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Cognitive development and low-level lead exposure in poly-drug exposed children

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ABSTRACT

The impact of early postnatal lead exposure measured at age 4 on children's IQ and academic achievement at and 11 years of age was examined. The sample consisted of 278 inner-city, primarily African American children who were polydrug exposed prenatally. Regression analyses indicated a linear effect of lead exposure on outcomes and no moderating effects of polydrug exposure. An IQ loss of about 4.1–5.4 Full Scale IQ points was estimated for each 10 μg/dL increase in blood lead level at ages 4, 9, and 11 years as a function of blood lead level at age 4. Decrements in scores on tests of non-verbal reasoning were consistently associated with higher lead levels at age 4, while verbal decrements became apparent only at age 11. Lower reading summary scores at 9 and 11 years were consistently associated with higher lead exposure, while decrements in mathematics were not apparent until 11 years. Subgroup analyses on children with blood lead levels <10 μg/dL showed detrimental lead effects even at the 5 μg/dL level, providing additional evidence of adverse effects occurring at blood lead levels below the current 10 μg/dL public health blood lead action level.

1. Introduction

The detrimental effects of early exposure to lead on children's development have been well documented [14,23,46,51]. Recently, the debate has centered on the effects of low levels of lead exposure [34,49,65], as public health agencies such as the Centers for Disease Control and Prevention (CDC) and the Environmental Protection Agency (EPA) continue to define the value of 10 micrograms per deciliter (μg/dL) in blood as a level of concern in public health advisories. With no apparent threshold identified [51], accumulated empirical evidence suggests that lead-associated intellectual and academic deficits occur at blood lead levels substantially lower than 10 μg/dL as well. Lanphear and colleagues [37], using a representative sample of US children and adolescents aged 6–16, reported an inverse relationship between concurrent blood lead level and academic performance among children with blood lead level <5.0 μg/dL. Similarly, a recent study [42] reported that blood lead level <5.0 measured in early childhood was associated with a decline in reading and mathematic scores in 4th grade. A pooled-analysis based on seven prospective lead cohorts [38] found a significant reduction of IQ scores in children even with a maximum blood lead level <7.5 μg/dL. Further, IQ decrements associated with an increase of concurrent blood lead levels were greater at blood lead levels <10 μg/dL than at lead levels ≥10 μg/dL, indicating a non-linear relationship with a more pronounced impact on cognitive functioning at lower lead level. This decrement was also previously demonstrated by Canfield et al. [11]. However, Chiodo and colleagues [13] found no such evidence and reported a gradual linear dose–response relation to IQ scores.

The negative impact of lead exposure on cognitive development is often complicated by other risk factors, such as prenatal drug exposure. Prenatal exposure to alcohol [9,31,66], tobacco [24,25,36], marijuana [15,27,28], and cocaine [4,8,43,54,55] has been related to poorer cognitive development. As high as 12.5%–36% of high risk polydrug exposed children were estimated to have elevated blood lead levels ≥10 μg/dL during preschool assessment [3,39,44], compared to the general population rate of 8.65% for African American children and 2.02% for caucasian children [40]. Although prenatal drug exposure is a major problem for inner-city urban children [16,33,45,64], few studies have adequately examined the effect of lead in conjunction with prenatal drug exposure. Women who reportedly used alcohol or drugs prenatally have been excluded in

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most prospective studies of lead exposure [2,7,11,18–20,50,60]. However, without biologic verification of substance use, one cannot conclude that they have been reliably excluded given a tendency to underreport due to the stigma attached to substance use during pregnancy. Only prenatal exposure to tobacco has been recognized in some studies by employing dichotomized measures of use [11,37,38]. Exposure to other substances prenatally could moderate the effects of lead exposure, through synergistic effects that could worsen or protect against adverse lead effects. To date, only one cross-sectional study of lead exposure effects [13] has assessed and quantified the exposure to prenatal alcohol, cigarette, marijuana, and cocaine. Thus, the generalizability of previous findings to prenatally drug-exposed children is questionable.

The present study examines the relationship between early lead exposure measured at 4 years of age and children's IQ and academic achievement at 4, 9, and 11 years of age. It extends the existing literature by examining urban, poor, prenatally polydrug exposed children who may be more vulnerable to lead effects. By controlling for multiple prenatal exposures of alcohol, tobacco, marijuana, and cocaine, the present study can aid in assessing the impact of lead exposure on cognitive development in children of low socioeconomic status within a naturalistic context in which multiple risk factors are clustered and embedded. Prenatal drug exposure was quantified with multi-determined methods including biological markers (meconium) and explored as a potential confounder or moderator of lead effects. We also estimated the effects of lead at a lower threshold using a predefined cutoff value, <5.0 μg/dL, for a subgroup of children whose lead levels were below 10 μg/dL to clarify adverse effects below the current level of public health action.

2. Methods

2.1. Sample

The sample consisted of 278 inner-city children for whom blood lead levels were obtained at 4 years of age. All children were drawn from a cohort recruited at birth between September 1994 and June 1996 from a large urban county teaching hospital to participate in a longitudinal prospective study on the effects of prenatal cocaine exposure [52–55]. Pregnant women considered to be high risk for drug use due to lack of prenatal care, behavior suggesting intoxication, history of involvement with the Department of Human Services, or self-admitted drug use, were given drug toxicology screenings at infant birth. Women with a psychiatric history, low intellectual functioning, HIV-positive status, or chronic medical illness were excluded, as were infants with Down syndrome, fetal alcohol syndrome, or medical illness. A total of 415 infants and their mothers were enrolled at birth, of which 218 infants were identified as cocaine-exposed (CE) based on positive screens of infant meconium or urine, maternal urine, or maternal self-report to hospital or research staff (see Arendt et al. [1] for a complete description of drug use assessment). Comparison (i.e., 197 non-cocaine exposed (NCE)) infants were negative on all indicators. Women who used alcohol, marijuana, or tobacco during pregnancy were included in both groups. Groups did not differ in race, socioeconomic status (SES), or infant gender.

From birth to 4 years, there were 11 (8 CE and 3 NCE) deaths in this sample. At 4 years, 376 children (190 CE and 186 NCE) were assessed, representing a 93% retention rate for living children. Venous blood samples were obtained at the 4 year assessment by trained pediatric phlebotomists from a nearby teaching hospital. Of the 376 children seen at the 4 year visit, blood samples could not be obtained from 98 children (48 CE and 50 NCE) due to parental refusal, inability to draw blood without undue stress, child sickness, or logistical difficulties. A greater percentage of African-American and married women consented for blood collections, with a lower percentage of foster parents consenting for blood collection. Of the 278 (142 CE and 136 NCE) children with 4 year lead data available, 273 (141 CE and 132 NCE) and 267 (138 CE and 129 NCE) children were followed up at 9 and 11 years and assessed for cognitive development, yielding a 96% retention rate for children with blood lead measured at 4 years.

2.2. Procedure

Maternal and infant urine samples and infant meconium were obtained immediately before or after labor and delivery and analyzed for cocaine and other drug metabolites. At the newborn visit, biological mothers were asked to recall frequency and amount of drug use for the month prior to and for each trimester of pregnancy [53,54]. This drug assessment was updated with the child's current caregiver at each follow-up visit to obtain an assessment of recent, postnatal, caregiver drug use.

Children were seen at the developmental research laboratory for approximately 5 h at 4, 9, and 11 years of age. All caregivers were given a monetary stipend for participation, along with lunch and transportation costs. The Institutional Review Board of the participating hospital approved the study. Parental written, informed consent, including consent to obtain biological samples, and child assent (at ages 9 and 11) were obtained. A writ of confidentiality (DA-98-91) was obtained from the Department of Health and Human Services, which exempted the study from legislative, judicial, or administrative attempts to obtain confidential information.

2.2.1. Blood lead measure

Blood collection and analyses of lead were performed by the affiliate University Hospital Laboratory Services Foundation accredited by the College of American Pathologists and in compliance with Clinical Laboratory Improvement Amendments (CLIA) regulations. The lab was enrolled in the CDC proficiency testing program for blood lead and was Occupational Safety and Health Administration (OSHA) approved for blood lead analysis. Approximately 5 ml of venous blood were drawn by syringe into a lead free container containing an anticoagulant. Blood lead concentration was determined by atomic absorption spectrophotometry using a graphite furnace and matrix modification to eliminate chemical interferences (Varian).

2.2.2. Outcome measures

Children's intelligence was assessed using the abbreviated Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R) [62] at 4 years and the entire Wechsler Intelligence Scales for Children- Fourth Edition (WISC-IV) [61] at 9 and 11 years. The WPPSI-R is an individually administered, standardized, normative measure for assessing intelligence in young children, which yields an overall Full Scale IQ as well as Verbal and Performance IQ scores. Six subtests were administered, including Arithmetic, Vocabulary, Comprehension (Verbal scale), Object Assembly, Block Design, and Picture Completion (Performance Scale). Summary IQ scores were computed based on instructions for prorating scaled scores. The WISC-IV yields four summary indices (Verbal Comprehension, Perceptual Reasoning, Processing Speed, and Working Memory) and a Full Scale IQ. School achievement in reading and mathematics was measured using the Woodcock Johnson-III Tests of Achievement (WJTA-III) [67] at 9 and 11 years. The WJTA-III yields two cluster scores in Math and Reading. Examiners were unaware of lead and prenatal drug exposures, including cocaine.

2.2.3. Covariates

2.2.3.1. Cocaine and other drug exposures. Prenatal cocaine exposure status was defined as a dichotomous indicator (yes/no) based on infant meconium or urine, maternal urine, or maternal self-report. The number of tobacco cigarettes and marijuana joints smoked, and the

number of drinks of beer, wine, or hard liquor per week was computed, with each drink equivalent to 0.5 oz of absolute alcohol. For cocaine, the number of "rocks" consumed and the amount of money spent per day were also noted, in addition to the dichotomous cocaine status variable. Frequency of use was recorded for each drug on a Likert-type scale ranging from 0 (not at all) to 7 (daily use) and converted to reflect the average number of days per week a drug was used, except for cigarettes, which was collected as the number smoked per day. Frequency was multiplied by the amount used per day to compute an average use score for the month prior to pregnancy and for each trimester. These scores were then averaged to obtain a total average score. This drug measure was re-administered at the 4, 9, and 11 year visits to quantify postnatal drug use for the prior 30 day period by the child's current caregiver. The continuous drug variables were used in analyses.

2.2.3.2. Other covariates. Birth, demographic, and medical characteristics were considered as potential confounders including SES as measured by the Hollingshead Scale [30], maternal age and marital status at birth, years of education of biological mother, number of prenatal care visits, parity, child's race and gender, and infant head circumference. Maternal vocabulary was assessed at birth using the Peabody Picture Vocabulary Test-Revised (PPVT-R) [21] and using its third edition (PPVT-III) [22] at age 6. The Block Design (BD) and Picture Completion (PC) subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [63] were used to estimate non-verbal intelligence at birth. Maternal psychological distress was assessed using the Brief Symptom Inventory (BSI) [17], a standardized self-report scale, administered at birth and at each follow-up visit. The Global Severity Index (GSI), a summary score of the BSI used as an indicator of overall stress symptoms, was computed at birth and each follow-up visit. At each visit, the child's placement (either biological mother/relative or foster/adoptive caregiver) was noted and the data on the current caregiver were updated to provide concurrent assessment of caregiver intelligence and psychological distress in addition to drug use. The quality of the caregiving environment was assessed using the Home Observation of the Environment (HOME) [10], with the early childhood version used at 4 years and the middle childhood version used at 9 and 11 years. Iron Deficiency Anemia (IDA) status was defined by abnormal hemoglobin levels (<11.0 g/dl at 2, <11.2 g/dl at 4) plus any two of three iron measures in the abnormal range, mean corpuscular volume ($\leq$70 μm^3 at 2, $\leq$73 μm^3 at 4), % transferring saturation ($\leq$10% at 2, $\leq$12% at 4), and serum ferritin ($\leq$12 μg/l at both 2 and 4) at 2 or 4 years of age [44].

2.2.4. Data analyses

Data that were positively skewed (e.g. drug variables and GSI) were transformed using the natural logarithm transformation prior to analyses. Means and standard deviations were reported for each variable using the original distribution for ease of interpretation, with transformations used in analyses. The blood lead level was retained on its natural scale despite any presence of skewness as it is the focus of this analysis. Pearson or Spearman correlations were estimated to examine inter-relationships between covariates.

To examine the effect of lead exposure measured at 4 years on concurrent cognitive outcomes as well as later cognitive outcomes, this study analyzed each time point separately using multiple regressions. A restricted cubic spline function was fit to the data (without covariates) to evaluate whether blood lead level was linearly associated with outcomes, which produced a curve that followed the data with no a priori assumptions about the functional form of the relationship [29]. The restricted cubic spline function allows testing the H_0 (null hypothesis): relationship is linear against the H_a (alternative hypothesis): relationship is non-linear. Significant ($p<.05$) non-linearity indicates acceptance of the H_a (non-linear relationship), while insignificant ($p\geq.05$) non-linearity indicates a failure to reject the H_0 (linear relationship) [29].

After an initial model was chosen, each covariate was assessed. Covariates correlated with outcomes at $p\leq.20$ were entered into the regression model stepwise and were retained if, on entry, they were significant at $p<.10$ or caused substantial change (>10%) in the blood lead coefficient [41,57]. Environmental and prenatal factors were considered first, followed by demographic and drug exposure variables in the following order: blood lead level, the HOME score, biological and current caregiver PPVT standard score, WAIS-R BD and WAIS-R PC scores, child test age, race, and gender, maternal age at child's birth, maternal years of education, parity, number of prenatal care visits, marital status, socioeconomic status, biological and current caregiver GSI, and prenatal and current caregiver measures of cigarette, alcohol, marijuana, and cocaine exposure, current child placement (non-relative foster-adoptive care vs. not), and IDA. Infant head circumference, shown to be affected by prenatal drug exposure [53–55], was entered last. Child race, gender, and prenatal drug variables (alcohol, tobacco, marijuana, and cocaine) were explored as potential moderators of lead effects. The restricted cubic spline models and test of linearity were reevaluated for the final model with covariates to ensure that the initial model was appropriate after adjustment of covariates [29].

To estimate lead effect at a lower level, a dichotomous lead exposure group was created a priori based on a low threshold value (above vs. below 5 μg/dL) examined in several previous studies [13,37,38]. Multiple linear regression analyses were performed for a

Table 1
Biological maternal and child characteristics ($N=278$).

	N (%)	Mean (SD)	Median (IQR)
Biological maternal at birth			
African American	238 (86%)		
Married	39 (14%)		
Low SES[a]	271 (98%)		
No prenatal care	34 (12%)		
Number of prenatal visits		7.23 (5.00)	7 (3–10)
Age at birth		27.63 (5.16)	27 (23–31)
Parity		3.19 (1.90)	3 (2–4)
Years of education		11.84 (1.59)	12 (11–12)
Prevalence of prenatal drug use			
Alcohol	206 (77%)		
Cigarette	165 (61%)		
Marijuana	84 (31%)		
Cocaine	142 (51%)		
Average amount of prenatal drug use			
Alcohol dose/week		5.44 (14.26)	0.5 (0–4.0)
Cigarette use/day		6.91 (9.14)	3 (0–11.25)
Marijuana dose/week		0.79 (2.66)	0 (0–0.06)
Cocaine units/week		10.73 (28.06)	0.13 (0–8.25)
Global Severity Index		0.6 (0.63)	0.40 (0.17–0.87)
PPVT-R Standard Score		76.23 (15.39)	74 (66–85)
WAIS-R Block Design		7.17 (1.82)	7 (6–8)
WAIS-R Picture Completion		7.04 (2.20)	6 (5–8)
Child			
African American	236 (85%)		
Male	133 (48%)		
Gestational age (weeks)		38.12 (2.64)	39 (37–40)
Birth weight (g)		2907.54 (669.30)	3002 (2435–3365)
Baby length (cm)		48.27 (3.70)	48.5 (46.0–51.0)
Head circumference (cm)		32.98 (2.20)	33 (32.0–34.5)
Lead level at 4 years (μg/dL)		7.01 (4.07)	6.1 (4.0–9.0)
<5 μg/dL	100 (36%)		
5 μg/dL–<7.5 μg/dL	71 (26%)		
7.5 μg/dL–<10 μg/dL	55 (20%)		
≥10 μg/dL	52 (19%)		
Iron deficiency anemia	11 (4%)		

IQR = Inter Quartile Range; PPVT-R = Peabody Picture Vocabulary Test-Revised; WAIS-R = Wechsler Adult Intelligence Scale-Revised.
[a] Hollingshead classification IV and V.

Table 2
Caregiver characteristics, Mean (SD).

	4 year ($N=278$)	9 year ($N=273$)	11 year ($N=267$)
HOME score	41.71 (6.29)	43.39 (5.90)	46.71 (5.81)
Non-relative adoptive/foster, *n* (%)	27 (10%)	28 (10%)	24 (9%)
Global Severity Index	0.36 (0.40)	0.36 (0.43)	0.39 (0.47)
PPVT Standard Score	77.93 (15.91)	85.17 (9.50)	85.56 (9.42)
WAIS-R Block Design	7.08 (2.19)	7.10 (2.23)	7.20 (2.02)
WAIS-R Picture Completion	7.03 (2.31)	7.06 (2.38)	7.20 (2.39)
Average drug use (past 30 days)			
Cocaine units/week	3.27 (36.8)	0.006 (0.09)	0
Alcohol dose/week	2.47 (7.56)	1.54 (3.90)	1.80 (6.05)
Marijuana dose/week	0.17 (0.90)	0.32 (2.19)	0.82 (5.39)
Cigarette use/day	6.13 (8.11)	5.11 (7.07)	4.75 (6.64)

PPVT = Peabody Picture Vocabulary Test, PPVT-R (Revised) used at 4 year; PPVT-III (Third edition) was used at 9 and 11 years; WAIS-R = Wechsler Adult Intelligence Scale-Revised.

subgroup of children whose lead level was <10 μg/dL using the dichotomous exposure measure on outcomes with lead effects ($p<.1$) based on the final regression analyses. Adjusted mean scores were calculated using the covariates identified from the final models. All analyses were performed using SAS 9 (SAS Institute, Cary, NC) except for the test of linearity, where R 2.5 (The R Foundation for Statistical Computing) was employed.

3. Results

3.1. Sample characteristics

The 278 children were primarily African American ($n=236$, 86%) and of low SES ($n=271$, 98%). Fourteen percent ($n=39$) of their mothers were married at the child's birth, and 39% ($n=108$) had not finished high school (mean years of education 11.8 (SD = 1.6)). A majority of the children ($n=246$, 88%) were prenatally exposed to at least one substance and two-thirds ($n=182$, 65%) to two or more substances. About half of the children (51%, $n=142$) were prenatally exposed to cocaine and 77% ($n=206$) to alcohol (Table 1). The mean blood lead level at 4 years of age was 7.0 μg/dL (SD = 4.1; range 1.3–23.8). Thirty-six percent of the children ($n=100$) had a lead level <5 μg/dL and 19% ($n=52$) had ≥10 μg/dL. Eleven children (4%, 9 CE and 2 NCE) had IDA at the preschool assessment. About 10% of the children were cared for by non-relative foster or adoptive parents at any one visit (Table 2). The mean Full Scale IQ (unadjusted) was 81 (SD = 13) at 4 years of age and 86 (SD = 13) at 9 and 11 years of age.

In this sample, a higher lead level was related to greater maternal parity ($r=.15$, $p<.01$), lower infant gestational age ($r=-.15$, $p<.02$), birth weight ($r=-.12$, $p<.06$), length ($r=-.12$, $p<.05$), and head circumference ($r=-.10$, $p<.09$), lower birth maternal WAIS-R BD score ($r=-.16$ $p<.02$), greater alcohol exposure during the 3rd trimester ($r=.12$, $p<.06$), and lower maternal education ($r=-.12$, $p<.06$). Lead level was also related to less optimal environmental and caregiver functioning as shown by lower HOME scores ($r=-.34$, $p<.0001$ at 4; $r=-.20$, $p<.003$ at 9), lower current caregiver's PPVT scores ($r=-.15$, $p<.02$ at 4; $r=-.24$, $p<.001$ at 9; $r=-.27$, $p<.0001$ at 11), lower WAIS-R BD score ($r=-.17$, $p<.02$ at 11), and higher GSI scores ($r=.15$, $p<.02$ at 4 years). Mean lead levels were higher for African American children (M = 7.18, SD = 3.93) than Caucasian children (M = 6.04, SD = 4.73, $t=-1.67$, $p<.10$), for NCE (M = 7.39, SD = 4.16) than CE children (M = 6.64, SD = 3.96, $t=1.55$, $p<.12$), and for children in birth mother or relative care (M = 7.16, SD = 3.95) than those in foster/adoptive care (M = 5.57, SD = 4.95, $t=1.94$, $p<.06$). Further analyses on the interrelationships among cocaine exposure, non-relative foster/adoptive care placement, and blood lead level revealed that CE children ($n=23$ at 4 years, for example) were more likely to be placed with non-relative foster/adoptive caregivers than NCE children ($n=4$ at 4 years). Also, the blood lead level of those children placed in non-relative foster/adoptive care ($n=23$, M = 4.47, SD = 3.27) was lower than that of CE children in birth families ($n=119$, M = 7.06, SD = 3.96) or NCE children ($n=136$, M = 7.39, SD = 4.16). Maternal PPVT standard score at birth, child gender, IDA, or other prenatal drug exposures were not related ($p>.20$) to lead.

3.2. Association of lead with cognitive functioning and school achievement

Examination of the restricted cubic spline models failed to provide evidence of a non-linear relation between lead and all of the outcomes. All models (without and with covariates) showed insignificant ($ps>.1$) non-linearity dose–response. Fig. 1 presents the dose–response relationship between concurrent blood lead and Performance IQ at 4 years of age adjusted for covariates as an example. Although it showed a seemingly steeper slope at lower lead levels (up to 7 μg/dL), it did not reach statistical significance ($F=1.6$, $df=3$, $p=.19$). Since the restricted cubic spline regression model did not provide evidence for a departure from linearity, the shape of the exposure–response relationship was assumed to be linear.

Table 3 presents the relationships of blood lead level with the outcomes before and after adjustment for covariates using the unstandardized regression coefficient (b). Covariates adjusted for each outcome are listed as footnotes. After adjusting for covariates, lead was significantly related to Full Scale IQ across all three assessment time points; a 1 μg/dL increase in blood lead level was associated with decreased Full Scale IQ by 0.50, 0.41, and 0.54 points at 4, 9, and 11 years respectively. At 4 years, Performance IQ, but not Verbal IQ, was related to blood lead level; a 1 μg/dL blood lead level was associated with a 0.77 lowering of Performance IQ. At both 9 and 11 years, significant lead effects were found on the Perceptual Reasoning Index and the WJTA Reading cluster scores; a 0.45-point decrement at 9 and a 0.61-point decrement at 11 years in Perceptual Reasoning Index scores and a 0.58-point decrement at 9 and a 0.60-point at 11 years in WJTA Reading cluster scores were associated with each 1 μg/dL increase in blood lead level. There was a significant negative association with the Verbal Comprehension Index and the WJTA Math cluster score at 11 years but not at 9 years. No relationship with the Working Memory or Processing Speed Indices was found at either time point. No interaction effects were found between the blood lead level and race, gender, prenatal alcohol, tobacco, marijuana, or cocaine exposure measures, or birth parameters (gestational age, birth weight or head circumference).

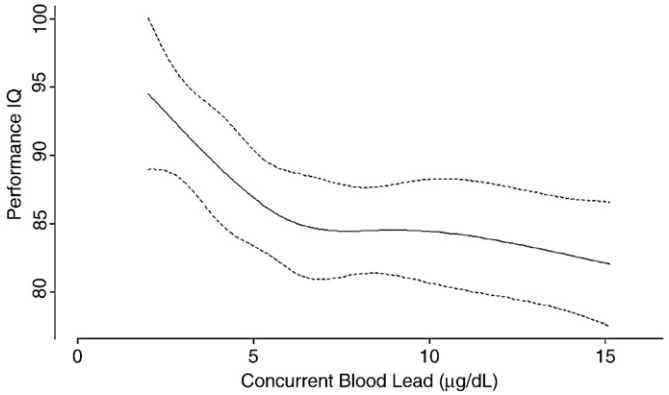

Fig. 1. Performance IQ at 4 years of age as a function of concurrent blood lead level adjusted for covariates presenting insignificant ($p>.18$) non-linearity using the restricted cubic splines model. The dotted lines are the 95% confidence intervals for the restricted cubic splines.

Table 3
Estimated regression coefficients (SE) of Lead in IQ and school achievement from simple and multiple regression analyses.

	Unadjusted b (SE)	Adjusted b (SE)
4 year (n = 278)		
Full Scale IQ[a]	−.87 (.19)****	−.50 (.20)*
Verbal[b]	−.52 (.18)**	−.20 (.19)
Performance[c]	−1.13 (.21)****	−.74 (.22)***
9 year (n = 273)		
Full Scale IQ[d]	−.69 (.19)***	−.41 (.19)*
Verbal comprehension[e]	−.63 (.18)***	−.35 (.18) †
Perceptual reasoning[f]	−.72 (.20)***	−.45 (.21)*
Working memory[g]	−.50 (.20)*	−.31 (.21)
Processing speed[h]	−.31 (.18) †	−.25 (.19)
WJTA Math[i]	−.50 (.18)**	−.33 (.18) †
WJTA Reading[j]	−.78 (.22)***	−.58 (.23)*
11 year(n = 267)		
Full Scale IQ[k]	−.73 (.19)****	−.54 (.19)**
Verbal comprehension[l]	−.70 (.17)****	−.51 (.17)**
Perceptual reasoning[m]	−.76 (.21)***	−.61 (.20)**
Working memory[n]	−.60 (.23)**	−.43 (.24) †
Processing speed[o]	−.23 (.20)	−.24 (.20)
WJTA Math[p]	−.61 (.20)**	−.45 (.20)*
WJTA Reading[q]	−.75 (.20)***	−.60 (.21)**

Note. Significant covariates are listed in italics.
*$P \leq .05$, **$P \leq .01$, ***$P \leq .001$, ****$P < .0001$, †$P \leq .10$.

[a] Adjusted for *Home Observation for Measurement of the Environment (HOME) score*, current caregiver's Peabody Picture Vocabulary Test-Revised (PPVT-R) at 4 years, child sex, *parity*, maternal marital status, and *head circumference at birth.*

[b] Adjusted for *HOME score, child sex*, parity, IDA, and *head circumference at birth*.

[c] Adjusted for *HOME score*, current caregiver's PPVT-R at 4 years, *parity, maternal marital status*, log of prenatal cocaine average, and *head circumference at birth.*

[d] Adjusted for *HOME score, birth maternal PPVT-R at birth, child race*, log of prenatal cocaine average, and *head circumference at birth*.

[e] Adjusted for *HOME score, child race, birth maternal years of education*, parity, IDA, and *head circumference at birth*.

[f] Adjusted for HOME score, *birth maternal PPVT-R at birth*, *birth maternal WAIS-BD,* child race, log of prenatal cocaine average, log of prenatal alcohol average, and *head circumference at birth.*

[g] Adjusted for *HOME score*, birth maternal PPVT-R at birth, log of prenatal alcohol average, and *head circumference at birth.*

[h] Adjusted for HOME score, *birth maternal PPVT-R at birth*, *current caregiver's WAIS-PC at* 9 years, child sex, and head circumference at birth.

[i] Adjusted for HOME score, *birth maternal PPVT-R at birth*, *IDA,* and head circumference at birth.

[j] Adjusted for *HOME score,* birth maternal PPVT-R at birth, current caregiver's WAIS-PC at 9 years, *child sex,* log of prenatal cocaine average, *log of prenatal alcohol average*, IDA, and head circumference at birth.

[k] Adjusted for *HOME score, birth maternal PPVT-R at birth, log of prenatal marijuana 1st trimester, and head circumference at birth*.

[l] Adjusted for HOME score, *birth maternal PPVT-R at birth*, *child race*, log of prenatal cocaine average, IDA, and *head circumference at birth.*

[m] Adjusted for HOME score, *birth maternal PPVT-R at birth, birth maternal WAIS-BD*, and *head circumference at birth*.

[n] Adjusted for *HOME score*, birth maternal PPVT-R at birth, *log of prenatal marijuana 1st trimester, and head circumference at birth.*

[o] Adjusted for HOME score, *birth maternal PPVT-R at birth,* current caregiver PPVT at 11 years, Current caregiver WAIS-BD at 11 years, *child sex,* log of prenatal cocaine average, current caregiver's marijuana use, and *head circumference at birth.*

[p] Adjusted for *HOME score,* birth maternal PPVT-R at birth, log of prenatal cocaine average, and *head circumference at birth.*

[q] Adjusted for *HOME score, birth maternal PPVT-R at birth, child sex*, log of prenatal cocaine average, *log of prenatal alcohol 2nd trimester*, current caregiver's alcohol use, and *head circumference at birth*.

3.3. Subgroup analyses for children whose lead level was below 10 μg/dL

Table 4 provides adjusted mean scores and the standard error (SE) for selected outcomes for a subgroup of children ($n = 226$, 81%) whose lead levels were below the current 10 μg/dL public health action level at 4 years. Children whose blood lead levels were between 10 μg/dL and 5 μg/dL performed more poorly in terms of Performance IQ at 4 years, the Perceptual Reasoning Index at 9 years and the WJTA Reading cluster score at both 9 and 11 years than children whose blood lead level was below 5 μg/dL.

4. Discussion

The present study demonstrated that cognitive functioning at 4, 9, and 11 years was inversely associated with blood lead levels measured at 4 years of age in low SES, primarily African–American, urban children who were polydrug exposed prenatally. Despite maturation, changes in the test used, and a remote lead measure for the 9 and 11 year assessments, the strength of the association of lead on Full Scale IQ from 4 to 11 years of age was remarkably consistent.

The present study indicates that specific cognitive domains might be vulnerable to lead exposure at different stages of development. Non-verbal reasoning decrements, as measured by WPPSI-R Performance IQ and WISC-IV Perceptual Reasoning Index were consistently associated with higher lead exposure throughout the preschool/elementary school ages, while verbal decrements were not apparent until 11 years of age. Also, a lower reading score was consistently associated with lead exposure at 9 and 11 years, while math scores were not affected until 11 years. Studies from longitudinal prospective cohorts have produced inconsistent findings, with different functional domains affected at different ages [47]. In the Yugoslavia study, higher lead exposure was more strongly related to lower Performance IQ than Verbal IQ at 7 years of age [60], but by ages 10–12 it was similarly related to both Performance and Verbal IQ [59], as in the present findings. In the Boston study on socio-economically advantaged children with relatively low lead exposure, lower Performance IQ was related to higher lead exposure at 57 months [5] but Verbal IQ decrements were not apparent until 10 years [7]. Other cohorts from Port Pirie, Australia, reported verbal, but not performance, decrements throughout the elementary school years [2,58].

Prior findings are also inconsistent with respect to lead and academic achievement, although some studies suggest reading may be more affected than mathematics [37,42,56]. Mixed findings may reflect methodological differences among studies, the relative insensitivity of outcome measures at certain ages (e.g., verbal ability in earlier ages), common underlying factors (e.g. attention) manifested differently over time [7], or inter-individual differences in vulnerability to lead effects [6], all of which, nevertheless, collectively demonstrate non-ignorable impairment resulting from lead exposure.

Consistent with Chiodo et al. [13], our formal test of linearity using a restricted cubic spline function showed insignificant non-linear dose–response relationships for each outcome. As some previous

Table 4
Adjusted mean (SE) of IQ and school achievement scores among children with blood lead level < 10 μg/dL.

	Lead level		
	<5 μg/dL	≥5 μg/dL	*P*
4 year	*n* = 100	*n* = 126	
Full Scale IQ	83.74 (1.35)	81.55 (1.16)	.23
Performance	90.37 (1.48)	85.36 (1.25)	.01
9 year	*n* = 98	*n* = 123	
Full Scale IQ	87.92 (1.31)	85.09 (1.13)	.11
Verbal comprehension	88.02 (1.28)	86.30 (1.12)	.32
Perceptual reasoning	92.57 (1.37)	87.84 (1.19)	.01
WJTA Math	97.57 (1.20)	94.55 (1.06)	.06
WJTA Reading	92.36 (1.49)	86.31 (1.32)	.003
11 year	*n* = 95	*n* = 121	
Full Scale IQ	88.03 (1.33)	85.90 (1.14)	.23
Verbal comprehension	86.36 (1.19)	84.56 (1.03)	.26
Perceptual reasoning	93.29 (1.37)	90.68 (1.20)	.16
Working memory	91.54 (1.68)	89.72 (1.44)	.41
WJTA Math	94.91 (1.37)	93.28 (1.20)	.37
WJTA Reading	92.45 (1.41)	88.59 (1.22)	.04

studies [11,35,38] have reported non-linear relationships with a steeper slope at lower lead levels, the issue of the functional form of lead-cognitive outcome relationships warrants further attention.

When lead exposure measured at 4 years of age was dichotomized at 5 μg/dL on a subgroup of children with low lead levels < 10 μg/dL, the decrements found in Performance IQ, the Perceptual Reasoning Index and the Reading cluster score, provide additional evidence of significant adverse effects occurring at blood lead levels below the current CDC action level. The present study supports public policy efforts and research studies calling for a reduction in the current action level to at least 5 μg/dL [11,13,37,38]. Gilbert and Weiss [26] proposed 2 μg/dL as the new CDC blood lead action level based on a review of the research literatures.

No interaction effects were found between lead and prenatal alcohol, tobacco, marijuana, or cocaine exposure. Prenatal drug exposure did not reduce or magnify the adverse effect of lead on the cognitive outcomes, which suggests that the lead effect documented in prior studies using non-drug exposed children may be extended to children who were prenatally exposed to drugs.

One limitation of the present study is the use of a single blood lead level measured at 4 years, which may be primarily an indicator of exposure at 4 years. Without multiple lead measures, especially during the period of 18–36 months of age when blood lead levels tend to be highest and most variable [32], our lead measure may not fully capture the true impact of overall lead exposure. Further, with the lack of lead levels measured at 9 and 11 years, we might miss later chronic lead exposure. Thus, relationships between lead and cognitive outcomes at 9 and 11 years might be underestimated, and our subgroup analyses on children with lead level < 10 μg/dL might include children whose lead level exceeded 10 μg/dL in earlier and later ages. Nevertheless, blood lead levels taken in early childhood track closely with subsequent blood lead levels [19,37]. Previous blood lead levels taken at 2 years were available for a sub-sample of our study children ($n = 123$), and the correlation between those two lead measures was $r = .78$. Studies indicate that later or concurrent lead levels provide the strongest predictor for lead related neurotoxicity [11,12,14,38,48,59] because later measures of blood lead are probably markers of physiologically based genetic factors reflecting blood lead metabolism and retention [14].

Our estimation of a 4.1–5.4 Full Scale IQ point loss for each 10 μg/dL at 4, 9, and 11 years of age as a function of 4 year lead level should be understood within the range of lead exposure in our sample (1.3–23.8). Due to the limited lead exposure in this sample, our data allowed us to study the effect of low lead level and its functional form on cognitive outcomes, but it may not extend its estimation to higher lead levels such as ≥ 25 μg/dL.

Despite these limitations, this study has significant strengths. A comprehensive list of covariates and confounders, including prenatal drug exposures and caregiving environment, were evaluated and controlled statistically when necessary. Assessment at multiple time points, combined with a remarkably high rate of retention at follow-up, allowed repeated observation of an association between lead and cognitive outcomes in different developmental stages, increasing confidence in the findings. Use of the restricted cubic spline models allowed a formal test of a suggested non-linearity relationship between lead level and cognitive outcomes found in some previous studies [11,35,38]. The low levels of lead exposure found in this sample make it appropriate to study the effect of lead exposure at low levels.

The present study provides additional evidence of the effects of early lead exposure persisting into late childhood, manifested by poor cognitive outcomes and school achievement. The impact of lead on cognitive and school outcomes appears quite robust across ages. Detrimental lead effects apparent even at 5 μg/dL provide further evidence that public health agencies such as the CDC and EPA need to reevaluate their current 10 μg/dL level of concern and take preventative measures to lower lead exposure risk for children.

Conflicts of Interest

The authors of this paper have no financial or personal relationship with people or organizations that could inappropriately influence the work submitted.

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