

## Neuropsychological function in children with blood lead levels <10 µg/dL

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### Abstract

Clear adverse effects of blood lead levels  $\geq 10$  µg/dL have been documented in children. Given that the majority of US children have levels below 10 µg/dL, clarification of adverse effects below this cutoff value is needed. Our study evaluated the associations between blood lead levels <10 µg/dL and a broad spectrum of children's cognitive abilities. Data were analyzed from 534 children aged 6–10, enrolled in the New England Children's Amalgam Trial (NECAT) from the urban area of Boston, Massachusetts and rural Farmington, Maine. Adjusting for covariates (age, race, socioeconomic status, and primary caregiver IQ), children with 5–10 µg/dL had 5.0 (S.D. 2.3) points lower IQ scores compared to children with blood lead levels of 1–2 µg/dL ( $p = 0.03$ ). Verbal IQ was more negatively affected than performance IQ, with the most prominent decrement occurring in children's vocabulary. Wechsler Individual Achievement Test scores were strongly negatively associated with blood lead levels of 5–10 µg/dL. In adjusted analyses, children with levels of 5–10 µg/dL scored 7.8 (S.D. 2.4) and 6.9 (S.D. 2.2) points lower on reading and math composite scores, respectively, compared to children with levels of 1–2 µg/dL ( $p < 0.01$ ). Finally, levels of 5–10 µg/dL were associated with decreased attention and working memory. Other than associations of lead exposure with achievement, which even persisted after adjustment for child IQ, the most pronounced deficits were in the areas of spatial attention and executive function. Overall, our analyses support prior research that children's blood levels <10 µg/dL are related to compromised cognition and highlight that these may especially be related to academic achievement.

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### 1. Introduction

It is well known that high levels of lead exposure can result in adverse neurocognitive and behavioral consequences in children (Juberg et al., 1997; Schwartz, 1994; Wakefield, 2002). However, given the pervasiveness of high lead levels before regulatory measures were taken, opportunities to study low lead levels in the US have been limited until recently. Due to increasing evidence of cognitive effects at lower exposures, the Centers for Disease Control's (CDC) guidelines regarding the lowest adverse level of lead have continued to shift downward,

resulting in a redefinition of an "elevated" blood lead level four times since the early 1970s (Koller et al., 2004). Although the CDC's current definition is 10 µg/dL, lead levels below 10 µg/dL have recently been associated with neurocognitive deficits in children (Canfield et al., 2003; Lanphear et al., 2000; Tellez-Rojo et al., 2006) and no "safe" level has yet been established (Wigle and Lanphear, 2005).

Determination of the lowest lead level that poses a threat to children has also been a subject of intense political debate (Ferber, 2002; Gilbert and Weiss, 2006; Juberg et al., 1997). The debate has been complicated by the finding that the impact of increased exposure at lower levels of lead might be greater than the proportional impact at higher levels (i.e., the dose–response curve is non-linear). That is, the effects of an increase in blood lead concentration of 1 µg/dL on IQ are greater in children with

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blood lead levels  $<10 \mu\text{g/dL}$  compared to the effects in children with blood lead levels  $>10 \mu\text{g/dL}$  (Lanphear et al., 2005).

National data from the Third National Health and Nutrition Examination Survey (NHANES III) indicates that the majority of children exposed to lead in the US have blood lead levels below  $10 \mu\text{g/dL}$  (Brody et al., 1994), and levels continue to decrease (CDC, 2005). The purpose of this study is to assess the associations between blood lead levels  $<10 \mu\text{g/dL}$  and a broad spectrum of children's neurocognitive abilities.

## 2. Methods

Data used in this study were originally gathered for the New England Children's Amalgam Trial (NECAT) (Bellinger et al., 2006), the aim of which was to assess the effect of amalgam dental fillings on children's neurodevelopment. NECAT recruited a cohort of 6- to 10-year-old children from the urban area of Boston, Massachusetts and rural Farmington, Maine. Children were eligible if they were English-speaking, had no prior or existing amalgam restorations, had two or more posterior teeth with dental caries, and, by parent report, had no physician-diagnosed psychological, behavioral, neurological immunosuppressive, or renal disease. Of 598 children found to be eligible, parental consent and child assent were obtained for the 534 who participated (291 from Boston, 243 from Maine). The institutional review boards of all participating sites approved this study.

At baseline (before placement of amalgam fillings), children were given an extensive battery of neuropsychological tests including tests of memory, learning, visual-motor ability, reading, reaction time, and IQ (see *Children's Amalgam Trial, 2003* for details). At this same time, sociodemographic information was collected from parents/guardians and blood lead level was measured.

### 2.1. Blood lead determination

Blood samples were obtained at baseline from 515 of the 534 children. Three of the 515 children had a blood lead level  $>10 \mu\text{g/dL}$  (range 11–13  $\mu\text{g/dL}$ ) and were excluded from this analysis.

Blood lead level was measured at the Clinical Chemistry Laboratory at Rochester General Hospital in Rochester, New York by an electrothermal process using an atomic absorption spectrometer with Zeeman background correction. Analysis was done on single samples using a Perkin-Elmer AA 600 atomic absorption spectrometer. A monthly quality check was done by WSLH PT (Wisconsin) and by the state in Albany. Blood samples, blood-based quality control materials and aqueous standards were diluted 1:9 with a matrix modifier solution containing nitric acid, Triton X-100 and ammonium dihydrogen phosphate.

### 2.2. Neuropsychological outcome measures

We selected the Full-Scale IQ on the Wechsler Intelligence Scale for Children -Third Edition (WISC-III) as our primary

outcome measure. This is an apical score that integrates a child's performance over a diversity of cognitive domains and for which scores frequently have been found to be inversely related to children's lead burden. Secondary outcomes included the Wechsler Individual Achievement Test (WIAT), and a battery of additional neuropsychological tests of memory, executive functions, fine motor skill, visual-motor integration, attention. The tests in the battery included the Wide Range Assessment of Visual Motor Ability (WRAVMA), the Wide Range Assessment of Memory and Learning (WRAML), the Stroop Color-Word Interference Test, the Wisconsin Card Sorting Test (WCST), the Trail-Making Test, a verbal cancellation task, tests of verbal fluency, finger tapping, and reaction time. Quality of the neuropsychological assessments was maintained by standardized training and certification of all examiners in both the Boston and Maine sites. Additionally, completed test protocols were rescored by a second individual, with internal consistency checked by computerized algorithms. Caregiver IQ was measured at baseline using the Kaufman-Brief Intelligence Test (K-BIT). The Life Stress score was measured with the Parenting Stress Index (PSI).

### 2.3. Statistical analyses

Analysis of covariance was used to model the association between neuropsychological test scores and blood lead level, adjusting for relevant covariates.

Bar graphs were created to show average IQ and other test scores versus blood lead by  $1 \mu\text{g/dL}$  increments to provide a sense of the shape of the dose-response relationships. After examination of these graphs and available sample sizes, we grouped blood lead into three categories: 1–2, 3–4, and 5–10  $\mu\text{g/dL}$ . Blood lead of 1–2  $\mu\text{g/dL}$  was used as the reference category.

We used a common set of covariates in the analyses performed on the different cognitive outcomes. Using WISC-III Full-Scale IQ as our primary outcome, we evaluated bivariate associations, with linear regression or analysis of variance, between thirteen sociodemographic variables and IQ: site (Boston or Maine), age, gender, race (non-Hispanic White, non-Hispanic Black, Hispanic, other), primary caregiver education ( $<$ high school, high school, college+), socioeconomic status (calculated using the method of Green, 1970), marital status of the primary caregiver, birth order, birthweight, parenting stress, maternal utilization of annual health care, maternal utilization of prenatal care, and primary caregiver IQ. The reason for age adjustment was to take into account the wide range of ages when blood lead was assessed. Variables found to be significantly associated with IQ in bivariate analyses ( $p < 0.2$ ) were included in a multivariate analysis of covariance model. Variables then found statistically significant ( $p < 0.2$ ) in multivariate analysis were included as covariates in all models for the association between IQ/other neuropsychological tests and blood lead level. Due to missing data on primary caregiver IQ and birthweight, the sample size was reduced from 512 to 389.

Two sensitivity analyses were conducted by: (1) including all covariates significant in bivariate analysis at the level of  $<0.2$  ( $N = 385$  due to missing data), and (2) omitting primary caregiver IQ and birthweight, for which considerable data were missing ( $N = 512$ ). All analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Further analyses were carried out to determine if lead-associated deficits were evident on the Wechsler Achievement Test adjusting for child full-scale IQ, along with the other covariates (adult IQ, age, socioeconomic status, race, and birthweight).

### 3. Results

Because of missing data, in our analyses we used subsets of the 534 children. Table 1 shows baseline characteristics of the

samples of 512 and 389 children respectively. The 512 children are those with non-missing WISC-III Full-Scale IQ and baseline blood lead level  $\leq 10$   $\mu\text{g}/\text{dL}$ , and the 385 children are those for whom birthweight and baseline primary caregiver IQ were collected.

Children in the two samples were similar in terms of most baseline characteristics. However, the sub-sample ( $N = 389$ ) included proportionally fewer children from the Boston site, and children had a higher mean IQ.

Of the thirteen potential covariates, bivariate analyses indicated that seven of them were significantly associated with IQ: site, age, race, SES, marital status of the primary caregiver, birthweight, and primary caregiver IQ (data not shown). Being from Boston (vs. Maine), being of Black or Hispanic race (versus non-Hispanic White), having an unmarried primary caregiver, or having a caregiver with a high school education or

Table 1  
Sample characteristics

	Children with IQ data and blood lead $\leq 10$ $\mu\text{g}/\text{dL}$ ( $N = 512$ ) <sup>a</sup>	Children with IQ data, primary caregiver IQ, birthweight, and blood lead $\leq 10$ $\mu\text{g}/\text{dL}$ ( $N = 389$ ) <sup>b</sup>
Site ( $N\%$ )		
Boston	272 (53.1%)	159 (40.9%)
Maine	240 (46.9%)	230 (59.1%)
Age (mean, S.D., range)	8.0, (1.4), 6.0–11.5	7.9, (1.4), 6.0–11.5
Gender ( $N\%$ )		
Female	277 (54.1%)	204 (52.4%)
Male	235 (45.9%)	185 (47.6%)
Race ( $N\%$ ) <sup>c</sup>		
Non-Hispanic White	320 (62.5%)	289 (74.3%)
Non-Hispanic Black	89 (17.4%)	62 (15.9%)
Hispanic	37 (7.2%)	11 (2.8%)
Other	66 (12.9%)	27 (6.9%)
Household income ( $N\%$ )		
$\leq \$20,000$	156 (31.3%)	102 (26.4%)
$\$20,001$ – $\$40,000$	213 (42.8%)	174 (45.0%)
$> \$40,000$	129 (25.9%)	111 (28.7%)
Education of primary caregiver ( $N\%$ )		
<High school	69 (13.7%)	39 (10.0%)
High school graduate	383 (76.1%)	313 (80.5%)
College graduate	51 (10.1%)	37 (9.5%)
Socioeconomic status (mean, S.D.)	52.4, (6.7), 29.4–75.8	52.9, (6.3), 30.6–75.8
Primary caregiver married ( $N\%$ )	315 (63.0%)	243 (63.1%)
Birth order (mean, S.D., range)	1.6, (0.8), 1.0–5.0	1.6, (0.8), 1.0–5.0
Birthweight, grams (mean, S.D., range)	3343, (542.3), 1600–4848	3368, (538.6), 1843–4848
Life stress (mean, S.D.) <sup>d</sup>	9.6, (9.2), 0–49	9.8, (9.3), 0–49
Maternal utilization of annual health care (yes) ( $N\%$ )	333 (73.2%)	281 (72.6%)
Maternal utilization of prenatal care (yes) ( $N\%$ )	441 (96.3%)	383 (98.5%)
Adult IQ (mean, S.D., range)	97.3, (12.8), 52–157	97.4, (13.0), 52–157
Child WISC-III <sup>e</sup> full scale IQ (mean, S.D., range)	95.7, (13.5), 62–141	97.5, (13.0), 62–141
Child blood lead level ( $\mu\text{g}/\text{dL}$ ) (mean, S.D., range)	2.3, (1.6), 1–10	2.2, (1.6), 1–10

<sup>a</sup>  $N = 512$  for site, age, gender, race, socioeconomic status, and Wechsler Intelligence Scale for Children-3rd Edition (WISC-III).  $N = 498$  for income.  $N = 503$  for education.  $N = 500$  for marital status.  $N = 504$  for birth order.  $N = 455$  for birthweight.  $N = 408$  for adult IQ composite.  $N = 440$  for family life stress.  $N = 458$  for prenatal visit.  $N = 455$  for annual health care visit.

<sup>b</sup>  $N = 389$  for site, age, gender, race, education, socioeconomic status, birth order, birthweight, prenatal visit, WISC-III, and adult IQ composite.  $N = 387$  for income and annual health care visit.  $N = 385$  for marital status.  $N = 381$  for family life stress.

<sup>c</sup> Race was self-reported by the parents of the children.

<sup>d</sup> This was part of the Parenting Stress Index.

<sup>e</sup> Wechsler Intelligence Scale for Children-3rd Edition.

less (vs. a college education) were related to lower child IQ (WISC-III) ( $p < 0.001$ ). Greater age, lower SES, lower birthweight, and lower primary caregiver IQ were also related to lower IQ scores in the children ( $p < 0.001$ ). Of these eight variables, five remained significant in multivariate analysis – age, race, SES, primary caregiver IQ, and birthweight – and were included in all subsequent outcome models.

Fig. 1 shows plots of average Full Scale WISC-III IQ, WIAT Reading Composite, WIAT Math Composite, and Wisconsin Card Sorting perseveration errors versus blood lead level for the 389 children for whom primary caregiver IQ scores were available. All four outcomes tend to decrease with increasing blood lead level.

Table 2 shows model results for Full-Scale WISC-III IQ. Compared to children with blood lead levels of 1–2  $\mu\text{g}/\text{dL}$ , children with levels of 3–4  $\mu\text{g}/\text{dL}$  and 5–10  $\mu\text{g}/\text{dL}$  had scores that were 0.12 ( $p = 0.94$ ) and 6.0 ( $p = 0.01$ ) points lower, respectively. Other covariates included in this multivariable model, adult IQ, child age, SES, and race, were statistically significant ( $p < 0.05$ ) except for birthweight ( $p = 0.14$ ).

Table 3 shows the association between blood level and each of the neurocognitive outcomes, in models adjusted for caregiver IQ, child age, socioeconomic status, race, and

Table 2

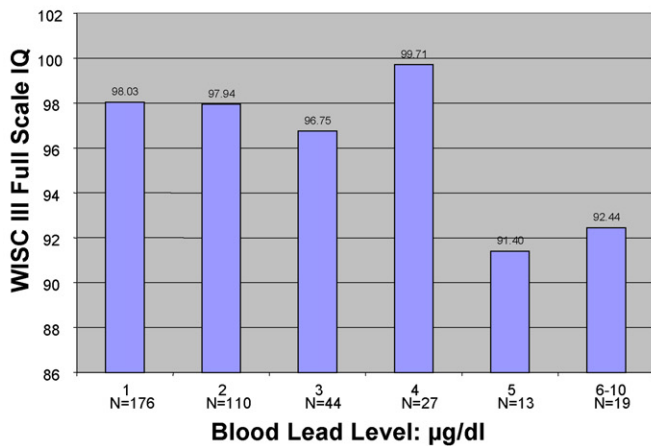
Dose–response model of WISC-III full-scale IQ and blood lead (1–2, 3–4, and 5–10  $\mu\text{g}/\text{dL}$ ), adjusted for adult IQ, age, socioeconomic status, race and birthweight

Variables	Coefficient (S.E.)	<i>p</i> -value
Lead level		
3–4 $\mu\text{g}/\text{dL}$ vs. 1–2 $\mu\text{g}/\text{dL}$	–0.12 (1.62)	0.941
5–10 $\mu\text{g}/\text{dL}$ vs. 1–2 $\mu\text{g}/\text{dL}$	<b>–6.04 (2.39)</b>	<b>0.012</b>
Adult IQ	<b>0.13 (0.06)</b>	<b>0.018</b>
Age	<b>–1.20 (0.44)</b>	<b>0.006</b>
Socioeconomic status	<b>0.36 (0.11)</b>	<b>0.002</b>
Race		
Black vs. White	<b>–5.14 (1.80)</b>	<b>0.005</b>
Hispanic vs. White	–3.12 (3.90)	0.424
Other vs. White	–1.98 (2.46)	0.422
Birthweight	0.002 (0.001)	0.142

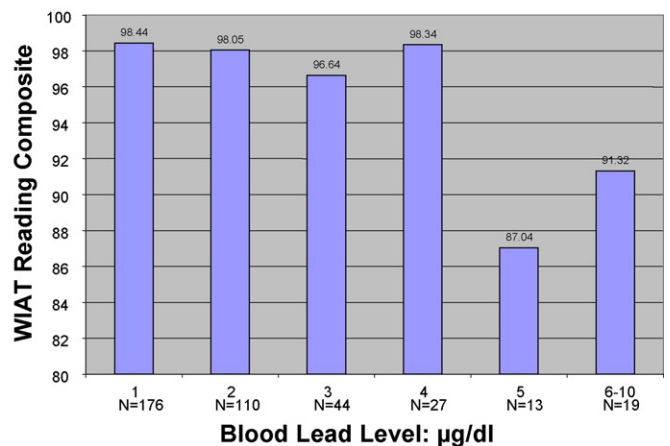
*N* = 389. *p*-values < 0.05 in bold.

birthweight. Children with blood lead levels of 5–10  $\mu\text{g}/\text{dL}$  had deficits in all components of the WIAT. Compared to children with levels of 1–2  $\mu\text{g}/\text{dL}$ , they had mean scores that were 8.7 and 7.9 points lower on the Reading ( $p = 0.001$ ) and Mathematics ( $p = 0.001$ ) Composite scores. Their mean scores

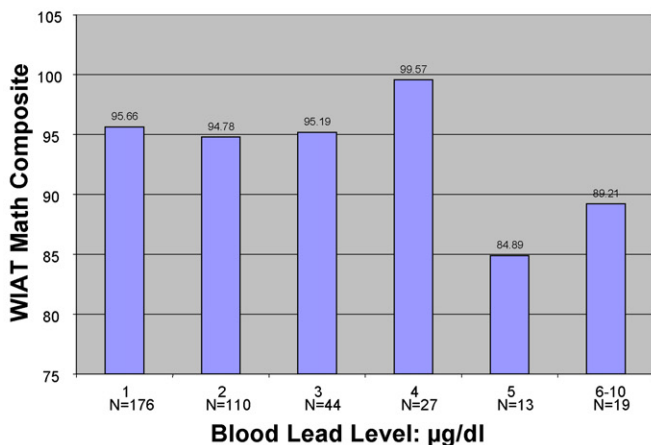
(a) WISC III Full Scale IQ and Blood Lead N=389



(b) WIAT Reading Composite and Blood Lead N=389



(c) WIAT Math Composite and Blood Lead N=389



(d) WCST Perseveration Errors and Blood Lead N=380

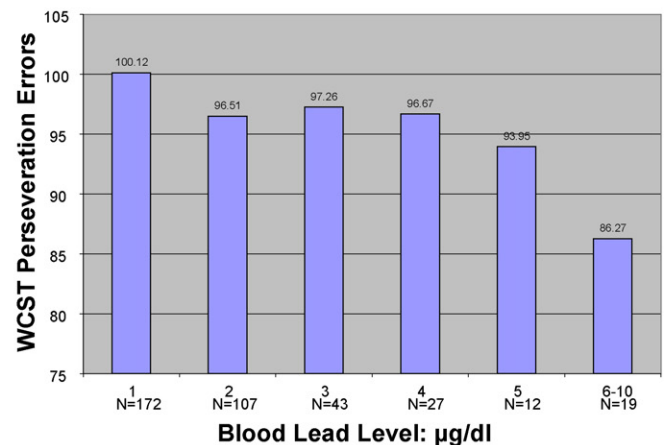


Fig. 1. (a–d) Relationships between selected neuropsychological tests and blood lead levels adjusted for age, adult IQ, SES, race, and birthweight.

Table 3  
Dose–response models of neuropsychological test scores and blood lead (1–2, 3–4, and 5–10  $\mu\text{g/dL}$ ), adjusted for adult IQ, age, socioeconomic status, race, and birthweight with reference lead level 1–2  $\mu\text{g/dL}$

Neuropsychological test	Coefficient (S.E.)			
	Lead level 3–4 $\mu\text{g/dL}$	<i>p</i> -value	Lead level 5–10 $\mu\text{g/dL}$	<i>p</i> -value
<b>Wechsler Intelligence Scale for Children-3rd Edition</b>				
Full-scale IQ	−0.12 (1.62)	0.941	<b>−6.04 (2.39)</b>	<b>0.012</b>
Verbal IQ	−0.86 (1.66)	0.605	<b>−5.95 (2.45)</b>	<b>0.016</b>
Performance IQ	0.05 (1.78)	0.978	<b>−5.37 (2.63)</b>	<b>0.042</b>
<b>Subtest scores</b>				
Information	−0.01 (0.37)	0.981	<b>−1.16 (0.55)</b>	<b>0.035</b>
Similarities	0.16 (0.42)	0.706	−1.19 (0.62)	0.054
Arithmetic	0.35 (0.37)	0.346	−0.63 (0.55)	0.258
Vocabulary	−0.55 (0.38)	0.150	<b>−1.43 (0.56)</b>	<b>0.011</b>
Comprehension	−0.19 (0.35)	0.593	−0.89 (0.52)	0.088
Digit span	<b>−0.72 (0.33)</b>	<b>0.031</b>	−0.24 (0.50)	0.623
Picture completion	−0.34 (0.37)	0.355	<b>−1.17 (0.54)</b>	<b>0.031</b>
Coding	0.03 (0.42)	0.937	−0.37 (0.62)	0.558
Picture arrangement	−0.20 (0.49)	0.686	−0.79 (0.73)	0.279
Block design	0.08 (0.38)	0.839	<b>−1.23 (0.57)</b>	<b>0.031</b>
Object assembly	0.30 (0.40)	0.455	−0.55 (0.60)	0.366
Symbol search	−0.19 (0.41)	0.651	<b>−1.68 (0.60)</b>	<b>0.006</b>
Mazes	−0.14 (0.43)	0.741	−0.61 (0.63)	0.332
<b>Wechsler Individual Achievement Test</b>				
<b>Composites</b>				
Reading	−1.01 (1.74)	0.564	<b>−8.74 (2.57)</b>	<b>0.001</b>
Mathematics	1.54 (1.61)	0.340	<b>−7.92 (2.38)</b>	<b>0.001</b>
<b>Scales</b>				
Basic reading	−0.88 (1.73)	0.612	<b>−7.73 (2.55)</b>	<b>0.003</b>
Reading comprehension	−0.83 (1.65)	0.615	<b>−8.52 (2.44)</b>	<b>0.001</b>
Mathematics reasoning	0.96 (1.41)	0.497	<b>−5.88 (2.09)</b>	<b>0.005</b>
Numeric operations	1.53 (1.59)	0.336	<b>−7.36 (2.35)</b>	<b>0.002</b>
Listening comprehension	−0.77 (1.66)	0.640	<b>−7.90 (2.44)</b>	<b>0.001</b>
<b>Wide Range Assessment of Visual Motor Ability</b>				
Visual-motor composite	−0.74 (1.66)	0.654	<b>−5.37 (2.45)</b>	<b>0.029</b>
<b>Subtest scores</b>				
Drawing	0.08 (1.63)	0.962	−0.99 (2.40)	0.680
Matching	0.55 (1.69)	0.744	<b>−7.98 (2.49)</b>	<b>0.002</b>
Pegboard	−2.20 (2.00)	0.272	−2.44 (2.95)	0.408
<b>Wide Range Assessment of Memory and Learning</b>				
<b>Indices</b>				
General memory index	−0.69 (1.90)	0.718	<b>−6.67 (2.79)</b>	<b>0.017</b>
Visual memory index	0.01 (1.86)	0.995	<b>−6.47 (2.75)</b>	<b>0.019</b>
Verbal memory index	−2.92 (1.81)	0.108	<b>−5.74 (2.67)</b>	<b>0.032</b>
Learning index	1.05 (1.97)	0.596	−3.41 (2.90)	0.239
<b>Scales</b>				
Picture memory	0.48 (0.38)	0.209	−0.37 (0.56)	0.511
Design memory	0.23 (0.36)	0.530	−0.29 (0.54)	0.587
Verbal learning	−0.20 (0.41)	0.616	−1.06 (0.60)	0.076
Story memory	−0.21 (0.42)	0.624	−0.92 (0.62)	0.137
Finger windows	<b>−0.79 (0.40)</b>	<b>0.051</b>	<b>−1.98 (0.60)</b>	<b>0.001</b>
Sound symbol	0.07 (0.36)	0.855	−0.23 (0.53)	0.661
Sentence memory	−0.56 (0.34)	0.103	<b>−1.17 (0.50)</b>	<b>0.021</b>
Visual learning	0.55 (0.39)	0.159	−0.07 (0.57)	0.901
Number/letter memory	−0.38 (0.32)	0.234	−0.61 (0.48)	0.201
<b>Wisconsin Card Sorting Test</b>				
Perseveration errors <sup>a</sup>	−1.65 (1.84)	0.370	<b>−9.19 (2.74)</b>	<b>0.001</b>
Number of categories achieved	−0.29 (0.19)	0.129	<b>−1.06 (0.29)</b>	<b>0.0003</b>
Trials to the first category	−3.76 (2.27)	0.098	4.93 (3.37)	0.144

Table 3 (Continued)

Neuropsychological test	Coefficient (S.E.)			
	Lead level 3–4 µg/dL	<i>p</i> -value	Lead level 5–10 µg/dL	<i>p</i> -value
Reaction time				
Mean reaction time on successful trials	0.02 (0.02)	0.169	0.05 (0.03)	0.066
Verbal cancellation				
Ordered errors	−1.33 (1.05)	0.208	1.62 (1.54)	0.293
Unordered errors	−0.96 (1.08)	0.373	2.02 (1.58)	0.202
Stoop test				
Color-word interference score	−0.33 (0.80)	0.675	0.75 (1.22)	0.541
Trial-making test				
Time to complete part A	2.13 (2.39)	0.372	5.54 (3.62)	0.127
Time to complete part B	3.84 (7.14)	0.591	6.09 (10.85)	0.575
Finger tapping				
Mean of five trials with dominant hand	<b>1.81 (0.89)</b>	<b>0.042</b>	1.34 (1.33)	0.312
Mean of five trials with non-dominant hand	<b>1.53 (0.73)</b>	<b>0.036</b>	−0.37 (1.08)	0.733

Sample sizes for all variables ranged between  $N = 381$ – $389$ , except perseveration errors and number of categories achieved (WCST) and time to complete part B (Trial-making test) that ranged between  $N = 373$ – $380$ , and the color-word inference score  $N = 312$ . *p*-values  $< 0.05$  in bold.

<sup>a</sup> A lower standardized score indicates more perseveration errors.

were 7.7 points lower on Basic Reading ( $p = 0.003$ ), 8.5 points on Reading Comprehension ( $p = 0.001$ ), 5.9 points on Mathematics Reasoning ( $p = 0.005$ ), 7.4 points on Numerical Operations ( $p = 0.002$ ), and 7.9 points on Listening Comprehension ( $p = 0.001$ ).

Child lead levels of 5–10 µg/dL were related to between 5 and 6 points lower scores on the Full-Scale WISC-III ( $\beta = -6.0$ ,  $p = 0.012$ ), as well as on the Verbal and Performance IQ domains ( $\beta = -6.0$ ,  $p = 0.016$ ;  $\beta = -5.3$ ,  $p = 0.04$ , respectively). With regard to WISC-III subtests, compared to children with levels of 1–2 µg/dL, children with levels of 5–10 µg/dL performed on average between 1.2 and 1.7 points lower on Information ( $p = 0.035$ ), Similarities ( $p = 0.054$ ), Block Design ( $p = 0.031$ ), Vocabulary ( $p = 0.011$ ), Picture Completion ( $p = 0.031$ ), and Symbol Search ( $p = 0.006$ ). Blood lead levels of 5–10 µg/dL were associated with a 5.4-point deficit on the Visual-Motor Composite ( $p = 0.029$ ) and an 8.0 point deficit on the Matching subtest of the WRAMA ( $p = 0.002$ ). Impairments on the WRAML were evident on all memory subtests, with 6.7 ( $p = 0.017$ ), 6.5 ( $p = 0.019$ ), and 5.7 ( $p = 0.032$ ) mean point

decreases on General Memory, Visual Memory, and Verbal Memory indices respectively, in children with blood lead levels 5–10 µg/dL. Children having blood lead between 5–10 µg/dL was associated with an average 2.0 ( $p = 0.001$ ) and 1.2 ( $p = 0.021$ ) lower score on the WRAML Finger Windows and Sentence Memory scales, respectively, compared to children in the 1–2 µg/dL range. On the WCST, children with blood lead levels of 5–10 µg/dL scored lower than children with levels of 1–2 µg/dL, making more perseveration errors (mean difference  $-9.2$ ,  $p = 0.001$ , note: a lower standardized score indicates more errors) and achieved fewer categories (mean difference 1.1,  $p = 0.0003$ ). The remaining neurocognitive tests and/or subscales were not significantly related to lead exposure in our sample. The sensitivity analyses yielded similar results.

After adjustment for all covariates and children's Full-Scale IQ, performance on most scales of the Wechsler Individual Achievement Test (WIAT) remained lower among children with lead levels of 5–10 µg/dL (Table 4). However, the magnitude of these associations was smaller but reached statistical significance at the  $p < 0.05$  level on all domains

Table 4

Dose–response models of the Wechsler Individual Achievement Test scores and blood lead (1–2, 3–4, and 5–10 µg/dL), adjusted for child full scale IQ, adult IQ, age, socioeconomic status, race and birthweight, with reference lead level 1–2 µg/dL,  $N = 389$

	Coefficient (S.E.)			
	Lead level 3–4 µg/dL	<i>p</i> -value	Lead level 5–10 µg/dL	<i>p</i> -value
Wechsler Individual Achievement Test				
Composites				
Reading	−0.93 (1.46)	0.523	<b>−5.20 (2.17)</b>	<b>0.017</b>
Mathematics	1.62 (1.23)	0.189	<b>−4.02 (1.83)</b>	<b>0.028</b>
Scales				
Basic reading	−0.81 (1.49)	0.586	<b>−4.42 (2.21)</b>	<b>0.047</b>
Reading comprehension	−0.75 (1.39)	0.590	<b>−5.16 (2.07)</b>	<b>0.013</b>
Mathematics reasoning	1.03 (1.06)	0.333	−2.40 (1.58)	0.130
Numeric operations	1.59 (1.37)	0.245	<b>−4.32 (2.03)</b>	<b>0.034</b>
Listening comprehension	−0.70 (1.34)	0.601	<b>−4.28 (2.00)</b>	<b>0.033</b>

except for Mathematics Reasoning. Compared to children with blood lead levels of 1–2  $\mu\text{g}/\text{dL}$ , those with 5–10  $\mu\text{g}/\text{dL}$  scored 5.2 points lower on the reading composite section of the WIAT ( $p = 0.017$ ) and 4.0 points lower on the mathematics composite section ( $p = 0.028$ ). Blood lead levels of 5–10  $\mu\text{g}/\text{dL}$  were associated with deficits of similar magnitude on Basic Reading, Reading Comprehension, Numerical Operations, and Listening Comprehension ( $\beta = -4.4$ ,  $p = 0.047$ ;  $\beta = -5.2$ ,  $p = 0.013$ ;  $\beta = -4.3$ ,  $p = 0.034$ ;  $-4.3$ ,  $p = 0.033$ , respectively).

#### 4. Discussion

Among participants in the NECAT, children with blood lead levels of 5–10  $\mu\text{g}/\text{dL}$  had significantly lower scores on IQ, achievement, attention, and working memory than did children in the referent group, who had levels of 1–2  $\mu\text{g}/\text{dL}$ . Children with a blood lead level of 3–4  $\mu\text{g}/\text{dL}$  differed from the referent group on only a few of the many test scores analyzed. Our overall findings are thus consistent with those of previous studies showing deficits in neuropsychological status among children exposed to low levels of lead (Environmental Protection Agency, 2006). An important aspect of our findings is that, at the time of neuropsychological assessment, all of the children included in the analyses had a blood lead level below 10  $\mu\text{g}/\text{dL}$ , the current screening guideline of the U.S. Centers for Disease Control (CDC, 1991). Therefore, like those of several recent studies, our findings suggest that it is inappropriate to regard 10  $\mu\text{g}/\text{dL}$  as a “lowest observed adverse effect” level (Chiodo et al., 2004; Kordas et al., 2006; Lanphear et al., 2000, 2005; Tellez-Rojo et al., 2006).

In some studies, a supralinear dose-effect relationship has been observed, with the inverse slope being steeper at blood lead levels  $<10$   $\mu\text{g}/\text{dL}$  than at levels  $>10$   $\mu\text{g}/\text{dL}$  (Kordas et al., 2006; Lanphear et al., 2005; Tellez-Rojo et al., 2006). Our study does not provide information on this point insofar as children with blood lead levels  $>10$   $\mu\text{g}/\text{dL}$  were excluded from the analyses. We did find, however, that the performance deficits were greater among children with a blood lead level of 5–10  $\mu\text{g}/\text{dL}$  than among children with a level of 3–4  $\mu\text{g}/\text{dL}$ . Although the neurobiological basis of possible supralinearity has not been identified such a form has been observed not only in epidemiological studies of children but in animal models as well. For example, biphasic functions have also been observed in rats with regard to lead exposure and long-term potentiation (Gilbert et al., 1999) and the release of GABA and glutamate in the hippocampus (Lasley and Gilbert, 2002).

Higher blood lead levels were associated not just with lower scores on tests of neuropsychological domains, but also with lower scores on tests of academic achievement. On all subscales of the WIAT, the mean scores of children with a blood lead level of 5–10  $\mu\text{g}/\text{dL}$  were approximately two standard deviations lower than the mean scores of children with levels of 1–2  $\mu\text{g}/\text{dL}$ . Inverse associations between blood lead level and reading and arithmetic scores have been previously reported (Fergusson et al., 1988, 1993, 1997; Lanphear et al., 2000; Needleman et al., 1990). We showed, moreover, that these academic deficits remained significant even after adjustment for children’s Full-

Scale IQ scores. This implies that the children’s academic achievement was significantly lower than would be expected based on their intelligence (i.e., an aptitude-achievement discrepancy). This is frequently used as a criterion for identifying children with a “learning disability,” and for allocating school resources such as remedial assistance.

Because of the detailed neuropsychological test battery administered at the baseline visits of the NECAT, we were able to evaluate the children’s performance within specific domains that might mediate the inverse associations between lead level and apical test scores such as IQ. It appeared to be within the domain of executive functioning that the children with lead levels of 5–10  $\mu\text{g}/\text{dL}$  showed their most consistent deficits, achieving significantly fewer categories and making more perseverative errors on the WCST. These findings suggest that working memory, cognitive flexibility, and ability to formulate, test, and adapt hypotheses might contribute to impaired scores on apical tests. Similar observations have been made in other studies of lead-exposed children (Bellinger and Dietrich, 1994; Evans et al., 1994; Stiles and Bellinger, 1993) and in studies using animal models. Monkeys treated with lead from birth or later (at 300 or 4000 days) had more perseverative errors on discrimination (Rice, 1992) or delayed alteration tasks 6–9 years later (Rice and Gilbert, 1990). In one study using an alternation task, some monkeys perseverated for as long as an hour over the longest intervals between task acquisition and performance (Rice and Karpinski, 1988).

The information we had regarding children’s lead exposure history was limited to a single measurement made at the time of enrollment in the NECAT. Therefore, we do not know what the children’s levels of lead were in earlier years or whether they had changed over time. Although the relatively short half-time of lead in blood, and the resulting risk of exposure misclassification, is often cited as a limitation of cross-sectional studies such as ours, recent studies have shown that concurrent blood lead level is often the exposure biomarker that is most strongly associated with children’s neuropsychological outcomes at school age (Lanphear et al., 2005).

We did not assess the quantity and quality of emotional and cognitive stimulation using an instrument such as the Home Observation for Measurement of the Environment Inventory. However, life stress (from the Parenting Stress Index) was not associated with child IQ in bivariate analyses. Also, we adjusted for both socioeconomic status and caregiver IQ, both of which are moderately correlated with child stimulation and parenting skills. The analyses pertain to baseline assessments conducted as part of the Children’s Amalgam Trial, before any amalgam restorations had been placed. Thus, none of the children had any exposure to dental restorations, providing an assessment of the effects of lead unconfounded by exposure to elemental mercury.

In summary, we found that blood lead levels of 5–10  $\mu\text{g}/\text{dL}$  in school-age children are associated with deficits in intelligence, visual-spatial skills, executive function, and IQ-adjusted academic achievement. These findings thus contribute to the accumulating evidence that we have yet to identify a threshold for lead-induced cognitive dysfunction in children, and that 10  $\mu\text{g}/\text{dL}$  is a level without biological significance.

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