information for a full description of the worldwide consequences of childhood lead exposure. However, with the exception of a report on performance of Saudi Arabian girls (Al-Saleh et al., 2001), which showed a significant association between class rank and PbB $<9\,\mu g/dL$, most of these recent studies have not specifically investigated the effects of very-low-level lead on cognition and achievement of school children. Documenting the possible consequences of low-level lead exposure in developing countries provides the most relevant information for local policymakers. For this reason, analyses of the association between very-low lead levels and cognitive performance similar to those reported in US children (Canfield et al., 2003; Chiodo et al., 2004; Lanphear et al., 2000) are needed in other cultural settings.

Age of assessment is an important factor in understanding the relation between exposure to neurotoxins and children's cognitive functioning. An advantage of studying children of school age, as compared to younger ages, is that their cognitive systems are sufficiently differentiated to allow the administration of a broad range of tasks. In addition, performance on cognitive tests in older children is substantially more reliable than in preschool children, and more predictive of later cognitive performance and educational achievement (Sattler, 1992).

We report on associations between PbB and cognitive performance of Mexican first-graders exposed to lead from a metal foundry, allowing us to expand on findings from previous studies in two important ways. First, we examined the relation between lead and global, as well as specific cognitive functions, such as memory, attention, and visual spatial abilities. Second, based on evidence that the relation between PbB and cognition, specifically IQ, may not be linear (Canfield et al., 2003; Chiodo et al., 2004; Lanphear et al., 2000; Muñoz et al., 1993), we described the nature of the lead–cognition relation using both linear and spline (segmented) regression methods. In spline analyses we examined specific PbBs at which slopes of the lead–cognition association changed and characterized the nature of this association below and above the cutoffs. Our population is well suited for this analysis because the large sample consists of a wide range of lead values, with 51% and 20% PbBs $\geqslant 10$ and $\geqslant 15\,\mu g/dL$, respectively. In contrast, in the Canfield et al. (2003) study, which had the strongest design to address this question, 55.8% of the 5-year-olds had *peak* PbBs $< 10\,\mu g/dL$, and the nature of the Pb–IQ relationship could not be characterized at PbBs $> 15\,\mu g/dL$.

2. Methods

2.1. Setting and participants

The study took place in the city of Torreón, Mexico. The present analysis involves baseline data from a randomized trial of iron and zinc supplementation to lead-exposed children. The parents of all first graders ($n = 724$) attending nine public elementary schools in the vicinity of a metal foundry were approached for study participation and 602 provided written consent. The exclusion criteria were PbB $> 45\,\mu g/dL$ or hemoglobin (Hb) concentration $< 9\,g/dL$. No children were excluded based on Hb. One child with PbB $> 45\,\mu g/dL$ was referred for clinical treatment. The sample included 46% girls; children's ages ranged from 6.2 to 8.5 years (51% 6-year-olds, 47% 7-year-olds, 2% 8-year-olds). The study was approved by committees on human research at the Johns Hopkins Bloomberg School of Public Health and the Institute of Medical Sciences and Nutrition in Mexico City. Additional approval was given by the Ministry of Education in the state of Coahuila, where the study took place.

Most children in this study live and attend school in neighborhoods within a 3-km radius of a metal foundry. The main source of lead exposure is a depository containing byproducts of the smelting process, including lead, located on foundry premises. Lead particles are swept from the depository by winds and settle in dust around schools and houses. Smelting also releases lead particles into the air. Because the region is arid and rains are infrequent, children inhale and pick up lead on their hands while outdoors. The exposure characteristics of children in this study were similar to the cohort studied in Port Pirie, Australia. The geometric mean PbB at age 7 years was $10.2\,\mu g/dL$ (range 2–43.8), similar to the 7-year geometric mean of the Port Pirie cohort ($11.6\,\mu g/dL$, range 2.1–37.7) (Tong et al., 1996). PbB was previously measured on some of the Torreón children ($n = 116$) when they were 5 years old as part of a screening campaign unrelated to our study. The geometric mean PbB at 5 years for these children was $16.6\,\mu g/dL$ (range 2–65.7), again similar to the Port Pirie 5-year data. In Port Pirie the correlation between 7-year PbB and lifetime average lead was 0.81. In Torreón the overall correlation between PbB at 5 and 7 years of age was 0.71 ($n = 116$; $P < 0.001$). Because exposure characteristics of the present sample resemble those in Port Pirie, we expect that our 7-year PbB measure is similarly representative of children's lifetime exposure.

2.2. Cognitive outcomes

The testing battery consisted of 14 paper-and-pencil or computer-based tasks that assess specific and global aspects of cognition (Table 1). The tests were divided into two groups and were administered, in the same order, on two different days by Mexican testers, all of whom held bachelor's degrees in psychology and had previous experience testing children. The examiners were unaware of children's blood lead concentrations. The testing days typically occurred within the span of a week. Each day's testing lasted approximately 65–70 min and took place in an isolated room at each school.

2.3. Blood lead measurement

Fasting venous blood samples were collected at the schools between 8:30 and 10 am. Between 5 and 7 mL of venous blood were obtained from each child by a registered nurse using sealed sodium heparine Vacutainer lead-free tubes (Beckton-Dickinson, USA). In the field samples were stored on ice in coolers and transported on the same day to the laboratory, where whole blood and serum were aliquoted and stored at $-70\,°C$ until analysis. Blood lead analysis was performed at the National Polytechnic Institute in Mexico, using atomic absorption spectrophotometry with a 2 ng/g limit of detection (Zeeman 5100, Perkin Elmer Corporation, Norwalk, CT) (Miller et al., 1987). Samples, analyzed in duplicate, were acceptable with CV $< 5\%$. Lead in bovine blood (NIST 955b) with three different concentrations (5.01, 13.53, and $30.63\,\mu g/dL$) served as standard reference. Recoveries ranged from 104% to 112% and the CV ranged between 3% and 10%. This laboratory participates in two quality control programs: the Trace Element External Quality Assessment Scheme at University of Surrey, UK and the Inter Laboratory Program of Quality Control at Zaragoza, Spain.

2.4. Measurement and selection of covariates

Covariates were chosen to include well-documented predictors of cognitive functioning and intellectual outcomes in children: child's age, gender, family socioeconomic status (home ownership, possessions, and crowding), maternal formal education, parental involvement in schooling, family structure, and birth order. All information was obtained from teacher and parent

Table 1
Description of cognitive tasks, in order of administration: 586 children assessed

Task	Description	Mean (SD) and range
Math achievement test	Measures performance on 1st-grade math curriculum. Consists of 39 items, numerical and pictorial, testing counting, 1–1 correspondence, addition, subtraction, counting by 10s. The dependent variable was *final score*.	31.4 (7.5) 3–52
Peabody picture vocabulary Test—Spanish language version (Dunn et al., 1986)	Test of receptive vocabulary. Consists of 111 cards, with 4 black-and-white sketches and one stimulus word for each card. Children choose the picture that is best described by a given word. The *PPVT standard score* was the dependent variable with a mean (SD) of 100 (15).	103.3 (15.6) 55–145
Freedom from distractibility factor (Sattler, 1992, p. 816; Wechsler et al., 1984)	Age-adjusted scores from the WISC-RM Arithmetic, Coding, and Digit Span subscales were summed into the *Freedom From Distractibility Factor*, which estimates one facet of attention. Similarly to an IQ score, this factor can be scaled to a mean of 100 and SD of 15. The Arithmetic subscale measures numerical knowledge and reasoning skills. The Coding subscale tests learning of unfamiliar tasks. It requires attention, short-term memory, cognitive flexibility and visual-motor speed and accuracy. The Digit Span subscale measures auditory short-term memory and attention.	94.5 (16.0) 52–133
Sequencing (Reitan and Wolfson, 1992)	Adapted from part A of the Trail Making Test, this task involves selective attention and mental flexibility. In the numbers part, children use a marker to draw a line connecting, in proper sequence, as many encircled numbers (4–18) randomly distributed on a page as possible in 60 s. In the letters part, children connect letters (D–P, including Ñ and Q). The *correct responses* on the combined parts were analyzed.	7.3 (4.2) 0–26
Sternberg memory	This is a measure of visual short-term memory scanning. A string of capital letters appears briefly on the computer screen, followed by a single capital letter. The child then touches the screen to indicate whether the single letter was among the initial string. The dependent variable was the *number of correct trials*.	12.2 (2.9) 4–20
Figure matching	A set of figures is shown simultaneously on a computer screen. A probe stimulus appears in the upper half of the screen and several response stimuli in the lower half. The child points out the figure in the bottom row, which matches the probe on top. The dependent variable was the *number of correct trials*.	24.7 (3.7) 8–32
Figure design	Children are shown an outline of a figure and are asked to construct that figure with a given set of puzzle blocks (squares, triangles or diamonds). Three levels of assistance are given upon request: showing the outline with one block drawn in, outline with all pieces drawn in or allowing design to be constructed on top of the complete outline. Figures range from 2 (practice) to 7-block designs. *Overall score* was analyzed.	19.7 (6.1) 2–40
Visual search	This is a test of visual selective attention and visual-motor speed. The child views a screen displaying many small rectangular boxes, each containing a single letter "b," "d," or "p" with 0, 1, or 2 dots next to, above, or below the letter (e.g.: "b:" or "·p"). The child touches, as quickly as possible, only the boxes with a "d" and 2 dots anywhere inside the rectangle. *Total number of correct* touches and commission errors were analyzed.	Number correct: 19.0 (7.3) 0–37 Errors: 11.6 (15.5) 0–95 57.7% children with $\geqslant$5 errors
Cognitive abilities test: stimulus discrimination (Detterman, 1988)	This test measures the ability to recognize a familiar form and quickly discriminate it from visually similar forms. Child responds using a keypad and a touch-sensitive computer monitor. First, a probe stimulus is briefly flashed onto the screen. Then, six similar-looking stimuli (one of which is the probe) appear simultaneously on the screen. The child is instructed to touch the stimulus that matches the probe. The dependent variable was the *mean decision time* (time from display of stimuli to lifting the pointing finger off the keypad) and *number of errors*.	Mean decision time: 6.0 (1.7) 3.0–16.3 Number of errors: 3.6 (7.1) 0–95 23.5% children without any errors
Stimulus discrimination	A single capital letter or object is shown briefly on the screen, followed by another screen with a string of different letters or objects. The child touches the letter that appeared initially. *Total correct* responses were analyzed.	17.6 (3.7) 1–20 29.0% children with perfect score
Visual memory span	Tests the ability to recall a sequence of spatial locations. An array of 12 squares of different colors appears on the screen. These squares are briefly illuminated in random order. After a brief delay the child is asked to touch the squares that were illuminated, repeating the exact order. The task begins with 1 square and progresses to 16. The *number of correct* responses was used in analysis.	6.5 (3.5) 2–24 18.9% children with $\geqslant$10 correct responses

interviews and questionnaires. Children's total arsenic (in urine) and venous Hb concentrations were also included. In addition, all models were adjusted for the tester administering cognitive tasks and the school each child attended. Not all covariates were statistically associated with lead exposure in the sample (Table 2) but all were part of the conceptual model and, therefore, included in the analysis.

Home ownership was scored 0 or 1 and crowding in the home as the number of family members per room. Maternal educational achievement was scored as having less than or at least high school education. Parents' involvement in children's schooling was indicated by a teacher's report of how often a child forgot homework (always, sometimes, never). Family structure was measured as either two-parent (1) or another family arrangement (0), and birth order included two categories (first child or second child and beyond). For the family possessions variable, parents were asked to indicate whether their household possessed the following specific

Table 2
Sample characteristics, given as mean (SD)

Covariate	N	Lead (μg/dL)	PPVT	MAT	Figure design
Gender	593				
Boys	321	11.7 (6.4)	104.2 (15.8)	31.5 (7.1)	20.6 (6.3)
Girls	272	11.1 (5.8)	102.3 (15.4)	31.2 (8.0)	18.7 (5.6)
Age, y[a]	593				
<7	304	11.3 (5.7)	102.7 (16.1)	30.1 (7.6)	18.7 (6.0)
7	289	11.5 (6.5)	103.9 (15.2)	32.7 (7.2)	20.8 (6.0)
Hemoglobin, g/dL[a]	591				
⩾12.4	534	11.4 (6.1)	103.4 (15.8)	31.4 (7.5)	19.7 (6.1)
<12.4	57	11.5 (5.8)	102.4 (14.2)	30.7 (7.3)	19.1 (5.8)
Lead, μg/dL[a]	589				
<10	293	7.1 (1.7)	106.4 (14.5)	32.5 (7.4)	20.3 (6.3)
10–14.9	177	12.1 (1.4)	101.5 (17.0)**	30.5 (7.4)**	18.8 (5.9)**
⩾15	119	21.0 (6.0)	98.4 (14.2)**	29.8 (7.5)**	19.3 (5.6)
Child forgets homework	580				
Never	211	10.5 (5.5)	108.7 (14.3)	34.0 (6.9)	21.1 (6.2)
Sometimes	314	11.7 (6.3)*	101.5 (15.4)**	30.2 (7.2)**	19.1 (6.0)**
Always	55	13.2 (6.4)**	91.8 (14.3)**	27.4 (8.6)**	18.0 (5.1)**
Luxury items	569				
None	122	12.3 (6.5)	100.9 (15.1)	29.9 (6.9)	19.1 (6.1)
1 or 2 items	385	11.5 (6.0)	103.1 (16.2)	31.2 (7.5)	19.7 (6.1)
Car + computer or 3 items	62	9.9 (5.3)*	109.4 (13.0)**	34.5 (7.5)**	21.3 (5.4)*
Mother's education	563				
<High school	310	12.4 (6.6)	99.8 (15.3)	29.9 (7.5)	18.9 (5.7)
⩾High school	253	10.4 (5.3)**	107.5 (15.5)**	33.0 (7.1)**	20.7 (6.4)**
Family structure	572				
Lives with both parents	446	11.4 (5.9)	103.7 (15.6)	31.6 (7.5)	19.8 (6.0)
Lives with one parent or others	126	11.7 (6.8)	101.7 (16.2)	30.3 (7.0)	19.4 (6.1)
Birth order	564				
First child	210	11.9 (6.7)	104.8 (16.2)	31.4 (7.9)	20.1 (6.3)
Second + child	354	11.2 (5.7)	102.4 (15.5)	31.2 (7.2)	19.5 (5.9)
Crowding (people/room)[a]	571				
⩽1	279	10.5 (5.7)	107.1 (15.2)	32.7 (7.4)	20.0 (6.1)
>1	292	12.4 (6.3)**	99.6 (15.5)	30.0 (7.2)	19.4 (6.0)
House ownership status	571				
Own a house	213	12.2 (6.8)	102.6 (15.3)	31.0 (7.6)	19.5 (5.9)
Do not own a house	358	11.0 (5.6)*	103.7 (16.0)	31.5 (7.4)	19.8 (6.1)
Arsenic (μg/L)[a]	583				
<100	525	11.2 (6.0)	104.1 (15.3)	31.7 (7.4)	20.0 (6.0)
⩾100	58	13.8 (6.4)**	97.4 (16.8)	28.4 (7.6)	17.4 (6.1)

Note: MAT—Math achievement test; PPVT—Peabody picture vocabulary test.
[a]Variable used as continuous in regression analysis; different from comparison group at $^{*}P<0.05$, $^{**}P<0.01$.

appliances or amenities: car, computer, VCR, TV set, stove, refrigerator, radio, and electricity. All homes had electricity and very few were without a radio, TV, stove, or refrigerator, making possession of these items uninformative. Sufficient variability was present for ownership of an automobile, computer, or VCR. Parents' answers to questions about the three items were grouped in the following manner: 0 indicated no items owned; 1 indicated ownership of one item, or two items for the combination video + computer or video + automobile. A score of 2 indicated ownership of all three items or the combination computer + automobile.

Hb was analyzed immediately following the blood draw using the Hemocue Photometer (Hemocue AB, Angelholm, Sweden). Arsenic exposure from potable water is a concern in this population and was measured here because of its potential adverse effects on cognitive functioning in children. Total urine arsenic was analyzed in samples (digested with nitric, sulfuric, and perchloric acids) by atomic absorption spectrophotometry (Del Razo et al., 1997). A Perkin Elmer 3100 spectrophotometer was used (Perkin Elmer Corporation, Norwalk, CT) with detection limit 1 ppb and CV of 4–5%.

Parents also provided information on whether their children were born prematurely, whether they were breastfed, and for how long (months). These variables were not included in regression models for three reasons: (1) the information was collected at a posttreatment evaluation with many children ($n = 87$) missing data on these variables; (2) these variables were not significantly associated with cognitive outcomes in bivariate analysis; and (3) based on changes in adjusted R^2, when entered into complete models these variables explained no additional variability in cognitive performance.

2.5. Statistical methods

Analyses were performed using STATA 6.0 (STATA Corp., College Station, TX). Only children aged less than 8 years were included in the analysis ($n = 594$). In the Mexican public school system all children aged 6–7 years are eligible to be enrolled in the first grade. There are no school readiness exams. It is likely that children older than 8 years were held back because of poor academic achievement or behavioral problems. Therefore, we removed all 8-year-olds from analysis ($n = 9$). We had complete data on 532 children.

The analysis was first conducted using unadjusted and adjusted linear regressions with the cognitive measures as dependent variables and lead as independent variable, untransformed and continuous. Quadratic terms for lead were tested and were not significant. Subsequent analyses focusing on the nonlinearity of the PbB–cognition outcome also used linear models, but they included an interaction term between the continuous lead variable and one of four dichotomous lead variables that represented four cutoffs for defining lower vs. higher exposure levels. These regressions yielded estimates of models with two nonintersecting lines. A significant interaction term indicated differing slopes for the two lines. Based on previous examination of scatter plots of lead and cognitive function with LOWESS smoothed lines (Hamilton, 1998), the four cutoff points were chosen at 8, 10, 12, and 14 μg/dL. For each cognitive outcome, models for all four cutoff values were estimated first in unadjusted analyses. For some of the outcomes, multiple cutoffs yielded significant interactions. For simplicity of presentation we report only one model for each outcome, either because it had a significant interaction term or because it had the highest adjusted R^2 of all the models tested for that outcome. Because in our approach we first explored multiple cutoffs and reported the "best" cutoff, we likely optimized the probability of significant findings. Adjusted segmented regressions for each cognitive outcome were modeled using the cutoffs reported for the unadjusted model. Regression diagnostics were performed on all models and did not reveal any deviations from assumptions. We did not adjust the P-values for multiple tests on the data set.

3. Results

3.1. Linear regressions

When estimated in unadjusted linear models, 8 of 13 outcomes were significantly associated with children's PbB (Table 3). Higher PbBs were associated with worse test performance. However, the estimated declines were small to modest and lead alone explained a small portion of variability in test scores (data not shown, 0.4–4.8%). Adjusting for covariates attenuated the estimates and only three outcomes (Math, PPVT, and Sternberg Memory test) remained significantly associated with PbB ($P < 0.05$). In this sample, a 10-μg/dL change in PbB was associated in adjusted linear models with a mean 1.7-, 3.5-, and 0.5-point decline in Math, PPVT, and Sternberg performance, respectively. For Figure Matching and CAT Stimulus Discrimination task errors, the adjusted coefficients were marginally significant ($P < 0.1$).

3.2. Indication of nonlinearity

Lowess-smoothed scatterplots of selected cognitive outcomes against lead suggest nonlinearity in these relationships (Fig. 1). The plots suggest that the slopes of these curves are steeper at lower than at higher PbB. In addition, the slopes appear negative at PbB values

Table 3
Change in select cognitive outcomes for every 1 μg/dL increase in blood lead

Test	Unadjusted analysis			Adjusted analysis[c]		
	B or OR[a]	95% CI	Adj-R^2	B or OR[b]	95% CI	Adj-R^2
Linear regressions						
Math	−0.24***	−0.34, −0.14	2.9	−0.17***	−0.28, −0.06	23.4
PPVT	−0.45***	−0.66, −0.24	9.4	−0.36***	−0.58, −0.13	23.6
Freedom from distractibility factor	−0.32***	−0.54, −0.10	3.7	−0.18	−0.42, 0.06	19.2
Sequencing	−0.07**	−0.13, −0.01	2.3	−0.05	−0.12, 0.01	12.6
Sternberg	−0.08***	−0.12, −0.04	5.5	−0.05**	−0.10, −0.01	13.4
Figure matching	−0.09***	−0.15, −0.04	3.4	−0.05*	−0.11, 0.002	14.0
Figure design	−0.10**	−0.18, −0.01	0.8	−0.07	−0.16, 0.03	12.2
Visual search—correct	−0.01	−0.11, 0.08	2.6	−0.01	−0.12, 0.10	11.1
CAT mean decision time[d]	0.01	−0.02, 0.03	5.4	−0.001	−0.02, 0.03	13.0
Logistic regressions						
Visual search errors (<5 vs. ⩾5)	1.02	0.99, 1.05	4.3	1.01	0.98, 1.05	11.9
Stimulus discrimination correct (<20 vs. 20)	0.98	0.95, 1.01	2.6	1.00	0.96, 1.04	10.3
Visual memory span correct (<10 vs. ⩾10)	0.99	0.95, 1.02	0.7	0.98	0.93, 1.03	9.6
CAT number of errors (0 vs. any errors)	1.04**	1.003, 1.08	1.5	1.04*	0.99, 1.08	4.8

[a]Linear lead coefficient or OR based on 582 children, adjusted for tester administering cognitive tasks.
[b]Linear lead coefficient or OR based on 532 children.
[c]Adjusted for gender, age, hemoglobin, family possessions, forgetting homework, house ownership, crowding, maternal education, birth order, family structure, arsenic exposure, tester, and school.
[d]Decision time corrected for outliers.
*$P<0.1$.
**$P<0.05$.
***$P<0.01$.

below about 10–15 μg/dL, above which they tend to plateau. This apparent change in slope suggests that linear models may not adequately explain the variability in cognitive performance along the entire continuum of blood lead concentrations in this sample. If the true model is nonlinear, as suggested by some reports, then linear models will underestimate the slope at lower lead values and overestimate it at higher lead values.

3.3. Segmented regressions

To examine more closely the nature of the lead–cognition association, segmented regressions were used to estimate parameters and test for differences in slope values above and below selected PbB levels (8, 10, 12, and 14 μg/dL). Fig. 2 shows fitted values for PPVT and Math Achievement Test modeled using two-segment regressions. The slopes describing the association of PbB with PPVT and Math below a cutoff of 12 and 10 μg/dL, respectively, are steeper than slopes above those cutoff points.

Table 4 shows slopes and odds ratios in unadjusted regressions for the cutoffs that generated the largest adjusted R^2. For nine of the outcomes, the estimates of the relationship between lead and cognitive performance below and above the cutoff were significantly different or tended towards significance (the interaction term created at the reported cutoff had a $P<0.10$). While it is the significance of the interaction term that determines whether the two slopes below and above a given cutoff are significantly different from each other, the pattern of differences between coefficients across various cognitive outcomes in our sample is also of interest. At lower (B1 or OR1) lead concentrations, the associations between lead and cognitive outcomes were consistently stronger and more negative than at higher PbBs (B2 or OR2). For linear estimates, B1 was at least 3.9 times higher than B2. Furthermore, with the exception of Math and Sternberg Memory task, the associations at higher PbBs were not different from 0 and similar in magnitude to the coefficients in Table 3. The pattern of steeper coefficients at lower lead values was preserved in models adjusted for covariates (Table 5), although the associations were attenuated and only the B1 coefficient for Figure Design was statistically significant ($P<0.05$). The coefficient for PPVT at PbB < 12 μg/dL tended toward significance ($P<0.1$).

3.4. Segmented regressions stratified by covariates

The previous analyses assumed that the effect of any given covariate on the association between PbB and cognitive performance does not differ at low and high exposures. To test this assumption and to explore segmented lead coefficients at various levels of covariates, a stratified analysis was conducted for three of the covariates: socioeconomic status, maternal education, and forgetting homework. Solely for the stratified analysis, two of the covariates were recalculated to form two-level variables: family economic status was expressed as either 0 or any luxury items, and forgetting homework was collapsed into never or ever.

Subsequently, spline regressions were modeled in each stratum and the pattern of lead coefficients at low and high lead levels was compared (Table 6 shows coefficients for PPVT and Figure Design). All regressions were adjusted for the tester who administered the tasks. The pattern of steeper estimates at low PbBs vs. higher PbBs was generally conserved in stratified analysis. Moreover, it is for the children who already tend to be at risk for poorer performance (fewer family resources, lower maternal education, low parental involvement in school work) that the nonlinear relationship is most pronounced. In these children the interaction terms at the given cutoffs were highly statistically significant.

4. Discussion

Our report shows that children's performance on cognitive tasks is inversely associated with their concurrent blood lead level, but the relation between

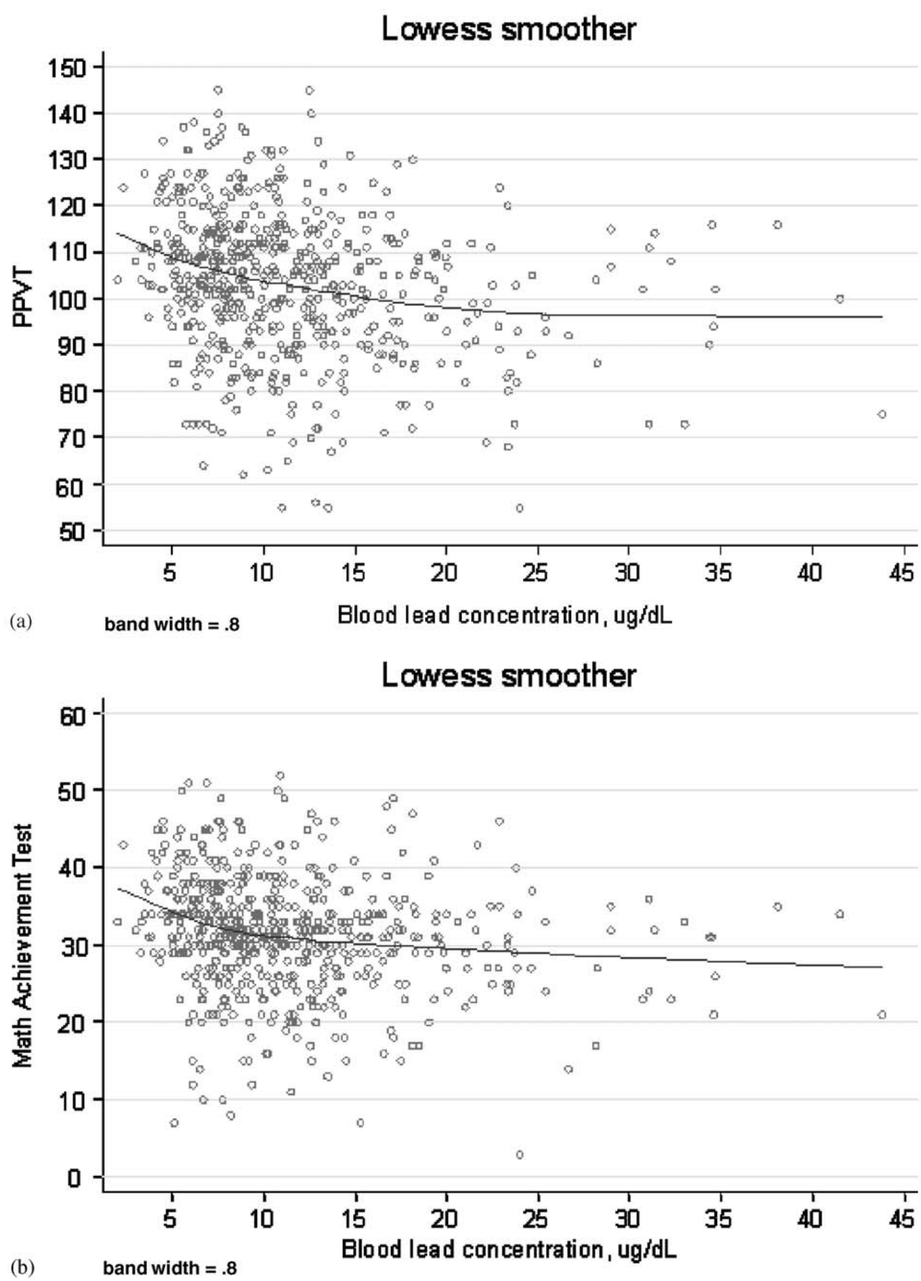


Fig. 1. LOWESS-smoothed plots of cognitive performance and PbB, unadjusted, $n = 582$.

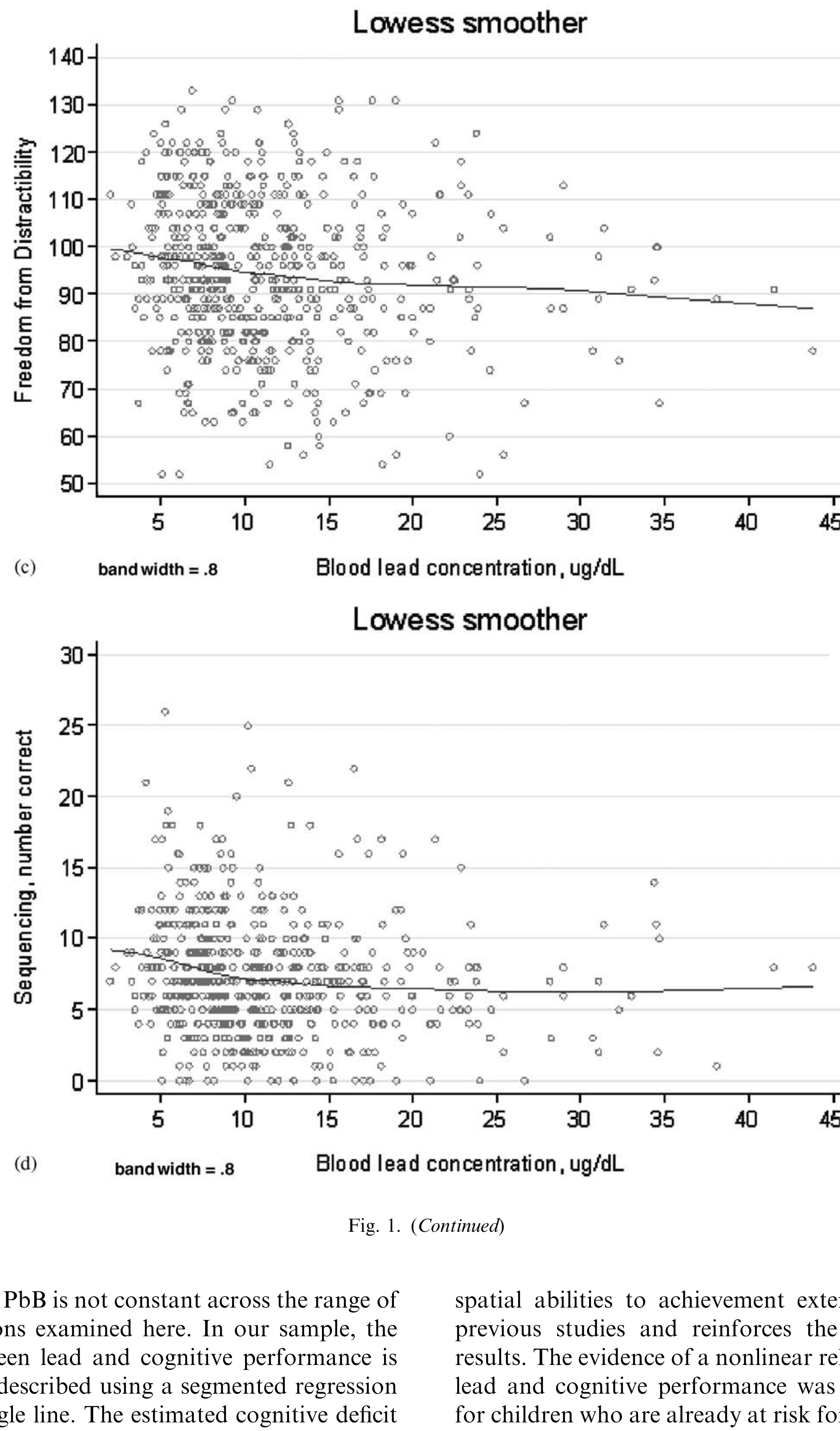
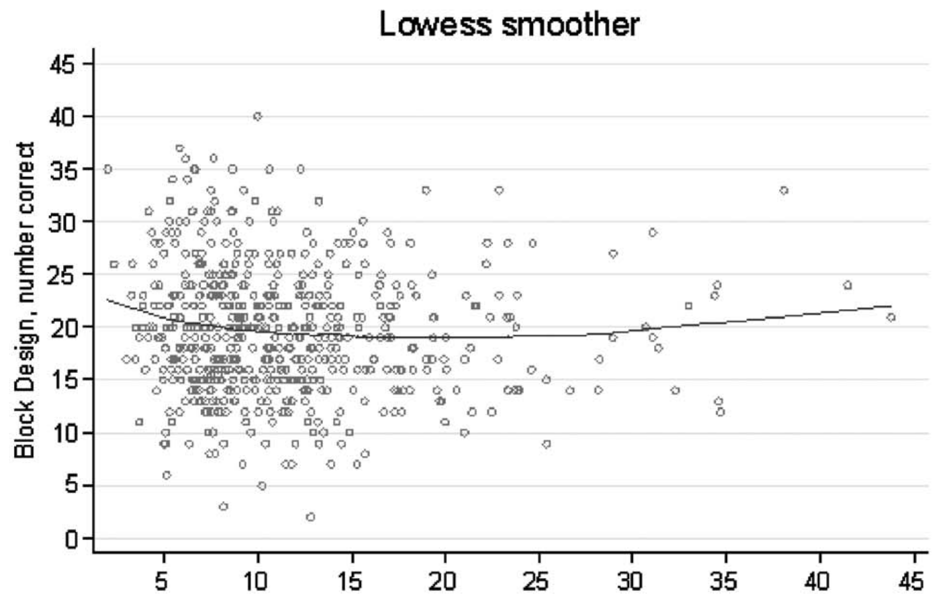
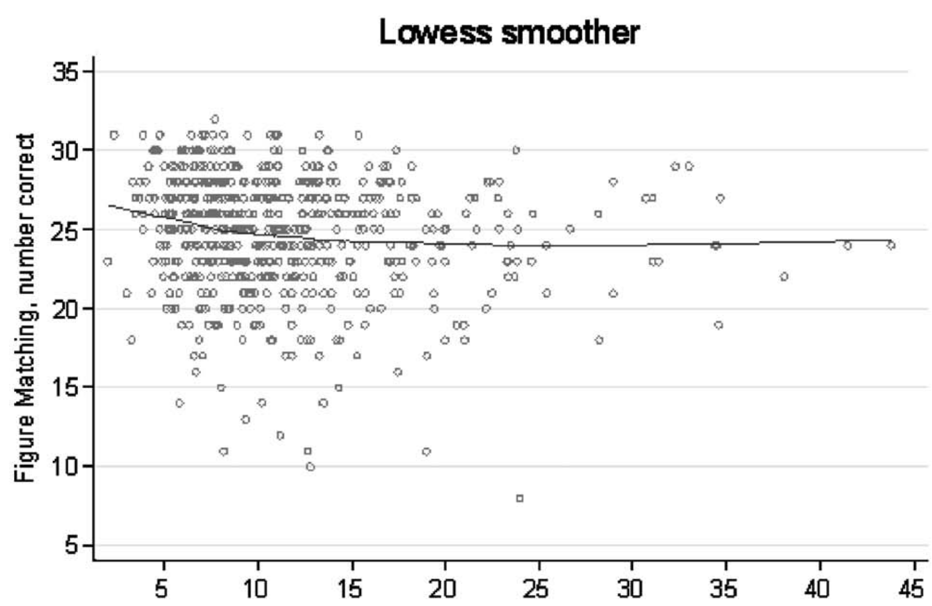


Fig. 1. (*Continued*)

performance and PbB is not constant across the range of lead concentrations examined here. In our sample, the association between lead and cognitive performance is more accurately described using a segmented regression model than a single line. The estimated cognitive deficit for each 1 μg/dL increase in the PbB of this population was greater across the range of PbB <10–14 μg/dL, than above this range. Previous studies also showed associations between lead <10 μg/dL and tests of IQ or achievement. The pattern of greater deficits at lower PbB observed in our study for tasks ranging from visual spatial abilities to achievement extends findings from previous studies and reinforces the validity of these results. The evidence of a nonlinear relationship between lead and cognitive performance was most pronounced for children who are already at risk for cognitive deficits. For the two outcomes we presented in stratified analysis (PPVT and Figure Design), the interaction terms for the given cutoffs were significant among children whose families had fewer resources, whose mothers did not complete high school, and whose parents were less involved in their children's school work.



(e) band width = .8



(f) band width = .8

Fig. 1. (*Continued*)

One caveat to our approach of investigating multiple cutoffs and reporting findings on multiple outcomes is that a large number of statistical manipulations of the same data may yield significant findings. We did not adjust for this in our analysis, and while this general caution needs be voiced, we believe that our results do represent one more piece of valid evidence that the relationship between lead and cognitive performance is nonlinear.

For each outcome we reported a single PbB, for which the slope of the lead–cognition association was steeper at levels less than, as compared to greater than, that particular value. It would be misleading, however, to conclude that they represent a unique cutoff, at which the nature of the lead–cognition relation changes. For ease of illustration we presented segmented regressions only for a single model—one based on the lead cutoff that yielded the highest R^2. However, neighboring PbB values resulted in similar slopes, so using R^2 was an arbitrary criterion. For certain outcomes, such as Math, PPVT, Sequencing, Figure Matching, and others, we found that several cutoffs between 10 and 14 μg/dL

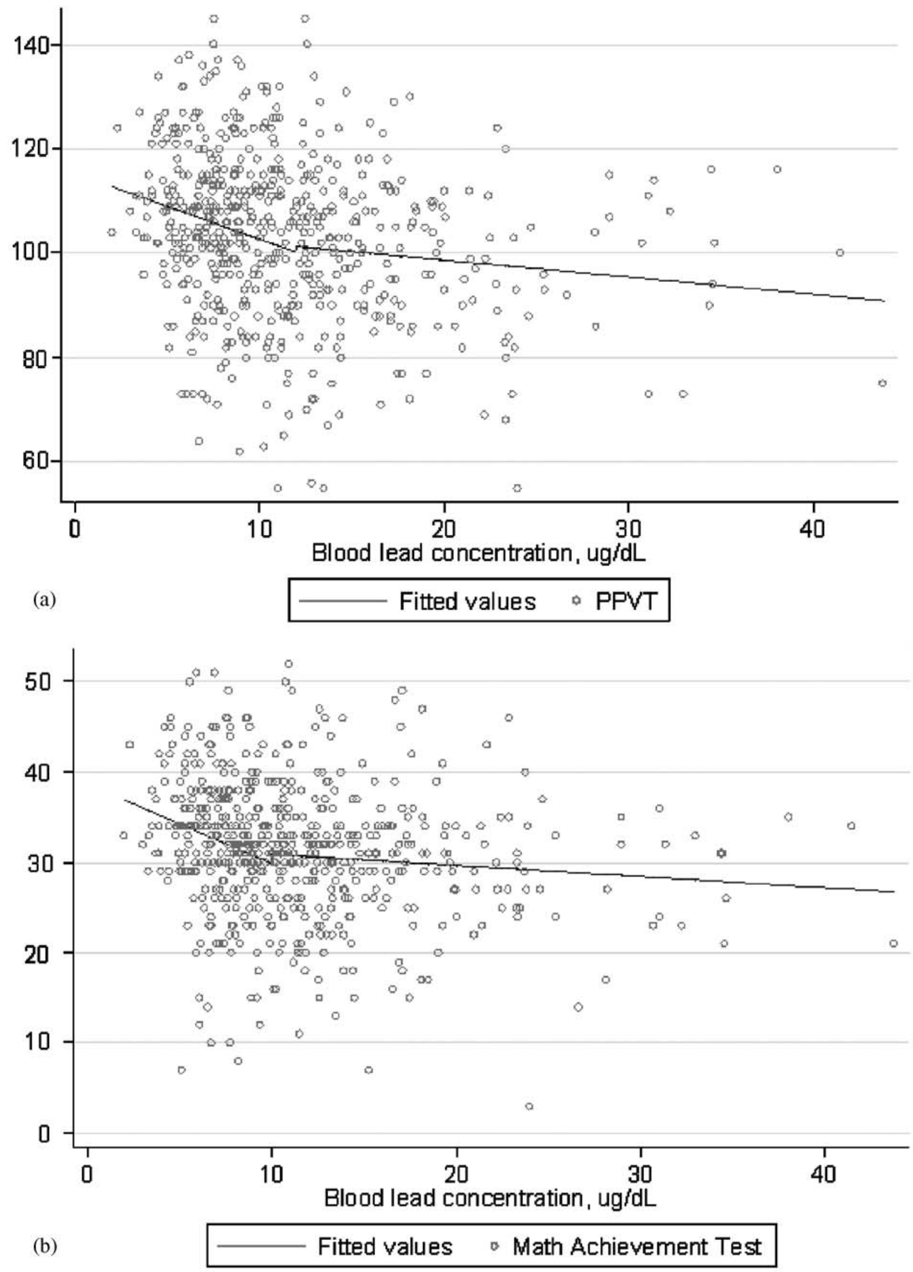


Fig. 2. Unadjusted performance on PPVT and Math as a function of PbB described by segmented regression models, $n = 582$.

yielded significantly different slopes. Furthermore, measurement errors in cognitive performance and lead concentrations, as well as individual differences in exposure characteristics (timing and dose) and performance may contribute to the existence of multiple cutoffs.

There are many examples of nonlinear dose–effect curves in toxicology and medicine (Calabrese and Baldwin, 2001). The initial damage caused by lead may reflect the disruption of different biological mechanisms than the more severe effects of high exposures that result in encephalopathy or frank mental disability. This might explain why, within the range of exposures not producing overt clinical effects, an increase in PbB beyond a certain level might cause little *additional* impairment in children's cognitive functioning. Even in the absence of an understanding of mechanisms, these findings, together with results from other studies, suggest the need to broaden our perspective on childhood lead poisoning to include children with lead concentrations below the current CDC level of concern. According to current practice these children are monitored and interventions are recommended only when their PbBs are above 10 μg/dL, although medical

Table 4
Unadjusted change in cognitive performance for every 1 μg/dL increase in blood lead for low and high lead exposure

Test	C[a]	B1 or OR1[b]	95% CI	B2 or OR2[c]	95% CI	Adj-R^2
Linear regressions						
Math	10[d]	−0.90***	−1.41, −0.38	−0.14*	−0.29, 0.002	4.0
PPVT	12[d]	−1.07***	−1.78, −0.37	−0.27	−0.62, 0.07	9.7
Freedom from distractibility factor	12[e]	−0.95**	−1.69, −0.20	−0.24	−0.60, 0.12	3.9
Sequencing	10[d]	−0.32**	−0.61, −0.03	−0.01	−0.09, 0.07	3.1
Sternberg	10[e]	−0.26**	−0.46, −0.06	−0.06**	−0.12, −0.01	5.8
Figure matching	10[d]	−0.35**	−0.60, −0.10	−0.04	−0.12, 0.03	4.2
Figure design	12[d]	−0.42**	−0.70, −0.13	0.04	−0.10, 0.17	2.0
Visual search correct	10	−0.36	−0.86, 0.14	−0.06	−0.20, 0.08	2.8
CAT mean decision time[f]	10[e]	0.10*	−0.02, 0.21	−0.01	−0.04, 0.03	5.6
Logistic regressions						
Visual search errors (<5 vs. ⩾5)	10[d]	1.18**	1.02, 1.37	1.00	0.95, 1.04	5.0
Stimulus discrimination correct (<20 vs. 20)	8	0.83	0.64, 1.07	0.98	0.94, 1.02	2.9
Visual memory span correct (<10 vs. ⩾10)	10	0.87	0.73, 1.03	1.01	0.96, 1.06	1.2
CAT number of errors (0 vs. any errors)	14	1.06	0.98, 1.15	0.98	0.91, 1.05	2.1

[a]Cutoff point.
[b]Regression coefficient or Odds Ratio below the PbB cutoff, adjusted for tester administering cognitive tasks.
[c]Regression coefficient or Odds Ratio above and including the PbB cutoff, adjusted for tester administering cognitive tasks.
[d]Slopes of lines below and above cutoff different at $P<0.05$.
[e]Slopes of lines below and above cutoff different at $P<0.1$.
[f]Stimulus discrimination task, decision time corrected for outliers.
*$P<0.1$.
**$P<0.05$.
***$P<0.01$.

Table 5
Adjusted change in cognitive performance for every 1 μg/dL increase in blood lead at low and high lead exposure

Test	C[a]	B1 or OR1[b,c]	95% CI	B2 or OR2[c,d]	95% CI	Adj-R^2
Linear regressions						
Math	10	−0.42	−0.92, 0.08	−0.11	−0.26, 0.03	23.4
PPVT	12	−0.71*	−1.43, 0.02	−0.28	−0.62, 0.06	23.4
Freedom from distractibility factor	12	−0.40	−1.17, 0.37	−0.20	−0.57, 0.16	19.0
Sequencing	10	−0.20	−0.50, 0.10	−0.01	−0.10, 0.07	12.7
Sternberg	10	−0.16	−0.37, 0.05	−0.04	−0.10, 0.02	13.3
Figure matching	10	−0.20	−0.47, 0.06	−0.01	−0.09, 0.06	14.2
Figure design	12[e]	−0.31**	−0.62, −0.01	−0.01	−0.15, 0.14	12.4
Visual search correct	10	−0.01	−0.52, 0.51	−0.07	−0.22, 0.07	11.0
CAT mean decision time[f]	10	0.05	−0.07, 0.17	−0.01	−0.05, 0.02	13.0
Logistic regressions						
Visual search errors (<5 vs. ⩾5)	10	1.09*	0.92, 1.28	1.0	0.96, 1.05	12.0
Stimulus discrimination correct (<20 vs. 20)	8	0.85	0.63, 1.13	1.00	0.95, 1.04	10.5
Visual memory span correct (<10 vs. ⩾10)	10	0.90	0.74, 1.10	0.98	0.92, 1.05	9.7
CAT number of errors (0 vs. any errors)	14	1.06	0.96, 1.17	0.97	0.90, 1.05	5.4

*$P<0.1$; **$P<0.05$; ***$P<0.01$.
[a]Cutoff point.
[b]Regression coefficient or Odds Ratio below the PbB cutoff.
[c]Adjusted for child's gender, age and hemoglobin, possession of household items, home ownership, crowding, maternal education, birth order, frequency of forgetting homework, family structure, arsenic, tester, and school.
[d]Regression coefficient or Odds Ratio at or below the PbB cutoff.
[e]Slopes of lines below and above cutoff different at $P<0.1$.
[f]Decision time corrected for outliers.

Table 6
The relation between low and high PbB and performance on PPVT and Figure Design, stratified by family possessions, maternal education, and forgetting homework

Stratified covariate	N	B1 or OR1[a]	95% CI	B2 or OR2[b]	95% CI	Interaction P-value
PPVT[c]						
No luxury items	121	−1.61**	−3.21, −0.01	0.01	−0.69, 0.72	0.07
Any luxury items	445	−0.84**	−1.64, −0.03	−0.39*	−0.80, 0.01	0.33
< HS education	308	−0.97*	−1.99, 0.04	−0.20	−0.60, 0.19	0.16
⩾HS education	252	−1.18**	−2.19, −0.16	−0.22	−0.91, 0.48	0.12
Never forgets homework	208	−0.33	−1.35, 0.69	−0.57	−1.25, 0.12	0.70
Does forget homework	364	−1.26***	−2.20, −0.33	−0.12	−0.51, 0.27	0.02
Figure design						
No luxury items	121	−0.58*	−1.20, 0.05	0.28**	0.002, 0.55	0.01
Any luxury items	445	−0.34**	−0.66, −0.01	−0.07	−0.24, 0.09	0.15
< HS education	308	−0.49**	−0.89, −0.10	0.06	−0.09, 0.21	0.01
⩾ HS education	252	−0.35	−0.79, 0.09	0.04	−0.26, 0.34	0.14
Never forgets homework	208	−0.24	−0.70, 0.21	0.03	−0.27, 0.34	0.32
Does forget homework	369	−0.43**	−0.80, −0.06	0.04	−0.11, 0.20	0.02

[a]Regression coefficient or Odds Ratio below the PbB cutoff, adjusted for tester administering cognitive tasks.
[b]Regression coefficient or Odds Ratio at or above the PbB cutoff, adjusted for tester administering the cognitive tasks.
[c]PPVT—Peabody picture vocabulary test.
*$P<0.1$.
**$P<0.05$.
***$P<0.01$.

treatment does not begin until PbBs reach at least 35 μg/dL. Because the amount of cognitive impairment per unit increase in PbB appears larger at lower PbB, not only will children benefit from preventing any increase in lead, but perhaps there will be greater return on investments in interventions if the goal is to reduce PbB to the lowest level possible.

The idea of stronger lead effects at lower PbBs may be counterintuitive, but our findings are in agreement with recent studies (Canfield et al., 2003; Chiodo et al., 2004; Lanphear et al., 2000) and with a reanalysis of earlier research (Bellinger and Needleman, 2003), although the magnitude of lead's impact on cognition is smaller in our study. However, many cohort-specific variables may influence the magnitude of the lead–cognition association, without diminishing the inferences that can be drawn from the data (Bellinger,1995). In our study, as in others (Canfield et al., 2003), more important than the magnitude of the association may be the fact that regression coefficients from a model including the entire range of lead values are less steep than the coefficients at low lead concentrations. While the consistency of these reports is not a substitute for a plausible biological mechanism, it should motivate inquiries of such phenomena in animal models. One note of caution for interpreting these results is that in a cross-sectional study we cannot speak of rates of decline in cognitive performance in an individual. These inferences can be applied to a population at one point in time. Although it appears that in a group of children with low PbBs the slope of association between cognitive performance and PbB is steeper than in children with higher PbBs, the intercepts are different. Children with low PbBs start at a higher ability level than children with higher PbBs, so it is still the children with higher PbBs who have a greater deficit in absolute terms. What is important about the present findings is that even low PbBs are associated with poor performance and that traditional ways of evaluating lead effects on cognition (linear models) likely underestimate the problem in children with low PbBs. As our findings show, such underestimation would be especially grave for children who already have other risk factors for poor cognitive performance, such as low economic resources, lower maternal education, or less parental involvement in schooling. For those children, we found very strong evidence of nonlinearity in the lead–cognition relationship.

Although a direct comparison between present findings and the results of previous prospective studies is limited because our lead samples were collected concurrently to the administration of cognitive tests, this study has public health relevance. Some children have their blood lead levels screened only once or infrequently during childhood. According to current action guidelines, a PbB only slightly <10 μg/dL is considered acceptable and the child would not be referred for additional testing. Our findings suggest, however, that additional testing and intervention may be warranted.

One limitation of our approach is lack of information on the exposure history for the cohort, which could result in biased estimates. For example, a possibility of censoring exists if children who had high PbBs at younger ages are underrepresented in our sample because they were more likely to move away from the study area or because they represent such a low level of mental abilities that they had to be enrolled in remedial classrooms. We have information, however, that leads us to believe that our sample represents a wide range of both abilities and previous exposures. In the public education system in Torreón, special education schools or classrooms are not common; nor is school readiness testing provided to identify children at risk. Children of all ability levels attend the same school. To reduce the likelihood that the present analysis included children retained in first grade from previous years, all children aged 8 years or more were excluded. Furthermore, in this geographic area, where many adults are employed by the ailing garment industry, families are likely to move away for financial reasons, not because of lead exposure.

Previous PbBs (taken at 5 years of age) were available for a subsample of our study children ($n = 116$). The geometric mean PbB for this group was 16.6 μg/dL (range 2–65.7), with only 11% <10 μg/dL. Though incomplete, this information suggests the history of exposure in our sample to be similar to the Port Pirie cohort, where 7-year PbBs were highly correlated with average lifetime PbB. Similarly, we expect our 7-year PbBs to reflect lifetime lead exposures, although absolute levels were likely greater at younger ages. Thus, we can say with some degree of confidence that the majority, if not all, of our study subjects had PbB >10 μg/dL at some point in their lives, and that their concurrent PbB measured at 7 years of age represents a decline from peak levels. Canfield et al. (2003) found the magnitude of the adjusted associations between Pb and 5-year IQ to be similar for the concurrent and the lifetime average PbB. Finally, a recent study showed that lead exposure concurrent to cognitive testing of primary school children makes a substantial and significant contribution to performance, independent of exposures at earlier ages (Chen et al., 2005).

Due to time and resource constraints, this study did not include some important covariates relating to cognitive performance, such as the HOME inventory or a maternal IQ. This study was part of a large placebo-controlled trial. The time frame of the trial and the large sample size, in addition to the wide range of cognitive tests administered to the study subjects, prevented us from concentrating on children's home environment or additional maternal measures. Although the absence of measures of maternal IQ and home environment has potentially serious implications for our findings, we believe the results reported here are still important for three reasons, detailed below.

First, while it is true that environmental variables are strongly correlated with tests of intelligence and achievement, they are only moderately related to reasoning ability scores and minimally related to spatial ability (Sattler, 1992). This suggests that adjustment for maternal IQ and home variables may be crucial for the PPVT, the Freedom from Distractibility factor and math achievement outcomes in our study, but marginally so for the spatial abilities tests. That the general pattern of performance indicative of steeper slopes at low PbBs compared to higher PbBs is similar in tests of achievement and spatial abilities, adds strength to our conclusions.

Second, other considerations are important in interpreting child cognitive performance. For example, (1) the home environment is likely not independent of family background characteristics, (2) the SES correlates at a level of 0.33 with child IQ scores, and (3) other characteristics of the home, such as parental involvement with their children, also explain variability in scores. In the present study, in addition to SES and parental education, we collected information from the teachers on the frequency with which children forget their homework. Parental involvement in schoolwork reflects an important aspect of parenting—monitoring children's academic progress, which has been shown to be a good proxy for the quality of children's home environment (Ginsburg and Bronstein, 1993). It may also serve as an indicator of drive for achievement parents instill in their children. We also included as covariates information not typically included in other lead studies: iron status, arsenic concentrations, and crowding. Iron status is associated with children's cognitive performance independently of lead exposure (Kordas et al., 2004; Wasserman et al., 1992), whereas crowding has been related to children's socioemotional adjustment (Evans et al., 2002). Finally, our aim was not to present definitive data on the differential relation between low vs. moderate lead exposure and cognitive performance. Rather, we wanted to provide additional points to the gathering pool of evidence and stimulate other research on this topic.

This study examined the nature of the relation between lead exposure and cognitive performance in school children. It revealed a consistent pattern of associations, with lower PbBs associated with steeper declines in performance than higher PbB. This pattern was observable after controlling for a range of covariates known to influence cognitive performance in children, and in different strata of variables describing family demographics. Furthermore, in unadjusted segmented analyses 9 of the 13 outcomes had significant or nearly significant interaction terms, suggesting that the slopes were statistically different from each other. These findings have important implications for lead prevention and treatment policies. Currently most practices concentrate on providing treatment to children with PbB >10 μg/dL. Perhaps a more effective approach would be to concentrate on prevention of *any* exposure because low-level PbBs are clearly damaging for child development and learning, especially in children already at risk for poorer outcomes.

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Appendix A. Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2005.07.007.

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