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Neurodevelopmental effects of postnatal lead exposure at very low levels☆

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Abstract

This study is among the first to examine specific neurobehavioral deficits in children exposed at very low lead levels. A systematic analysis for the presence of a threshold of lead exposure was conducted. The sample consisted of 246 African American, inner-city children from whom blood lead concentrations were assessed at 7.5 years of age. The results consistently show neurobehavioral deficits in relation to low levels of lead in the areas of intelligence, reaction time, visual–motor integration, fine motor skills, attention, including executive function, off-task behaviors, and teacher-reported withdrawn behaviors. Effects were identified in the specific domains of attention, executive function, visual–motor integration, social behavior, and motor skills, which have been previously suggested as part of lead's "behavioral signature". Visual inspection of nonparametric regression plots suggested a gradual linear dose–response relation for most endpoints. No threshold discontinuity was evident. Regression analyses in which lead exposure was dichotomized at 10 μg/dl were no more likely to be significant than analyses dichotomizing exposure at 5 μg/dl. Given that associations were found between lead levels as low as 3 μg/dl for multiple outcomes, these data provide additional evidence that there is no apparent lower bound threshold for postnatal lead exposure.

Keywords: Lead; Blood lead concentration; Threshold; Neurobehavioral development; Environmental contaminant; Nonparametric regression

1. Introduction

In 1995, the World Health Organization [72] reviewed the extensive literature on postnatal lead exposure and children's neurobehavioral development and determined that the effects of lead are credible and persistent, and there appears to be no safe threshold for lead exposure. Bellinger, Dietrich, and others have proposed that the principal endpoints affected by lead exposure ("behavioral signature") are attention, executive function, visual–motor reasoning skills, vestibular–proprioceptive control and social behavior, and Lanphear et al. have concluded that there is no safe threshold [46]. Thus, Lanphear et al. have reported significant associations where poorer cognitive performance was evident at exposure levels lower than 5 μg/dl. Despite these reports, most government agencies have continued to use 10 μg/dl as a criterion in public health advisories. For example, the U.S. Environmental Protection Agency [25] and the Center for Disease Control [14] recommend that lead levels above 10 μg/dl be avoided. As a result of extensive efforts to reduce lead levels in the environment, mean lead level in children has decreased from 15 μg/dl in the 1970s to 4 μg/dl in the 1990s [7]. Nevertheless, many children continue to be exposed above the recommended "avoid" level. For example, an assessment of Mexican-American children showed that approximately 5% of children of all ages still have lead levels above 10 μg/dl [57].

Because postnatal lead exposure is often associated with socioenvironmentally more disadvantaged homes, researchers have assessed a broad range of control variables in an attempt to distinguish the effects of lead exposure from other socioenvironmental influences. Confounding variables have been assessed so comprehensively that it has been argued that some studies have "overcontrolled" for the social environment, misattributing lead effects to the environment [3]. Even so, after controlling statistically for these confounding effects, most studies continue to find associations of lead exposure with IQ [9,21,30,46,49,66] and visual–motor integration [19,30,31]. Significant associa-

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tions have also been reported in the areas of achievement, including reading [27,29,55,75], math, and spelling [9,11,28,75]. Postnatal lead exposure has also been found to be associated with deficits in motor skills (specifically, speed and dexterity), memory abilities, advanced spatial functions and attention [20,26], and slower reaction times in laboratory assessments [51,55,73,74].

Attention is one domain that has been examined in particular detail [10,11,31,46,63,76]. Bellinger et al. [10] attempted to identify the specific aspects of attention that are affected by exposure to lead. Using a middle-class sample whose mean blood lead levels were reported as low (79.2% of the sample was below 5 μg/dl), Bellinger et al. administered Mirsky's attention battery, which assesses sustained attention, focused attention, shift (executive function), and encoding (working memory). Significant associations were found solely in the domains of focus and executive function.

In the past few years, increased attention has been directed to examining behavior problems in lead exposed children. Byers and Lord [12] had noted that heavily exposed children are distractible, impulsive, and aggressive. More recently, antisocial, delinquent, and aggressive behaviors have also been reported in children exposed to low levels of lead [11,23,56], even in very young children. In a study of 1- to 3-year-olds, whose mean lead level was 10.4 μg/dl, Mendelsohn et al. [50] found that children exposed to lead had more difficulties with emotional regulation and behavior orientation. These children were more hyperactive, impulsive, and easily frustrated, more withdrawn and lacking in interest.

Although lead exposure has been linked to a broad range of neurobehavioral endpoints, the domains affected are not always consistent across studies. Faust and Brown [26] did not find consistent results on the Achenbach's Child Behavior Checklist (CBCL [1]), the measure used to identify aggressive and delinquent children in the studies cited previously. Silva et al. [63] found no association with intelligence. Needleman et al. [56] found no relation with reaction time and found associations only in the vigilance domain, but not the focused and executive function factors on Mirsky's attention battery reported by Bellinger et al. [10].

Our study examined postnatal lead exposure in a sample of children with very low levels of exposure (mean = 5.4 μg/dl). The levels are markedly lower than in earlier low-level lead studies [e.g., Bellinger et al. [10] (mean = 10 μg/dl); Dietrich et al. [20] (mean = 11.8 μg/dl, for similar-aged children); McMichael et al. [48] (mean = 19 μg/dl); Winneke et al. [74] (mean = 8.2 μg/dl)] and slightly lower than some of the more recent studies of very low postnatal lead exposure [Bellinger et al. [9] (mean = 6.5 μg/dl); Fergusson et al. [28] (mean = 6.2 μg/dl)]. To date, only one study has reported levels lower than those presented in this research [Lanphear et al. [46] (geometric mean = 1.9 μg/dl)]. In our study, we examined the specific domains where deficits have been previously identified to determine similarities and differences compared with the findings reported in previous studies. In addition, we attempted to identify a lower bound threshold for lead exposure, using nonparametric regression, in several cognitive and behavioral domains where the effects of lead have been shown to be harmful.

2. Methods

2.1. Sample

The sample consisted of 237 African American, inner-city children for whom blood lead levels were obtained while they were participating in a larger study ($N = 337$) on the effects of prenatal alcohol exposure on child development [37–40]. Their mothers had been recruited at their first visit (mean = 23.4 weeks of gestation, S.D. = 8.2) to the prenatal clinic of a large, inner-city maternity hospital serving primarily (92%) African American women. Each mother was interviewed regarding her alcohol consumption during the 2 weeks preceding the clinic visit and retrospectively at conception, using an interview designed by Sokol et al. [64] and recently described in Jacobson et al. [40]. All women reporting alcohol consumption at conception averaging at least 0.5 oz absolute alcohol/day (AA/day) at conception (the equivalent of about one standard drink per day) and a random sample of approximately 5% of the lower-level drinkers and abstainers were invited to participate in the study. To reduce the risk that alcohol would be confounded with cocaine exposure, which was prevalent in that population at that time, a subsample of women were recruited who were heavy users of cocaine (at least 2 days/week) and consumed low levels of alcohol (< 0.5 oz AA/day). Infant exclusionary criteria were birthweight less than 1500 g, gestational age less than 32 weeks, major chromosomal anomalies or neural tube defects, and multiple births.

Venous blood samples were obtained at the 7.5-year assessment by one of three phlebotomists from a nearby children's hospital. Blood lead concentration was measured by graphite furnace atomic absorption spectrometry by Varian AA-400. Both internal and external quality control programs were utilized. In the internal quality control program, three levels of whole blood with known concentration of lead level were included in each batch of specimens. If the results of the control samples were not within the specified range, the analyses were repeated. In addition, every month, a three-level precision study was performed to assure the accuracy of the instrumentation. Multiple external quality control programs were also utilized, including monthly participation in the Quebec Interlaboratory Comparison Program. The limit of detection used was 2 μg/dl.

Of the 337 children assessed in the larger alcohol study at 7.5 years, lead was not available for 91 children. Of these, 45 refused the blood draw; there was no phlebotomist available for 35 of the children; there were difficulties in collection for 10 of the children; and the data were lost for 1 child. Among the 246 children for whom blood lead assessments were obtained, 9 were excluded from the analyses reported here due to heavy prenatal exposure to alcohol. Three of these children were diagnosed with fetal alcohol syndrome (FAS), and six were very heavily exposed (mean ≥ 2 oz AA/day or the equivalent of ≥ 4 drinks/day). Mean lead levels for these nine children were not different from those of the rest of the children in the sample [mean ± S.D. = 4.4 ± 3.1 μg/dl vs. 5.4 ± 3.3 μg/dl, respectively; $t(244) = 0.82$, n.s.]. Among the 237 children whose data are reported here, 11 were heavily exposed (1.00 to 1.99 oz AA/day), 21 moderately exposed (0.50 to 0.99 oz AA/day), 165 exposed at low levels (0.01 to 0.49 oz/day), and 40 children were not exposed to alcohol.

2.2. Procedure

2.2.1. Neurobehavioral assessments

Children and their mothers were transported to our laboratory by a community-based staff driver for a neurobehavioral assessment at 7.5 years of age. Examiners were blind to lead and other drug exposures, including alcohol. This assessment included the Wechsler Intelligence Scales for Children-III (WISC-III; [70]), which is a standard intelligence measure that has been used extensively in previous research examining lead exposure (e.g., Refs. [9,30,46,49,66]).

Following Mirsky et al. [52], four domains of attention were examined: "sustained attention", the ability to maintain focus and alertness over time; "focused attention", the ability to maintain attention in the presence of distraction; "shift" or executive function, the ability to alter a mental set in response to feedback, as well as the ability to plan and monitor one's ongoing activities, and "encoding" or working memory, assessed in terms of the amount of information and length of time information can be kept "on-line". Sustained attention was measured using a Continuous Performance Test (CPT; [58]). In this task, a series of letters is presented sequentially on an LCD display. The child presses a button whenever a designated target stimulus appears. In the "X task", the target is the letter X; in the "AX task", it is the letter X only if immediately preceded by the letter A. In the auditory task, the child is told to press the button only in response to a high-pitched tone; low-, medium- and high-pitched tones are presented. These three tasks take about 20 min to administer.

The Talland Digit Cancellation [68] provided a measure of focused attention. In this task the child is asked to cross out all of the "3's" and "7's", as quickly as possible, on a page of single digits presented in a random order. The child is then asked to repeat the task while being distracted by hearing a random list of digits simultaneously read aloud on an audiotape. Number of errors of omission and errors of commission are recorded. Another measure of focused attention was provided by the Coding subscale from the WISC-III. In this task, the child copies simple symbols that are paired with numbers in a number–symbol key displayed at the top of the page. Next to each number, the child draws the symbol that corresponds to that number. There is a 120s time limit for this task.

Three measures of executive function were administered, the noncomputerized version of the Wisconsin Card Sorting Task (WCST; [32]), the Tower of London [61], and a Verbal Fluency task [47]. In the WCST, the child is asked to match each one of 128 cards presented in succession to one of four criterion cards with drawings that vary along three dimensions: color, form, and number. The child is not told the sorting criteria in advance but is told whether each sorting choice is correct. Once s/he sorts the cards according to a given criterion for 10 correct sequential trials, the "correct" criterion is switched; thus, challenging the child to "shift" criteria in response to feedback. The criterion is switched six times. The number of categories and perseverative errors, error percentile, and the number of conceptual level responses were assessed. Because children younger than 8 years of age (in this cohort) found the WCST too difficult, only children 8 years or older ($N = 48$) were included in the analyses.

In the Tower of London [61], the child is presented with a board containing three pegs that vary in height and three colored wooden beads. The child is instructed to arrange the beads according to a pattern displayed on a card within a certain number of moves. In order to make the task more understandable to younger children, we included the monkey cover story, which was used in the Tower of Hanoi studies conducted by Welsh et al. [71] with young children (also see Ref. [44]). Planning ability was assessed as the number of trials in which the child was able to sort the beads to match a given design within the given number of moves allowed. Each trial was weighted by problem difficulty. In the Verbal Fluency task from The McCarthy Scales of Children's Abilities [47], the child is asked to name as many items as possible within 20 s from each of the following categories: animals, things to eat, things to wear, and things to ride.

The Seashore Rhythm Test [60] provided a measure of auditory working memory. In this task, the child listens to pairs of tonal sequences and is asked to determine if the sequences are the same or different. Two other measures of working memory examined were the Arithmetic and Digit Span subscales from the WISC-III. In the Digit Span task, the child listens to a series of increasingly longer sequences of single numbers repeating each sequence in the same order as it was presented. This procedure is then repeated, and this time the child is asked to recite the sequence in reverse order to the one presented.

Five measures of information-processing speed were administered: the Sternberg Short-Term Memory task [65], a Mental Rotation task [42], two Magnitude Estimation tasks [43], and a color naming task. In the Sternberg Short-Term Memory task, each child is shown sets of one, three, or five digits on a computer screen and asked to study each set for 4 s. The child is then shown a single digit and asked to recall if the digit was among the set s/he just studied. The child is instructed to press the "yes" button on the computer if the digit was previously displayed and the "no" button, if it was not. Mean number correct was computed across 72 trials, and mean reaction time for correct responses was generated for the correct "yes" and "no" responses separately. In the Mental Rotation task, the child is shown a series of letters on a computer screen. Each of the letters is displayed either forwards or backwards (a mirror image) at one of the five angles from the vertical: 0°, 30°, 60°, 90°, or 120°. The child is asked to indicate if the letter is in a "forward" or "backward" (mirror image) presentation. Eight trials with each rotation were presented in random order. Again, mean number correct and mean reaction time for correct responses were assessed.

Two Magnitude Estimation [43] procedures were administered, a number task and an arrow task. In the number task, the child is asked to determine which of two single digits presented on a computer screen is larger. If the digit on the right is larger, the child is asked to press the arrow facing right; if the one on the left side is larger, the arrow facing left. This judgment is easier to make when the numerical difference between the two digits is larger (e.g., Refs. [1,10]), than when it is smaller (e.g., Refs. [4,5]). Mean reaction time decreases as the absolute difference between the digits increase. Mean number correct and mean reaction time for correct responses were measured. In the arrow task, two arrows are presented on a computer screen. One consists of a triple arrow (⋙); the other, a single arrow. The child is asked to indicate which side the triple arrow is pointing to. The distance between the two arrows varies. There are five levels of distance differences. In addition, there is a sixth presentation where the single arrow is omitted altogether. The difficulty increases when the two arrows are closer to each other on the computer screen. Mean number correct and mean reaction time for correct responses were measured.

In the color naming task, a series of color patches are displayed sequentially on a page. The child is asked to name as many of the colors, in the order presented on the page, as possible, in 45 s. If the child makes a mistake, s/he is asked to correct his/her response and continue.

Two verbal memory tasks were administered from the Wide Range Assessment of Memory and Learning (WRAML; [62]). In Verbal Learning, the examiner reads a 13-item word list four times, asking the child to repeat the list from memory after each presentation. After presentation of the Story Memory task, the child is again asked to recall the 13-item word list. In Story Memory, the examiner reads two stories to the child. The child is then asked to repeat each story immediately after hearing it and to recall both stories following a 35min delay.

The Grooved Pegboard Test [69] is a test that assesses complex visual–motor coordination. In this task, the child is asked to use his/her dominant hand to insert all of the pegs into the board, as quickly as possible; to place the pegs sequentially, row by row; and not to skip any holes on the board. Upon completion, s/he is asked to perform the same task with his/her nondominant hand. Time to complete each round and the number of pegs the child dropped were recorded.

The Corsi Test [16] is a visual–spatial analogue of Digit Span. In this task, the child is shown nine blocks glued to a board in an irregular array and asked to point to specific blocks in the order demonstrated by the examiner. Starting with two trials of two blocks each, the sequence increased to a maximum of nine blocks. In a second round, the child points to the blocks in the inverse order from that demonstrated. The Matching Familiar Figures Test [41] provides an assessment of processing efficiency in the context of visual scanning and analysis. In our adaptation of this test, the child is asked to select from four variants one stimulus that is identical to a standard. Both reaction time and accuracy were scored for all 24 problems. In the Beery Test of Visual–Motor Integration [6], the child is presented with a progressively more difficult sequence of 24 geometric forms that s/he is asked to copy.

2.2.2. Behavioral assessments

A copy of the Achenbach Child Behavior Checklist Teacher Report Form (TRF; [1]), a widely used behavior rating scale, was sent to each child's teacher. The teacher was also asked to complete the Barkley–DuPaul Attention Deficit Hyperactivity Disorder (ADHD) Scale [4]. In the TRF, the teacher is asked to rate 112 behaviors as 0 (*not like the child*), 1 (*somewhat like the child*), or 2 (*very much like the child*). Eight behavior problem scales were constructed from these behavior ratings: Withdrawn, Somatic, Anxious/Depressed, Delinquency, Aggression, Social, Thought, and Attention. Three summary scores were also computed: Externalizing, comprises the Delinquency and Aggression ratings; Internalizing, comprises Withdrawn, Anxious/Depressed and Somatic ratings; and an overall total score. *T* scores of 70 are considered in the clinical range; scores between 67 and 69 are considered "borderline".

The Barkley–DuPaul Scale [4] consists of 14 behavior rating scales (ranging from 0 to 3) and provides three measures of ADHD. The first consists of the number of ratings scored as 2 or 3 to provide a total ADHD score. Boys met criterion for ADHD if 10 or more items are rated 2 or 3; girls, if eight or more items are rated 2 or 3. Six of the items comprise the Inattention–Restlessness subscale (a total of the item scores); eight comprise the Hyperactivity–Impulsivity subscale.

The Child Behavior Checklist—Direct Observation Form (CBCL-DOF; [4]) was completed by the examiner. This task was administered during the first two tasks (X and AX) of the CPT, described above. In this assessment, the frequency of eight behaviors were recorded: off-task behaviors, fidgeting, vocalizations, vocalizations directed to the examiner, negative vocalizations from the child, the number of times the examiner needed to redirect the child, and the number of times the child was out of his/her seat. Each behavior was recorded as present or absent in each 30s interval of the task for a total of 24 intervals. A tape-recorded beep, which the child could not hear, was used to cue the observer after each 30s interval had elapsed.

2.2.3. Control variables

2.2.3.1. Alcohol and drug use. Prenatal alcohol exposure was determined from maternal interviews conducted at each prenatal clinic visit [40]. At each visit, the mother was interviewed regarding her drinking during the previous 2 weeks on a day-by-day basis. She was asked to describe her consumption of beer, wine, and liquor for each day, using specific events and activities to cue recall. Drinking volume was calculated for each day, converted to oz absolute alcohol (AA)/day, and then averaged across all clinic visits to create an average alcohol per day (AAD) measure. Mothers were also asked about their drug use and smoking at each prenatal visit. Marijuana, cocaine, and opiate use were quantified in terms of number of days used per month; smoking, as number of cigarettes smoked per day. A similar procedure was used in the 7.5-year assessment. The primary caregiver was asked to recall her drinking over a typical 1-week period and her use of marijuana, cocaine, opiates, and smoking during the previous year [39].

2.2.3.2. Other control variables. In addition to the alcohol and drug exposure variables, 19 variables were considered as potential confounders: socioeconomic status as measured by the Hollingshead Scale [33]; age, marital status, and years of education of the primary caregiver; child's gender and parity; number of children in the household; the Home Observation for Measurement of the Environment (HOME, school-age version; [13]), an assessment of parenting quality; primary caregiver's vocabulary as measured by the Peabody Picture Vocabulary Test—Revised (PPVT-R; [24]); the caregiver's level of depression as measured by the Beck Depression Inventory (BDI; [5]); crowded living conditions (a dichotomous measure coded when there was more than one person per room in the child's household); disruption in caregiving (a dichotomous measure coded if the child's caregiver had changed for a period of 4 months or longer); Symptom Checklist-90 Revised (SCL90-R; [17]), which assessed primary caregiver psychological symptoms, such as anxiety and hostility; Personality Diagnostic Questionnaire-R (PDQ-R; [35]), which provided a continuous measure of severity of personality disorder (if any) for the caregiver; the Family Environment Scale (FES; [53]), which assesses family function; the Life Events Scale for the primary caregiver (LES, [34]) and for the child (LES-C; [15]), which assesses the number of life events experienced in the past year, which were weighted by the degree of stress experienced in response to each event; domestic violence experienced by the mother on the Conflict Tactics Scale [67]; the age of the child at the 7.5-year visit; and the examiner.

2.3. Data analysis

The relation of child blood lead level to each of the neurobehavioral outcomes was examined by multiple regression analysis, controlling for potential confounding variables. Because a control variable cannot be a confounder unless it is related to both exposure and outcome, association with either exposure or outcome can be used as the criterion for statistical adjustment [59]. In this study, control variables were selected for inclusion in the regression analyses based on their relation to outcome, which has the additional advantage of increasing precision by also including covariates unrelated to exposure [45]. Pearson correlation was used to examine the relation of each control variable to each outcome, except for the examiner whose relation to each outcome was examined by analysis of variance (ANOVA). All control variables, even weakly related to each outcome (at $P<.10$), were adjusted statistically by regressing the outcome on child lead level and the control variables related to it. Control variables which met this criterion for each of the endpoints are presented as footnotes in Tables 2–5. The association of the neurobehavioral outcome with lead was considered significant only when $P<.05$, after controlling for the potential confounders. In the tables presenting the results of the regression analyses, the bivariate correlation of blood lead level with the endpoint is shown as Pearson r; the relation of lead to the endpoint after adjustment for confounders is shown as β, the standardized regression coefficient.

The endpoints in each neurobehavioral domain most strongly related to blood lead level in the multiple regression analyses were then examined in two sets of analyses focusing on dose–response and threshold. Dose–response was examined initially by nonparametric regression. In nonparametric regression, regression lines are fitted locally to each region of the data. Then, a smoothing spline is used to produce a smooth curve from these short lines to identify the shape of the distribution, which allows for visual inspection for the presence of a threshold. In a second set of analyses designed to identify a threshold for lead exposure, which was modeled after Lanphear et al. [46], four dichotomous lead exposure groups were created based upon the four threshold values examined in the Lanphear et al. study (above vs. below 10 μg/dl, above vs. below 7.5 μg/dl, above vs. below 5 μg/dl, and above vs. below 3 μg/dl). Separate regression analyses were run for each of these dichotomous exposure measures. The same covariates identified for the sample as a whole, which are listed in Tables 2–5, were used in each of these analyses.

3. Results

3.1. Sample characteristics

The sample was predominantly lower class with more than 68% receiving some form of public assistance (Table 1). Only 15.9% of the children's primary caregivers were married. The majority of the children (86.5%) were raised by their biological mothers; while 2.5% were raised by their fathers, 8% by a grandparent, 2.1% by an aunt, and fewer than 1% by an adoptive parent. In addition, 19% of the children were cared for by a caregiver other than their parent for at least 4 months. The mothers/primary caregivers in this sample were poorly educated; 30% of the primary caregivers had not graduated from high school, 10% had attended college, and fewer than 3% had a college degree. Only 7.6% of the children ($n = 21$) had lead concentrations at or above 10 μg/dl. To reduce the influence of outliers, lead concentrations were log transformed.

Mean IQ scores were low (Table 1), as is commonly found in economically disadvantaged, inner-city cohorts. Almost 12% of the children scored more than 2 S.D.'s below the normative mean of 100 on full-scale IQ, and 3.7% had full IQ scores less than 60. On the teacher ratings, 17.4% of the boys and 9.0% of the girls were above the cutoff for ADHD symptoms according to DSM-III-R [2] criteria. Teachers reported many children with significant behavior problems; 4.4% scored in the clinical range on Internalizing; 12.6% on Externalizing; and 10.9% on Total scores.

Table 1
Sample characteristics

	N	Mean or %	S.D.	Range
Maternal				
Socioeconomic status (SES)^{a}	237	25.3	10.8	6–66
Education (year)	236	12.2	1.9	2–18
Marital status (% married)	236	16.5	–	–
Welfare (% receiving)	237	69.2	–	–
Beck Depression Inventory	236	8.7	7.4	0–40
Peabody Picture Vocabulary Test	236	73.0	13.3	40–127
HOME^{b}	236	33.4	6.7	13–49
Age at 7.5-year visit	237	36.1	9.5	22–72
Child				
Primary caregiver (% mother)	237	86.5	–	–
Age at 7.5-year visit	237	7.8	0.3	7.2–8.9
Gender (% male)	237	59.5	–	–
Lead (μg/dl)	237	5.4	3.3	1–25
WISC-III				
Full scale IQ	237	84.2	12.4	45–116
Verbal comprehension	237	87.4	12.2	50–122
Perceptual organization	237	82.1	13.1	51–128
Freedom from distractibility	237	94.0	14.4	55–131
Processing speed	237	91.5	16.7	50–131
Achenbach Teacher Report Form				
Internalizing *t* score	175	52.0	10.2	36–82
Externalizing *t* score	175	56.6	11.1	39–89
Total *t* score	175	56.0	10.8	32–84

[a] Hollingshead Four Factor Index of Social Status [32].

[b] Home Observation for Measurement of the Environment [13].

Table 2
Relation of lead exposure to WISC-III IQ scores ($N = 237$)

	r	*β*
Summary scores		
Full IQ^{a,b,c,d,e,f,g,h}	−.32***	−.20**
Verbal IQ^{a,b,c,d,e,f}	−.28***	−.14*
Performance IQ^{a,b,c,d,e,f,g,h}	−.30***	−.21***
Verbal comprehension^{a,b,c,d,e,f}	−.29***	−.15**
Perceptual organization^{a,b,c,d,e,g,h}	−.30***	−.21**
Freedom from distractibility^{a,b,d,e,f,i}	−.19***	−.11
Processing speed^{a,b,c,d,f}	−.18**	−.09
Verbal subtests		
Information^{a,b,c,d,e,f,j,k,l}	−.32***	−.20**
Similarities^{a,b,c,d,e,f,l,m}	−.18**	−.05
Arithmetic^{a,b,d,e,f,i}	−.16**	−.07
Vocabulary^{a,b,c,d,e,h}	−.22***	−.10
Comprehension^{a,b,c,d,e}	−.22***	−.13*
Digit span^{a,b,e,g,i,n}	−.17**	−.13*
Forward^{a,b,g,i,k,m,n}	−.11†	−.11
Backward^{a,b,e,f,i,m,o}	−.21***	−.16*
Performance subtests		
Picture completion^{a,b,c,d,e,g,j,o,p}	−.24***	−.16*
Coding^{b,f,m}	−.13*	−.09
Picture arrangement^{a,b,c,d,e,i,p}	−.23***	−.14*
Block design^{a,b,c,e,q}	−.25***	−.21***
Object assembly^{a,b,c,e,g,h}	−.16**	−.08
Symbol search^{a,b,c,d,e,f,h,i}	−.18**	−.07
Mazes^{a,c,g,m,n}	−.16**	−.11

[a] SES.

[b] Education.

[c] Number of children < 18 years.

[d] HOME.

[e] PPVT-R.

[f] Gender.

[g] Parity.

[h] FES.

[i] Prenatal alcohol exposure.

[j] Crowding.

[k] Life stress—child.

[l] Life stress—caregiver.

[m] Child's age.

[n] Prenatal cocaine.

[o] Prenatal marijuana.

[p] Conflict tactics.

[q] Prenatal smoking.

* $P \leq 0.05$.

** $P \leq 0.01$.

*** $P \leq 0.001$.

† $P \leq 0.10$.

Only data from children at least 8 years of age were included in the analysis of the WCST. Examination of the data indicated that children younger than this age did not fully understand this task. Children in the analyses did not differ on lead exposure or any of the demographic variables ($t = 0.76$) from children not included in this analysis.

3.2. Associations of lead with child outcomes

There was a significant effect between lead exposure and full-scale, verbal, and performance IQ after adjusting for confounding (Table 2). The relation between blood lead concentration and IQ was strongest with performance IQ. Among the performance subtests, picture completion (PC), picture arrangement, and block design (BD) were related to lead exposure, as were information, comprehension and backwards digit span from the verbal IQ scale. It is interesting that blood lead concentration was related to the Verbal Comprehension and Perceptual Organization factors but not to Freedom from Distractibility and Processing Speed.

Although there was no evidence of a relation between lead and focused attention, lead exposure was associated with the number correct on the "X" and "AX" tasks of the CPT, a measure of sustained attention, and both the Seashore Rhythm Task and the WISC-III Digit Span subtest, two measures of working memory (Table 3). Lead exposure was negatively related to the number of errors percentile score and the number of conceptual level responses on the WCST. In addition, there were significant correlations with categories completed and number of perseverative errors, but these associations were not significant, after controlling for potential confounders, possibly due to the small sample size for these endpoints. Lead exposure was also related to poorer performance on the Beery Visual–Motor Integration task, mean number correct on the Matching Familiar Figure task, and number of pegs dropped, but not time to completion, on the Grooved Pegboard task.

Lead exposure was associated with slower reaction time on all of the processing speed tasks, except the Sternberg "No" response and the Magnitude Estimation Arrows task, which fell just short of traditional levels of significance (Table 4). By contrast, there was no relation between lead exposure and number correct on any of the processing speed tasks. Lead exposure was also associated with slower performance on the color naming task.

Among the behavioral assessments, lead exposure was associated with higher ADHD and Inattention scores on the Barkley–DuPaul Scale and poorer Attention on the TRF (Table 5). The Barkley–DuPaul Impulsivity Scale was not related to lead exposure, suggesting that lead affects the distractibility but not the impulsivity component of attention. Lead exposure was also related to the Withdrawn subscale on the TRF, and the off-task behavior on the Barkley direct observation scale.

Table 3
Relation of lead exposure to neuropsychological tasks

	N	*r*	*β*
Mirsky's Attention Battery			
Sustained attention			
CPT—visual			
Number correct[a,b,c]	225	−.21***	−.14*
Errors of commission[a,c,d]	236	.04	.02
Reaction time[e,f,g]	234	.06	.10
CPT—auditory			
Number correct[a,b,c,f,h,i,j,k]	221	−.14*	−.08
Errors of commission[l]	210	−.05	−.05
Reaction time[d,f,m]	201	.02	.03
Focused attention			
Digit cancellation			
Errors of omission[a,d,e,i]	236	.06	.01
Errors of commission[e,n,o,p,q]	225	.01	−.04
WISC-III coding[d,e,f]	231	−.13*	−.09
Working memory			
Seashore rhythm[d,e,h,i,m,r,s]	237	−.17**	−.15*
WISC-III arithmetic[a,c,e,f,h,i]	236	−.16**	−.07
WISC-III digit span[a,c,e,g,i,m]	236	−.17**	−.13*
Executive function			
Wisconsin Card Sorting Task			
Perseverative errors[a,b,c,e,f,i,o]	48	.28*	.20
Conceptual level responses[a,e,f,g,i]	48	−.35*	−.31*
Percent error[a,c,e,f,i,o]	48	.37**	.30*
Number of categories[a,c,e,i]	48	−.32*	−.22
Tower of London[e,p,t]	235	−.07	−.02
Verbal fluency[a,b,c,e,h,i,p]	236	−.19***	−.12†
Other neuropsychological tests			
Beery visual–motor integration[a,c,e,r]	232	−.23***	−.20**
Matching familiar figures			
Number correct[a,c,d,e,f,k,p]	230	−.25***	−.19**
Time to completion[d,l]	230	−.04	−.04
Pegboard			
Time to completion[a,d,e,f,u]	235	−.18**	−.10
Number of pegs dropped[n,u]	235	−.18**	.17**
Corsi Spatial Span			
Forward[a,e,f,h,p,r]	236	−.10†	−.04
Backward[a,d,e,f,m]	236	−.12*	−.09
WRAML			
Verbal learning[a,c,j]	208	−.13*	−.08
Story memory[a,c,d,e,f]	236	−.21***	−.12†

Notes to Table 3:
[a] SES.
[b] Number of children < 18 years.
[c] PPVT.
[d] Child's age.
[e] Education.
[f] Gender.
[g] Prenatal cocaine.
[h] HOME.
[i] Prenatal alcohol.
[j] Disruption in caregiver.
[k] Life stress—child.
[l] Examiner.
[m] Parity.
[n] Crowding.
[o] FES.
[p] SCL-90-R.
[q] Prenatal smoking.
[r] Caregiver's age.
[s] Conflict tactics.
[t] Current hard drug use.
[u] Prenatal marijuana.
* $P \le 0.05$.
** $P \le 0.01$.
*** $P \le 0.001$.
† $P \le 0.10$.

Table 4
Relation of lead exposure to processing speed

	N	*r*	*β*
Sternberg			
"Yes" condition			
Number correct[a,b]	232	−.08	−.02
Reaction time[c,d,e,f,g,h]	165	.16*	.16*
"No" condition			
Number correct[a,c,d,e,f,i,j,k]	231	−.17*	−.11†
Reaction time[a,c,d,e,f,l]	165	.14*	.14†
Mental rotation			
Forward			
Number correct[f,g,i]	228	−.08	−.06
Reaction time[e]	191	.16*	.15*
Backward			
Number correct[f,i,l]	230	−.04	−.04
Reaction time[e,f,m,n]	190	.13*	.14*
Magnitude estimation			
Arrows			
Number correct[a,d,f,g,o,p]	233	−.19**	−.11
Reaction time[c,e,i,l,m,q]	212	.14*	.13†
Numbers			
Number correct[a,b,c,d,f,k]	231	−.13*	−.06
Reaction time[c,f,h,l]	207	.12*	.15*
Color naming[b,d]	237	−.17**	−.15*

[a] HOME.
[b] Gender.
[c] SES.
[d] Education.
[e] Prenatal alcohol.
[f] Child's age.
[g] PPVT-R.
[h] Current hard drug use.
[i] Marital status.
[j] FES.
[k] Prenatal marijuana.
[l] Life stress—caregiver.
[m] Current alcohol use.
[n] Life stress—child.
[o] Prenatal cocaine.
[p] Number of children <18 years.
[q] Beck Depression.
* $P \le 0.05$.
** $P \le 0.01$.
† $P \le 0.10$.

As noted above, the PPVT-R was used to control for potential confounding by maternal intellectual competence. Some researchers have suggested that a domain-specific measure of maternal nonverbal intellectual competence be used as a covariate for the nonverbal child endpoints, such as the performance IQ scales, the Beery Test of Visual–Motor Integration, and the Corsi. Data were available for 73.0% of the mothers on the WAIS BD and PC subtests. When maternal BD and PC scores were substituted for the PPVT-R scores in the regressions for the nonverbal endpoints, all the previously significant lead effects remained significant, with the exception of the child's PC score, which fell just below conventional levels of significance, $\beta = -.13$, $P=0.09$.

3.3. Identification of a threshold

Nonparametric regression analyses were performed on the association between blood lead concentration and 15 endpoints to identify the presence of a threshold below which lead exposure has no apparent effect. Graphic representation of a subset of these analyses is shown in Fig. 1.

Examination of these nonparametric regression lines indicated a linear relation between lead and all of the neurobehavioral endpoints examined. Visual inspection provided no instance where the line flattens at lower levels of exposure and the associations were no longer apparent. The

Table 5
Relation of lead exposure to child behavior

	N	*r*	*β*
Barkley–DuPaul ADHD scale			
ADHD score[a,b,c]	179	.19**	.16*
Impulsivity factor[a,b]	169	.12†	.10
Inattention factor[a,b,d]	164	.23**	.18*
Child Behavior Checklist-TRF			
Attention[a,b,d,e,f]	175	.19**	.15*
Aggressive[a,b,e,g]	175	.13*	.11
Anxious[c,h]	175	.05	.03
Delinquent[a,b,c,d,f,g,i,j,k]	175	.17**	.09
Social problems[a,b]	175	.08	.07
Somatic[g,l,m]	175	.04	.02
Thought problems[a,b,f,g,l,m]	175	.11†	.10
Withdrawn[i,n,o]	175	.22**	.18*
Internalizing[c,h,i]	175	.13*	.11
Externalizing[a,b,e,g]	175	.14*	.12†
Total score[i,o,p]	175	.13*	.12
Barkley direct observation[q]			
Off task[a,b,o,r]	233	.20***	.14*
Fidgeting[c,g,i,s,t]	232	.05	.07
Total[a,b,i,t]	230	.09	.07

[a] Gender.
[b] Prenatal alcohol exposure.
[c] Life stress—child.
[d] HOME.
[e] Disruption in caregiver.
[f] Prenatal smoking.
[g] Child's age.
[h] Life stress—caregiver.
[i] Marital status.
[j] Number of children <18 years.
[k] FES.
[l] Conflict tactics.
[m] Prenatal cocaine.
[n] SES.
[o] PPVT.
[p] Education.
[q] Only behaviors that occurred on an average of five or more trials are included.
[r] Current hard drug use.
[s] Parity.
[t] Crowding.
* $P \le 0.05$.
** $P \le 0.01$.
*** $P \le 0.001$.
† $P \le 0.10$.

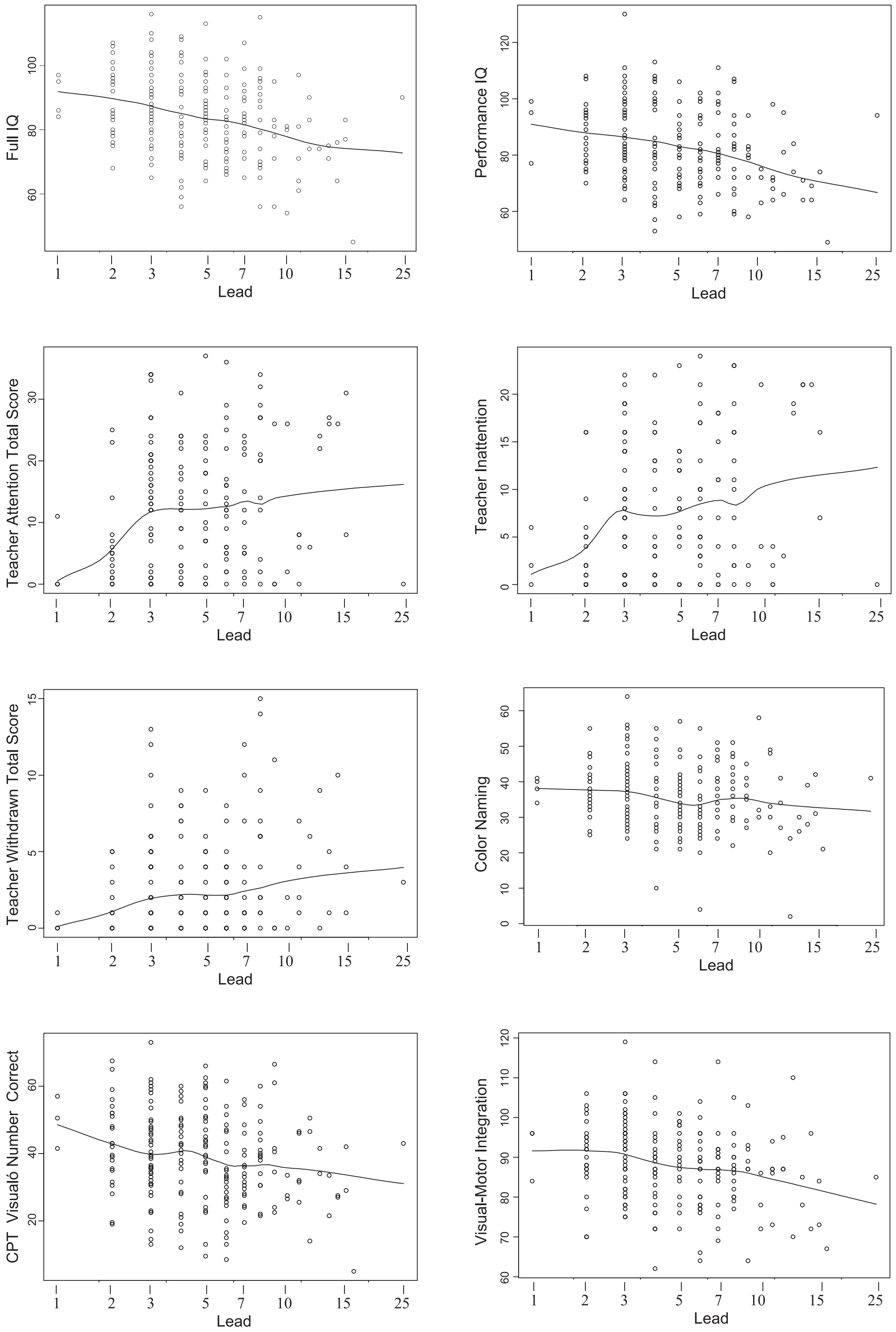

Fig. 1. Nonparametric regression analyses relating blood lead level to eight neurobehavioral endpoints.

linear relation was particularly clear for full IQ, performance IQ, the Achenbach Withdrawn Scale, the Continuous Performance Task, and Beery Visual–Motor Integration. For the other three outcomes, the dose–response relation appeared to have a nonlinear component. ANOVA was performed for each outcome measure to test for a deviation

Table 6
Regression analyses for selected neurobehavioral outcomes for lead exposure dichotomized at four cut-points

	N	Lead groups							
		< 10 μg/dl		< 7.5 μg/dl		< 5 μg/dl		< 3 μg/dl	
		r	*β*	*r*	*β*	*r*	*β*	*r*	*β*
Full scale IQ	237	−.25***	−.18**	−.24***	−.14*	−.23***	−.12†	−.18**	−.10†
Performance IQ	236	−.24***	−.19**	−.25***	−.17**	−.23***	−.13*	−.13*	−.08
Block design	235	−.17**	−.15*	−.14*	−.10	−.24***	−.21**	−.13*	−.11†
Digit span backwards	236	−.11*	−.09	−.18**	−.14*	−.17**	−.12†	−.08	−.03
Beery visual–motor integration	232	−.16**	−.14*	−.14**	−.10	−.20***	−.16*	−.10†	−.08
MFF (number correct)	230	−.15**	−.12†	−.16**	−.12†	−.22***	−.14*	−.15*	−.11
Attention—TRF	175	−.07	.05	.15*	.13†	.14*	.11	.26***	.24***
Barkley—inattention	164	.12†	.09	.16*	.12†	.18**	.15*	.23**	.20**
Withdrawn—TRF	175	.08	.06	.25***	.21**	.14*	.10	.20**	.17*
Barkley off-task	233	.17**	.13*	.08	.03	.16**	.13*	.12*	.08
Sternberg RT “Yes”	165	.05	.05	.06	.06	.15*	.15*	.19**	.18**
Color naming	237	−.11*	−.10	−.04	−.03	−.18**	−.17**	−.08	−.07
CPT visual (number correct)	225	−.15**	−.10	−.08	−.02	−.14*	−.10	−.15**	−.11†
Seashore rhythm	237	.11*	.12†	.06	.06	.11*	.09	.13*	.13*
Mental rotation RT “forward”	191	.16**	.15*	.16**	.15*	.07	.06	.12*	.12

* $P \leq 0.05$.
** $P \leq 0.01$.
*** $P \leq 0.001$.
† $P \leq 0.10$.

from linearity. Among the 15 variables assessed, only three had a significant nonlinear component: Color Naming, the Achenbach Attention Scale, and the DuPaul Inattention scale. In all three instances, the nonlinearity was due to a steeper slope at lower or moderate levels of exposure, not the flattened slope that would be seen in a threshold model.

In a second attempt to identify a threshold for lead exposure, four dichotomous lead exposure groups were created based upon the four threshold values examined by Lanphear et al. [46] (above vs. below 10 μg/dl, above vs. below 7.5 μg/dl, above vs. below 5 μg/dl, and above vs. below 3 μg/dl). Separate multiple regression analyses were run for each of these dichotomous exposure measures. Every child was included in each regression: 31 had lead levels < 3 μg/dl; 115 < 5 μg/dl; 193 < 7.5 μg/dl; 216 < 10 μg/dl. As can be seen in Table 6, children with blood lead concentrations greater than or equal to 10 μg/dl performed more poorly than children exposed at lower levels, suggesting a possible threshold. However, the data provide equally compelling evidence for a threshold at 5 μg/dl. In addition, for two of the endpoints that relate to attentional function, the strongest associations were seen when the sample was dichotomized at 3 μg/dl.

4. Discussion

The results of this study show consistent neurobehavioral deficits in relation to low levels of lead exposure in a lower SES, urban sample. These deficits were found in the domains of overall IQ, performance IQ, reaction time, visual–motor integration, fine motor skills, attention including executive function, off-task behaviors, and withdrawn behaviors on the TRF. Although at least one other study [46] has found deficits in children exposed to levels less than 5 μg/dl, the research presented here identified effects on attention at levels as low as 3 μg/dl.

Ours is one of a small number of studies to look beyond traditional IQ tests to examine the neurocognitive domains specifically associated with postnatal lead exposure, including a domain-specific examination of attention. Using Mirsky’s attention battery, we found significant relations between lead exposure and sustained attention, executive function and working memory, thus confirming the findings of Needleman et al. [56] implicating lead exposure in deficits in sustained attention and partially confirming the findings of Bellinger et al. [10] that lead impairs executive function. This study did not replicate Bellinger et al.’s focused attention finding.

In an attempt to identify a behavioral signature of lead exposure, Lanphear et al. [46] suggested four domains—attention, executive function, visual–motor integration, and social behavior, all of which were related to lead exposure in our study. Dietrich et al. [22] suggested a similar behavioral signature for lead, adding the domains of fine motor coordination and balance. Although some studies have reported social behavior problems in the domains of delinquency, antisocial behavior, and aggression [11,23,56], these studies evaluated children much older than 7.5 years of age. Studies of younger children have reported findings more consistent with the relation found here of lead exposure with teacher reports of withdrawn behavior problems and off-task behavior on the Barkley observational scale. Mendelsohn et al. [50] found that toddlers exposed to lead had more difficulties with emotion regulation and behavior orientation. These children were more hyperactive, impulsive, and easily frustrated, and had more withdrawal and disinterest behaviors. Thus, lead exposure appears to be associated with increased withdrawn, easily frustrated, hyperactive, and inattentive behavior in early childhood; whereas by adolescence, many lead-exposed children may become aggressive, antisocial, and delinquent.

Of interest when considering the behavioral signature of lead is the differential specificity of neurochemical toxins [36]. Among the IQ factors on the WISC-III, the factors verbal comprehension and perceptual organization were related to postnatal lead exposure. There was no association between blood lead concentration and the remaining two factors freedom from distractibility and processing speed. By contrast, prenatal alcohol exposure has been found to be negatively associated with freedom from distractibility [39]. Domain-sensitive result patterns between different toxins adds to the understanding of both behavioral signatures, alcohol and lead, and thus, to the understanding of the specific affected brain regions. Although lead has been shown to have adverse effects on a range of central nervous system processes, including synaptogenesis, myelination, catecholamine metabolism, and capillary integrity, it is not clear how these processes mediate the effects on the neurobehavioral endpoints identified in children [18].

Analyses to identify a threshold value for lead exposure yielded findings that were consistent with the conclusions reached by Needleman [54], Fulton et al. [29], Bellinger and Dietrich [8], Lanphear et al. [46], and others, that there is no apparent threshold for lead effects. Visual inspection of the nonparametric regression plots suggested a gradual linear dose–response relationship for each endpoint. Among the 15 neurobehavioral outcomes assessed, three of the nonparametric regression lines deviated significantly from linearity, but in no case was this deviation consistent with a threshold model.

Regression analyses in which lead exposure was dichotomized at 10 μg/dl were no more likely to be significant than analyses dichotomizing exposure at 5 μg/dl. In fact, negative associations with lead exposure were found as low as 3 μg/dl in the areas of behavior problems both on the teacher-reported attention and withdrawn subscales, as well as on reaction time and auditory attention. At 5 μg/dl, deficits were identified in several domains of IQ (e.g., BD), visual–motor integration, and attention. With the exception of digit span backwards and two sustained attention measures, all endpoints assessed showed a negative association between lead and neurobehavioral outcome at either 5 or 3 μg/dl.

One limitation of this study is that only one blood lead measure was available. It was not obtained until the children were 7.5 years old, several years after peak exposure to lead, which usually occurs at 2 years of age. Many neurocognitive processes are undergoing rapid growth during the first 2 years of life. It is, therefore, not clear if the deficits seen at 7.5 years are due to current lead exposure or exposure during the first 2 years of life. This limitation is not specific to this study (see Ref. [46]). The Cincinnati Lead Study [19] has reported high correlations between blood lead levels reported in infancy and at later ages. For example, the correlation between peak blood lead level during the first 2 years of life and blood lead during the third and fourth years was r=.82. Moreover, a recent pooled analysis of data from seven prospective studies found that concurrent lead levels provided the strongest index for lead associated neurotoxicity (Lanphear, personal communication).

Although our cohort was recruited to overrepresent children exposed prenatally to alcohol, the lead effects observed here cannot be attributed to alcohol. The children exposed to high doses of alcohol were excluded from the data analyses, and wherever prenatal alcohol exposure was correlated with a neurobehavioral outcome at $P < .10$, alcohol exposure was controlled statistically in the analyses. Unfortunately, data on maternal and child nutritional status, including iron deficiency, are not available, so we cannot control for their possible influence on the association between lead and neurobehavioral outcomes reported here.

It should also be noted that the effect sizes reported here are small (range = 1.4–3.9%). The magnitude of the association of neurobehavioral outcomes and lead is reduced when socioenvironmental and other control variables are included in the analyses, in part, because lead exposure co-occurs with socioenvironmental variables, and the full impact of the lead effect is difficult to isolate. The results reported here are consistent with those found in previous research. Dietrich et al. [21] reported a seven-point decrease in performance IQ following covariate adjustment, which is comparable to the six-point decrease found here (raw regression coefficient = – 6.0).

This research provides additional support for the conclusion that neurobehavioral deficits are consistently associated with blood lead concentrations below 10 μg/dl and suggests that it may be appropriate for the Center for Disease Control and the Environmental Protection Agency to re-evaluate the 10-μg/dl level of concern currently articulated for postnatal lead exposure. It must be emphasized that peak lead exposure typically occurs in children at an age when cognitive processes are rapidly developing, and the child is likely to have limited resources to counteract this environmental insult. Thus, although the effects reported at low levels are relatively subtle, these data provide additional evidence that there is no apparent lower bound threshold for postnatal lead exposure.

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