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Lead exposure, IQ, and behavior in urban 5-7 year olds: Does lead affect behavior only by lowering IQ?

Aimin Chen, MD, PhD[a,e], **Bo Cai, PhD**[b], **Kim N. Dietrich, PhD**[c], **Jerilynn Radcliffe, PhD**[d], and **Walter J. Rogan, MD**[a]

[a]*Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina*

[b]*Biostatistics Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina*

[c]*Department of Environmental Health, University of Cincinnati, Cincinnati, Ohio*

[d]*Department of Psychology, Children's Hospital of Philadelphia, and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania*

Abstract

Background—Lead exposure in childhood lowers IQ scores, but its effect on children's behavior is less clear. Since IQ *per se* affects behavior, measuring lead's direct effect requires measuring and then adjusting for IQ. In addition, either peak blood lead concentration, usually at age 2 years, or the lower blood lead measured at school age may be the most relevant. Few studies have all this information.

Objective—To differentiate the direct effect of lead on behavior and the indirect effect through IQ, and to examine the strength of the association for peak and concurrent blood lead concentration.

Methods—Data come from a clinical trial of the chelating drug succimer to prevent cognitive impairment in 780 urban 12-33 month olds with blood lead concentration of 20-44 μg/dL. The children were followed from ages 2 to 7 years. The trial data were analyzed as a prospective observational study.

Results—Blood lead concentration at age 2 years was not associated with Conners' Parent Rating Scale-Revised (CPRS-R) scores at age 5 years or Behavioral Assessment Systems for Children (BASC) scores at age 7 years. Blood lead at age 7 years had direct effects on the BASC Behavioral Symptoms Index, Externalizing, and School Problems at age 7.

Conclusions—Concurrent blood lead concentration was associated with Externalizing and School Problems scales at age 7 years, and the effect was not entirely mediated through lead's effect on IQ.

Keywords

lead; cognition; behavior; child; longitudinal studies

Corresponding author: Walter J. Rogan MD, Epidemiology Branch, NIEHS, MD A3-05, P.O. Box 12233, Research Triangle Park, NC 27709, USA Tel: (919) 541-4578, Fax: (919) 541-2511, E-mail: rogan@niehs.nih.gov.
[e]Currently Department of Preventive Medicine, Creighton University School of Medicine, Omaha, Nebraska

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INTRODUCTION

Even small amounts of lead exposure in childhood appear to lower scores on Intelligence Quotient (IQ) tests. Multiple cohort and cross sectional studies give similar estimates of the size of the effect.[1-5] Although the Centers for Disease Control and Prevention had set a "level of concern" at 10 μg/dL blood lead concentration, a threshold below which lead does not affect IQ has not been determined, and recent studies have extended the relation to below 10 μg/dL.[6-8] Whether lead exposure produces other psychological or behavioral damage in children is less well studied. These other dimensions are important because they may affect learning and school performance even in children with higher IQ. Older reports suggested associations between lead exposure and poorer classroom performance,[9] impaired educational attainment,[10, 11] inattention and hyperactivity,[12, 13] juvenile delinquency,[14] motor development,[15-17] or behavioral problems.[18-25] Lead was associated with externalizing (i.e., aggression) and internalizing (i.e., worry) problems in several studies using behavioral measures such as the Child Behavior Checklist.[19, 20, 25]

Studying behavior in the presence of an effect of lead on IQ presents both practical and inferential problems. First, understanding how lead exposure might affect the child's psychological and emotional function at school and at home is approached both by questioning the parent and teacher about the child's behavior and by testing specific relevant functional domains of mood and behavior. However, the tests may not isolate the specific domain of interest from IQ, and in practice are often significantly correlated with IQ. Moreover, IQ may be on the pathway leading to behavioral problems.[26] So, without appropriate control for IQ, the nature of the lead effect on behavior cannot be distinguished.[25, 27] Second, exposure to lead may continue from the fetal period through childhood. Even though children's lead concentrations correlate over time, the trajectories vary enough that a single measurement of blood concentration is insufficient to characterize an individual child's exposure over time. In particular, we need to be able to distinguish whether peak blood lead, which occurs at about age 2 years in the US, or concurrent blood lead, which is usually lower by school age when IQ and behavioral testing is done, accounts for any effect on behavior.

In the Treatment of Lead-exposed Children (TLC) study, we measured blood lead concentration periodically from age 2 to 7 years and have IQ, neuropsychological, and behavioral test scores at ages 5 and 7. Thus, we can analyze the association between lead and behavior while taking IQ into account, and examine the relative strength of association between blood lead concentrations at different ages, IQ, and behavioral test scores.

SUBJECTS AND METHODS

The TLC study was a multi-center, randomized, placebo-controlled clinical trial of 780 children 12 to 33 months old (mean 2 years, standard deviation 0.5 year) who had blood lead concentrations of 20-44 μg/dL, to investigate effects of succimer, an oral chelating agent, on cognitive, behavioral and physical development.[28] The study was approved by the institutional review boards at the clinical centers, the Harvard School of Public Health, the Centers for Disease Control and Prevention, and the National Institute of Environmental Health Sciences. The parent(s) of all children provided written informed consent. Although up to three courses of treatment with succimer was effective in lowering blood lead concentrations for about 9-10 months, it did not improve scores on tests of cognition, behavior, or neuropsychological function in children at 36 months[29] or 60 months of follow-up[30] as compared with placebo. Since the succimer treatment did not affect lead concentrations at baseline and ages 5 and 7, nor did it affect IQ and behavior scores at ages 5 and 7, the succimer and placebo study groups can be combined to study prospectively the effect of blood lead concentrations on the scores of neuropsychological and behavioral tests.

Blood lead concentrations

Venous blood was collected with lead-free containers twice before randomization and on day 7, 28, and 42 after the beginning of each course of treatment. After treatment ended, blood lead concentrations were measured every 3 to 4 months. We use the second blood sample before randomization (n=780) as baseline (at about age 2), the blood sample at 36 months follow-up (n=731) as the age 5 sample, and the last blood sample at 60 months follow-up (n=623) as the age 7 sample. The blood lead concentrations were measured at the Nutritional Biochemistry Branch of CDC by atomic absorption spectrometry based on the methods described by Miller et al.[31] For blood lead concentrations at 7 years, one child who had a very high blood lead concentration of 51 μg/dL was excluded, leaving 622 for use in this analysis.

Cognitive tests

At about age 5 years, the child's IQ was determined with the Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R);[32] at age 7 years, child IQ was tested with the Wechsler Intelligence Scale for Children-III (WISC-III).[33] At one of the visits between enrollment and the 36 months follow-up, the caregiver's IQ (the mother for 88% of children, the father for 4%, and another caregiver for 8%) was measured with the two subtest version of the Wechsler Adult Intelligence Scale-Revised.[34, 35]

Behavioral test batteries

At about 5 years of age, the Conners' Parent Rating Scale-Revised (CPRS-R)[36] was administered. The CPRS-R is a 27-item scale and yields an Oppositional Index, Hyperactivity Index, Attention Deficit Hyperactivity Disorder (ADHD) Index; the average of these three indices yields what we called the Behavioral Index.

At age 7 years, the children were tested with the Behavior Assessment System for Children teacher rating scale (BASC-TRS) and BASC parent rating scale (BASC-PRS).[37] The BASC for parents yields 4 composite scales: Adaptive Skills, Behavioral Symptoms Index, Externalizing Problems, and Internalizing Problems. The BASC for teachers yields those 4 scales plus a School Problems scale. Both CPRS-R and BASC yield T scores that have a mean of 50 and a standard deviation of 10 in the general population. Higher CPRS-R and BASC scores generally indicated worse behavioral problems except the BASC Adaptive Skills scale where higher scores were optimal.

Statistical analysis

We examined the lead and behavioral associations while controlling for the lead effect on IQ. First we did a correlation analysis of behavior scores and concurrent IQ (i.e., behavior at age 5 and IQ at age 5). Then we examined the lead and behavior associations using scatter plot and non-parametric spline regressions with S-PLUS software (Insightful Corp., Seattle, WA). Because spline regressions showed an approximately linear relation, we used linear models for examining the lead effect. Blood lead concentrations in TLC children were part of the eligibility criteria, and thus have a restricted spread. This allows us to use the original (i.e., untransformed) values of blood lead concentrations, facilitating the interpretation of the models. Based on the literature and our previous work with the data,[19, 24, 25, 38, 39] *a priori* covariates include clinic center (Baltimore, Newark, Philadelphia, and Cincinnati), race (black, white and others), gender (male, female), language (English or Spanish), parent's education (under 12 years, 12 years, over 12 years), parent's employment (neither working, either working), single parent (yes, no), age at blood lead concentration test, and caregiver's IQ. Treatment *per se* was not associated with behavior scores, and additional adjustment for treatment group did not markedly change the results and thus was not included in subsequent analyses.

We simultaneously estimated the strengths of lead effects on behavior, both the direct and indirect (through IQ), by using path analysis, a special case of structural equation modeling, which tests the fit of the correlation matrix against two or more causal models. In path analysis, a regression is done for each variable in the model (in our case, the behavioral test scores) as dependent on others that may be causal. When the model has two or more causal variables (in our case, lead and IQ, plus covariates), path coefficients are partial regression coefficients that measure the extent of effect of one variable on another in the path model controlling for other prior variables. Path coefficients can be used to decompose associations into direct and indirect effects. A more detailed description of this procedure can be found in several references.[40,41] The path analysis was tested via the LISREL 8 program,[42] using a maximum likelihood structural equation model, which provides unstandardized regression coefficients and their standard errors for both direct and indirect effects.[43] The total effect of lead on behavior would be the sum of direct and indirect effects.

Blood lead concentrations in the same child are correlated, and multiple measures in one model are collinear and the coefficients are difficult to interpret. We thus constructed separate models for the different blood lead concentrations, either peak (at ~ age 2 years) or concurrent with behavioral and IQ testing (5 or 7 years). All the tests were two-sided. Due to the difference in the number of children tested for each follow-up measurement, the sample sizes in the various regression models differ slightly.

For BASC scores at 7 years, we also did logistic regression on the percentage of children with BASC problem scores ≥ 60, including at risk for (score 60-69) and with clinical behavioral problems (score over 70), by concurrent blood lead concentration. Mplus software was used to calculate the direct and indirect effect of lead in the logistic models.[44]

RESULTS

Four centers were involved in the recruitment, treatment and follow-up of a total of 780 children in the TLC study: Baltimore (n=213), Newark (n=208), Philadelphia (n=165), and Cincinnati (n=194). Three hundred and ninety six children were randomly assigned to receive succimer and 384 to placebo. There were no differences between treatment and placebo groups in age, gender, race, and socioeconomic status at recruitment. Overall the children were mostly black (77%), spoke English (95%), with a single parent (72%), and with parent receiving public assistance (97%). Females accounted for 44% of children, 40% of children had parents with less than 12 years education, and 58% of children had neither parent employed.

Blood Lead concentrations

At baseline, the mean blood lead concentration was 26 μg/dL. It declined to 12 μg/dL (range 2-35 μg/dL) at 36 months follow-up and to 8 μg/dL (range 0-26 μg/dL) at 60 months follow-up (Table 1). There were no differences in blood lead concentrations between succimer and placebo groups at these three age points (mean±SD age: 2.0±0.5, 5.0±0.5, and 7.0±0.2 years, respectively).

Cognitive tests

The cognitive scores (mean±SD) in TLC children at baseline, age 5 and age 7 are shown in Table 1. Caregiver's IQ of these children had a mean of 80 and a standard deviation of 11. Again, these cognitive scores of both children and caregivers did not differ by treatment group.

Behavioral tests

The behavioral test scores (mean±SD) at 5 and 7 years are shown in Table 1. Also shown are the correlation coefficients of these test scores with IQ measured at the same age.

Lead and behavior association

We first plotted blood lead concentration and behavior scores and did spline regression. As examples, results of CPRS-R (at age 5) and teacher-rated BASC (at age 7) are shown in figures 1 and 2. Behavioral problems tend to increase with increasing blood lead concentration at both ages 5 and 7 in the unadjusted data. In the path analysis for the CPRS-R, however, there were no statistically significant direct effects of blood lead at age 2 or age 5; indirect effects were small and not consistent (Table 2). At age 7, there were no statistically significant direct or indirect effects of blood lead concentration at age 2 (data not shown). Blood lead concentration at age 7 had a statistically significant direct effect on BASC-TRS behavioral symptoms index, externalizing problems, and school problems, and BASC-PRS externalizing problems (Figures 3 and 4). There were indirect effects of blood lead concentration at age 7 on all measurements except BASCTRS externalizing problems, and BASC-PRS internalizing problems.

In the logistic regression analysis examining at-risk of or having clinically significant behavior problems, a 10 μg/dL elevation in 7-year lead was associated with increased risk in teacher-rated externalizing and school problems and parent-rated behavioral symptoms index by direct effect (Table 3).

DISCUSSION

In data from a clinical trial of lead-exposed children, we found that lead exposure was associated with behavior problems in urban 5-7 year olds. Using a modeling strategy designed to separate direct and indirect effects of lead, we found that, in 5 year olds, concurrent blood lead concentration had no direct effect on behavior, and indirect effects were small and inconsistent, although some were statistically significant. Thus, we believe that, if lead exposure is affecting behavior in 5 year olds, it is doing so mostly though IQ, and direct effects have not emerged or are not measurable with the methods we used. Although the oppositional index in CPRS-R and parent-rated BASC externalizing problem scores were correlated (with correlation coefficient 0.49), these two indices may not capture the same behavioral dimension. In 7 year olds, there is no effect of blood lead concentration at age 2. However, for the blood lead at 7 years, there are direct, relatively large effects on the Teacher Rating Scale of BASC (Behavioral Symptoms Index, Externalizing Problems, and School Problems); indirect effects on these are smaller (the indirect effect on Externalizing Problems was only borderline significant). For Adaptive Skills, the indirect effect is significant. Internalizing Problems (excessive anxiety or worry) is the scale with the least effects, with a small but significant indirect effect and a similar but less precisely estimated direct effect. The results from the Parent Rating Scale of the BASC are consistent with teacher report, showing a large direct effect on Externalizing Problems and a smaller but significant indirect effect on Adaptive Skills. In general, the results are consistent with a direct effect at age 7 of contemporaneously measured blood lead on behavior, specifically conduct and school problems, and an indirect effect through IQ on most other neuropsychological test scores.

The lead and IQ association has long been the focus of investigation for lead effects on the child's nervous system, partly because of the easiness, reliability, and validity of IQ tests and the easy interpretation for both researchers and regulators.[27, 45] Non-cognitive effects of lead, on the other hand, are much more complex to study. Further, it has not been the norm in studies that did include behavioral or other measures to tease apart the lead effects on IQ in order to isolate a direct effect on behavior, even when IQ was measured. The Port Pirie cohort study reported that both externalizing and internalizing behavior problem scores were negatively associated with lead after controlling for child's IQ;[25] we find relatively large direct effects of lead on externalizing problems, and smaller, indirect effects on internalizing problems.

In the studies of lead effects on child IQ, it has long been held that the cross-sectional association between lead and IQ in school-age children could be the residual effects of peak blood lead concentration at about age 2.[1, 4, 5] Recent analysis of TLC data[39] and pooled analysis of seven international cohort studies[8], however, show that concurrent blood lead concentration has the strongest association with IQ scores. For behavior, such analyses are scarce; Burns et al found postnatal lead measures had associations with Child Behavior Checklist total behavior problem scores "qualitatively similar" to lifetime average lead exposure in Port Pirie study.[25] In our study, for both teacher and parent BASC scores, concurrent blood lead generally had a stronger association than earlier blood lead measures. This is consistent with our previous analysis of the lead and IQ association.[39] The results suggest that prevention of lead exposure should continue into later childhood and not cease soon after peak blood lead begins to fall at about age 3.

The biological mechanism of lead effects on cognitive function and neurobehavior has been studied for a long time. Lead has been found to affect synaptogenesis, postsynaptic N-methyl-D-aspartate receptor sensitivity, calcium-mediated events, neurotransmitter dopamine release, and mitochondria activities.[46-48] However, the possible pathway of lead effects on behavior is still to be determined.

Our study has the strength of large sample size, long follow-up period, high retention rate of subjects in the follow-up, multiple measurements of behavior, and good quality control in the measurements. The limitations of the study are lack of Home Observation for Measurement of the Environment (HOME) score and limited generalizability to the general population because of the high blood lead at enrollment (mean 26 μg/dL in TLC study vs. 2 μg/dL in US children). Although it may be that effects of lead on behavior occur only in children with relatively high exposures such as those in TLC, experience with lead and IQ is not reassuring, in that the dose response curve appears to be at least linear and may be steeper at lower levels of exposure.[7, 8] Nonetheless, in the eastern US cities where TLC was done, poor housing, lead exposure, poverty, and other social stressors are strongly confounded, and so the causal nature of the lead and behavior association cannot be proven absolutely by observational study.

With the regulation of leaded gasoline and paint, the mean blood lead concentration in US children declined remarkably in the past three decades. However, the best estimate of the number of children aged 1-5 years with blood lead concentration over 10 μg/dL in 1999-2002 was 1.6% (approximately 310,000 children).[49] If lead effects on behavior are independent of its effects on IQ, the adverse effects of lead exposure in children would be larger than currently thought, but the benefits of prevention of lead exposure would also be magnified. Further studies are needed to study the associations between baseline and concurrent blood lead levels and neuropsychological function and behavior problems among children older than 7, and into adolescence. How exposure to urban violence or other stressors associated with poverty impact lead-exposed children as they enter adolescence is yet to be determined, although there are now at least two studies in which lead exposure in early life is associated with later delinquent behavior.[14, 47]

CONCLUSIONS

We have found concurrent blood lead concentration was associated with externalizing and school problems at age 7 years and the effect was not entirely mediated through the lead effect on IQ. On the other hand, higher blood lead concentration at about age 2 years of age was not associated with behavior at age 7 years. Finding both direct and indirect effects of concurrent blood lead concentration upon behavior among school-age children lends further urgency to the necessity of preventing lead exposure in children, preferably continuing into school age.

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ABBREVIATION

ADHD, Attention Deficit Hyperactivity Disorder; BASC-PRS, Behavioral Assessment Systems for Children – Parent Rating Scale; BASC-TRS, Behavioral Assessment Systems for Children – Teacher Rating Scale; CPRS-R, Conners' Parent Rating Scale – Revised; IQ, Intelligence quotient; TLC, Treatment of Lead-exposed Children study; WISC-III, Wechsler Intelligence Scale for Children-III; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence – Revised.

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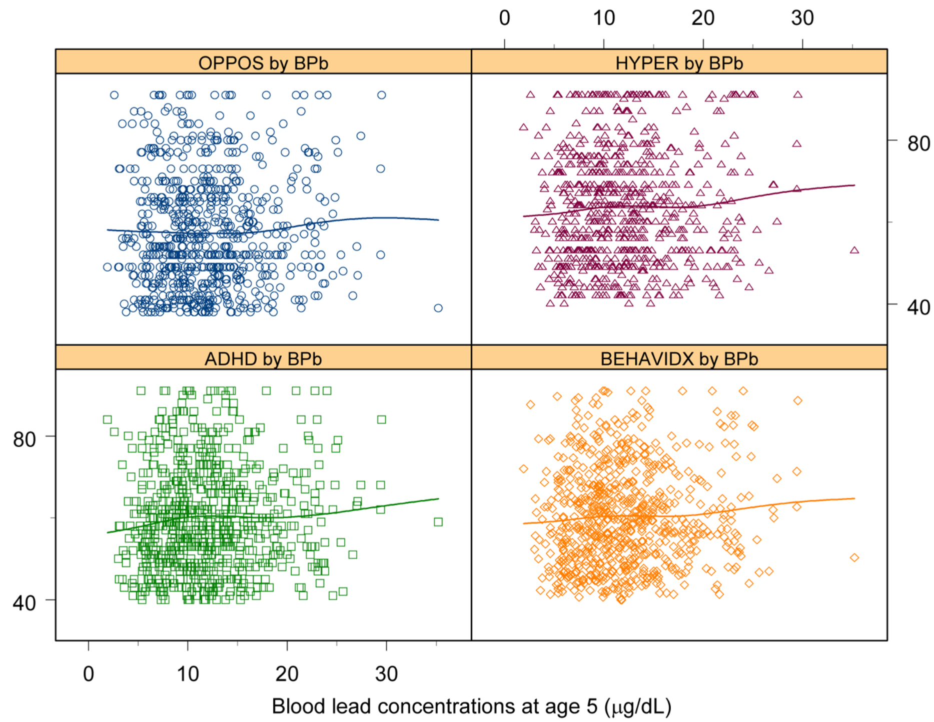

Figure 1.
Scatter plot of concurrent blood lead concentrations and CPRS-R test scores at age 5 and smoothed spline regression curves. OPPOS, HYPER, ADHD and BEHAVIDX denote CPRS-R Oppositional Index, Hyperactivity Index, ADHD Index, and Behavioral Index, respectively.

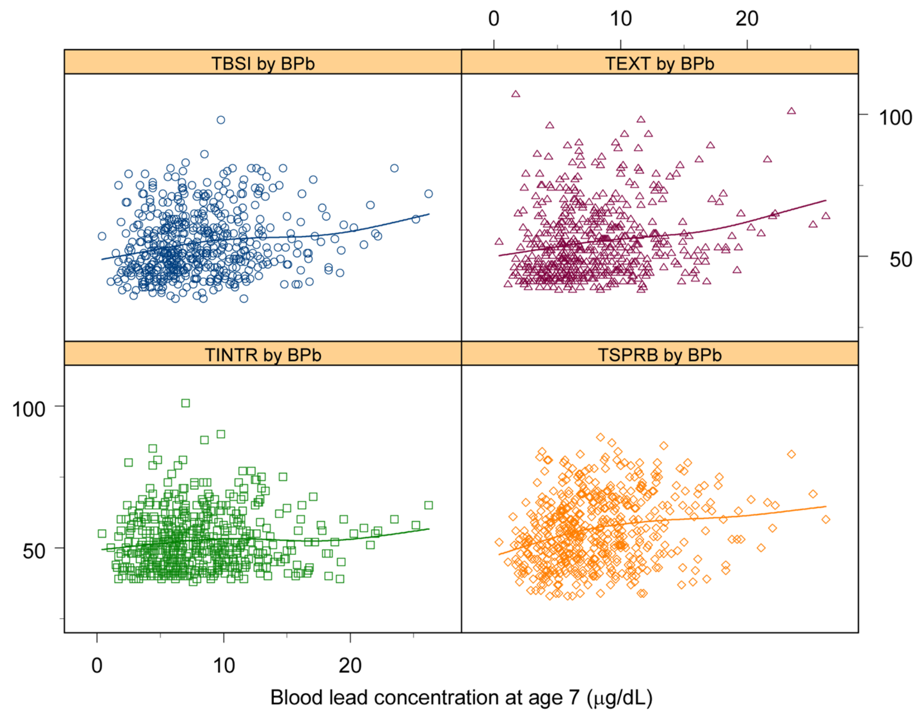

Figure 2.
Scatter plot of concurrent blood lead concentrations and teacher-rated BASC test scores at age 7 and smoothed spline regression curves. TBSI, TEXT, TINTR, TSPRB denote teacher-rated BASC score of Behavioral Symptoms Index, Externalizing Problems, Internalizing Problems, and School Problems, respectively.

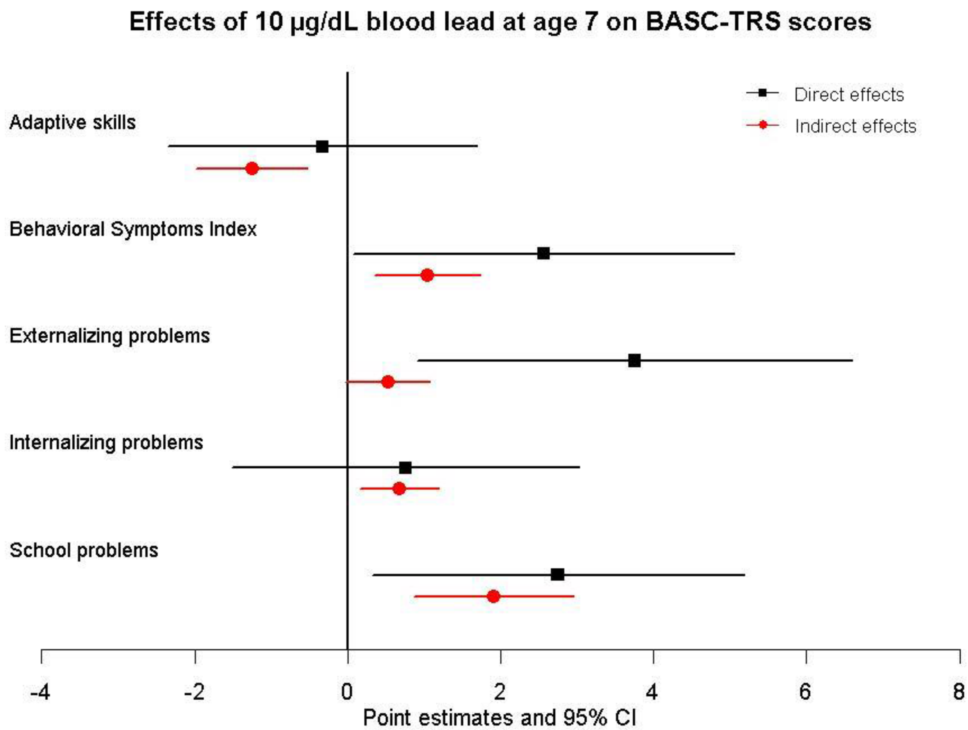

Figure 3.

Estimates (and 95% confidence intervals) of direct and indirect effects of blood lead concentration at age 7 on the Teacher version of the Behavioral Assessment System for Children. Units are change in behavioral test score per 10 µg/dL increase in blood lead concentration.

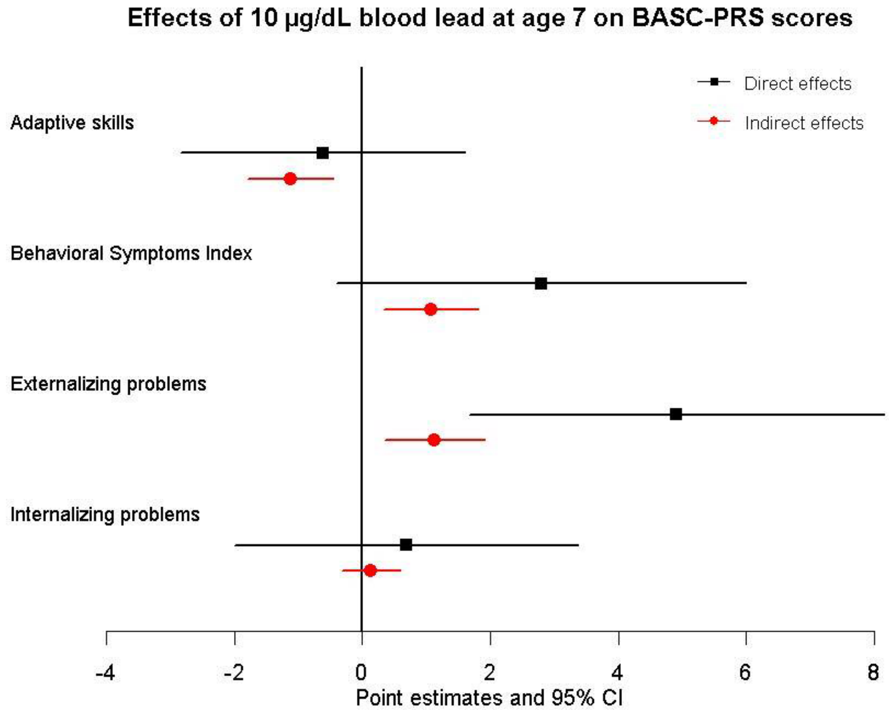

Figure 4.
Estimates (and 95% confidence intervals) of direct and indirect effects of blood lead concentration at age 7 on the Parent version of the Behavioral Assessment System for Children. Units are change in behavioral test score per 10 µg/dL increase in blood lead concentration.

Table 1

Mean and standard deviation (SD) of blood lead concentrations, IQ, and non-IQ outcomes and the correlation coefficients between IQ and blood lead concentrations and non-IQ outcomes at specific age in TLC children

Age	Variables	n	Mean±SD	Correlation with concurrent IQ*
2 years	Blood lead concentration (μg/dL)	780	26.2±5.1	
5 years	Blood lead concentration (μg/dL)	731	12.0±5.2	−0.20
	IQ	727	80.6±13.3	1
	CPRS-R			
	Oppositional Index	721	57.6±13.9	−0.14
	Hyperactivity Index	721	63.6±13.7	−0.14
	ADHD Index	721	59.9±12.8	−0.25
	Behavioral Index	721	60.4±12.0	−0.20
7 years	Blood lead concentration (μg/dL)	622	8.0±4.0	−0.23
	IQ	643	86.7±13.3	1
	BASC-TRS			
	Adaptive Skills	530	46.3±9.4	0.39
	Behavioral Symptoms Index	540	54.5±11.5	−0.28
	Externalizing Problems	539	55.2±13.0	−0.18
	Internalizing Problems	541	52.4±10.1	−0.17
	School Problems	541	56.2±12.2	−0.47
	BASC-PRS			
	Adaptive Skills	647	45.7±11.0	0.33
	Behavioral Symptoms Index	647	55.6±14.9	−0.21
	Externalizing Problems	647	58.0±15.4	−0.23
	Internalizing Problems	647	50.1±12.1	−0.06

* all P<0.05 except for parent-rated internalizing problems at age 7

Table 2

Direct and indirect effects* (95% confidence interval) of 10 μg/dL blood lead concentration on behavioral test scores at age 5

Behavioral Tests at age 5	Blood lead at age 2		Blood lead at age 5	
	Direct	**Indirect**	**Direct**	**Indirect**
CPRS-R				
Oppositional Index	1.19 (−0.75, 3.13)	0.35 (0.02, 0.68)†	1.18 (−0.84, 3.20)	0.51 (−0.25, 1.27)
Hyperactivity Index	0.93 (−0.89, 2.75)	0.34 (0.05, 0.63)†	1.10 (−0.80, 3.00)	0.50 (−0.83, 1.83)
ADHD Index	0.54 (−1.17, 2.25)	0.61 (−0.39, 1.61)	0.54 (−1.22, 2.30)	0.90 (0.35, 1.45)†
Behavioral Index	0.89 (−0.72, 2.50)	0.44 (−0.46, 1.34)	0.94 (−0.73, 2.61)	0.64 (0.23, 1.05)†

*Adjusted for clinic center, race, sex, language, parent's education, parent's employment, single parent, exact age at blood lead concentration measurement, and caregiver's IQ

†P<0.05

Table 3

Direct and indirect odds ratio* for BASC scores ≥ 60 per 10 μg/dL concurrent blood lead concentration at age 7, adjusted for 7-year IQ

BASC	n	% score ≥60	OR (95% CI) per 10 μg/dL concurrent lead	
			Direct	Indirect
BASC-TRS				
Behavioral Symptoms Index	540	30	1.25 (0.90, 1.73)	1.09 (1.02, 1.17)†
Externalizing Problems	539	30	1.42 (1.03, 1.97)†	1.04 (0.98, 1.11)
Internalizing Problems	541	23	1.07 (0.76, 1.52)	1.03 (0.97, 1.09)
School Problems	541	39	1.39 (1.05, 1.86)†	1.17 (1.07, 1.28)†
BASC-PRS				
Behavioral Symptoms Index	647	33	1.52 (1.13, 2.05)†	1.07 (1.01, 1.14)†
Externalizing Problems	647	39	1.27 (0.96, 1.68)	1.08 (1.02, 1.15)†
Internalizing Problems	647	18	0.98 (0.69, 1.40)	1.02 (0.96, 1.07)

* Adjusted for clinic center, race, sex, language, parent's education, parent's employment, single parent, exact age at blood lead concentration measurement, and caregiver's IQ

† $P<0.05$