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Postnatal Exposure to Methyl Mercury and Neuropsychological Development in 7-Year-Old Urban Inner-City Children Exposed to Lead in the United States

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Abstract

Background—The most common route for general population exposure to methyl mercury (MeHg) is fish consumption. Recommendations to pregnant women about consuming fish contaminated with MeHg are also applied to children, but there are few studies available about the effects of low level postnatal MeHg exposure in them.

Objectives—To investigate the association between postnatal methyl mercury exposure and neuropsychological development in a study of children also exposed to lead, both measured at 7 years.

Methods—We measured MeHg concentrations in blood samples from the Treatment of Lead-exposed Children (TLC) trial in which 780 children with elevated concentrations of lead in blood were followed with neuropsychological tests from ages 12–33 months through 7 years. Here we examine blood MeHg concentration and neuropsychological test scores, both measured at age 7 years. We used a maximum likelihood method to estimate geometric mean MeHg concentration and generalized linear regression models to analyze MeHg and neuropsychological test scores.

Results—Geometric mean MeHg concentration was 0.56 (95% confidence interval: 0.52, 0.59) μg/L. A 1 μg/L increase in MeHg was associated with a 2.1 (95% confidence interval: 0.4, 3.8)

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

Conflicts of interest:

The authors declare that there are no conflicts of interest.

point increase in Full Scale IQ and 0.2 (95% confidence interval: 0.02, 0.4) point increase in Learning Slope index T score on a test of verbal memory.

Conclusions—Our results suggest that the relatively low MeHg exposure in US school-aged children from this population has no detectable adverse effect on neuropsychological development. The positive associations observed between MeHg and neurodevelopment may indirectly reflect consumption of beneficial polyunsaturated fatty acids from seafood.

Keywords

Methyl mercury; Lead; Postnatal exposure; Neuropsychological tests; Cognition; IQ

Introduction

The common route for general population exposure to mercury (Hg), in the form of methyl mercury (MeHg), is through fish consumption. The fetus is particularly sensitive to MeHg toxicity, and can be exposed to through maternal consumption of fish or other contaminated foods such as seed grains (Amin-Zaki et al., 1974; Harada, 1995). As children grow and begin to consume fish themselves, further MeHg exposure can occur. Most US children have low, but detectable, amounts of MeHg in their blood (Schober et al., 2003).

Although postnatal exposure, measured as hair Hg concentration, at 6 months of age is moderately correlated with prenatal exposure, exposure at school age is not (Myers et al., 2009). The effects of postnatal exposure to MeHg may not be the same as those of prenatal exposure (Takeuchi, 1968), and there are few studies addressing the effects of postnatal exposure. Two informative studies from populations with high seafood consumption– in the Faroe Islands (Debes, Budtz-Jorgensen, Weihe, White, & Grandjen, 2006; Grandjean et al., 1999; Grandjean et al., 1997) and the Seychelles (Davidson et al., 2010; Davidson et al., 1998; Myers et al., 2003) investigated associations between postnatal Hg exposure and children's neurodevelopment at various ages, with no consistent findings between the studies or across ages or psychological domains. However, in the Seychelles, Myers et al. used three metrics for measuring postnatal exposure at multiple time points, and found that boys with consistently higher concentrations of postnatal Hg had higher IQ than boys with consistently lower concentrations (Myers et al., 2009).

Compared to both populations, US children consume less seafood and have lower Hg concentrations. For example, in the US, the average hair Hg concentration was 0.22 μg/g among children aged 1–5 years (McDowell et al., 2004); in the Seychelles, it was 6.5 μg/g in 66 month olds (Davidson et al., 1998). There is little information available on the neurodevelopmental effects of such low level postnatal MeHg exposure in the US. However, this question has significant public health implications. "Fish advisories" issued by the US Food and Drug Administration (FDA), the US Environmental Protection Agency (EPA), and many of the US states target pregnant women, but are also used for children, since it appears safer to treat young children as if they were as susceptible to MeHg effects as the fetus (US Environmental Protection Agency, 2004). The reference dose for MeHg (Rice, Schoeny, & Mahaffey, 2003) is based on the cohort studies, especially the Faroes study, that showed adverse effects in the children from prenatal MeHg exposure (Grandjean et al., 1997).

However, fish is a major source of n-3 polyunsaturated fatty acids, which are important for brain development (Innis, 2003, 2005). Given the lack of evidence of adverse effects from postnatal Hg exposure and beneficial effects of n-3 polyunsaturated fatty acids, it is not clear whether it is appropriate to apply the reference dose and fish guidance for pregnant women to children, especially school aged children. More data on the effects of background postnatal exposures would be useful.

We have previously reported that blood MeHg concentrations in toddlers from a clinical trial of chelation for lead (Pb) poisoning had no inverse associations with IQ or behavior at ages 2, 5 and 7 (Cao et al., 2010). We also demonstrated that chelation therapy with succimer had no discernible impact on toddler's blood MeHg concentrations at background levels (Cao et al., 2011). Furthermore, unlike other metals such as manganese and cadmium (e.g., Kim et al., 2012; Henn, et al., 2011), there is presently no evidence of toxic synergisms between MeHg and Pb (Cao et al. 2010). However, as previously noted, MeHg exposure may change as children grow and their diet stabilizes, and so here we examine the relation between postnatal MeHg exposure and neuropsychological and behavioral development, all measured at school age.

Methods

Study design

The Treatment of Lead-exposed Children trial (TLC) enrolled and followed children between 1994 and 2003 in Baltimore, Cincinnati, Newark, and Philadelphia. A total of 780 children with blood Pb concentrations of 20–44 μg/dL, 12–33 months of age, were randomly given the metal-chelating drug succimer (dimercaptosuccinic acid, Chemet®) (n = 396) or placebo (n = 384) and followed with tests of IQ and behavior through age 7 years. 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 (CDC), and the National Institute of Environmental Health Sciences. The parents of all children provided written informed consent. Detailed information can be found in previous publications (Dietrich et al., 2004; Rogan et al., 2001).

Blood Hg measurement

Among the 780 children at enrollment, 627 (80 %) blood specimens were collected from children at age ~7 years. Total Hg was measured using inductively coupled plasma-dynamic reaction cell mass spectrometry, while both MeHg and inorganic Hg were measured using high performance liquid chromatography/ inductively coupled plasma mass spectrometry, by the Division of Laboratory Sciences at the National Center for Environmental Health of the CDC. Most samples (66%) had MeHg concentration below the limit of detection (LOD), 0.48 μg/L, using the specific method. Therefore, instead of using it as the exposure, we calculated MeHg as total Hg minus inorganic Hg when inorganic Hg was detectable and as total Hg when inorganic Hg was undetectable, as we did in our previous report (Cao et al., 2010). The LOD for total Hg was 0.33 (μg/L). Among the 627 specimens, 14 were of insufficient quantity or quality to be measured; and 138 samples had MeHg concentration below LOD, 0.33 μg/L.

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Neuropsychological and behavioral tests

At age 7 years, we administered an array of standardized neuropsychological instruments. The global domains and selected subscales were originally chosen to demonstrate the adverse effect of Pb exposure (Dietrich et al., 2004), but they provide extensive information about the child's cognitive and neurobehavioral status as they enter the early elementary years of education (Table 1).

The child behavioral questionnaires for parents were completed by trained examiners reading questions aloud and providing clarification of items as necessary. Performance times for the right- and left-handed Rapid Sequential Movements from the Neurological Examination for Subtle Signs (NESS) were converted to z-scores using the standard deviation obtained from normative data for 7-year-old right- and left- handed boys and girls. These z-scores were averaged across tasks to obtain a composite index of Neuromotor Speed. Higher scores are better for Full Scale IQ, Broad Reading, List A Memory and Learning Slope, Attention/Executive Functions from the Neuropsychological Assessment, Adaptive Skills, and Hit Reaction Time. Lower scores are better for parent ratings of Externalizing and Internalizing Problems, teacher rating School Problems, d-Prime and Sequential Movements Time (Dietrich et al., 2004). The TLC examiners were unaware of the children's blood Hg and Pb concentrations. More details about the design, scoring and results of evaluations can be found in our previous reports (Dietrich et al., 2004; Rogan et al., 2001; Liu et al., 2002).

Statistical analysis

All statistical analyses were performed with SAS 9.2 (SAS Institute, Inc. Cary, NC). The geometric mean (95% confidence interval, CI) was used to describe the central tendency of blood MeHg concentration. MeHg concentrations below the LOD were treated as left-censored data for a maximum likelihood estimation method (MLE) to estimate the geometric means.

Scatter plots showed a roughly linear trend between MeHg and test scores, so we used linear regression models to detect influential points (defined as beta_MeHg>2/sqrt[n]) (Belsley et al, 1980) and collinearity and examine the associations. To deal with MeHg concentrations below the LOD, we applied two approaches: excluding the concentrations below the LOD; and using a linear regression model developed by Nie et al. (Nie, Liu, Cole, Vexler, & Schisterman, 2010) in which concentrations below the LOD were treated as left-censored data for MLE to estimate the parameters.

Covariates in the models included gender, race, exact age at date of testing, caregiver's IQ, concurrent blood Pb concentration which was more closely related to IQ at age 7 years than blood Pb concentration at age 2 years (Chen, Dietrich, Ware, Radcliffe, & Rogan, 2005), blood MeHg at age 2 years, treatment group (succimer or placebo), clinical center, language spoken at home, parent's education, either parent working, and single parent, all of which were used in our previous analysis using MeHg and/or Pb at age 2 years (Cao et al., 2010; Chen et al., 2005; Chen, Cai, Dietrich, Radcliffe, & Rogan, 2007).

Results

Demographic characteristics

Among the 780 children who participated in the TLC study, 613 children had blood MeHg concentrations available at age 7 years. The total geometric mean MeHg concentration was 0.56 μg/L (95% CI: 0.52, 0.59) and geometric means by demographic characteristics are shown in Table 2. The geometric mean MeHg concentration in children from the Cincinnati center was lower than that from the other three centers. White children had lower MeHg concentration than non-white children. Succimer had little effect on MeHg concentrations and no effect on test scores (Rogan et al., 2001; Cao et al., 2011); therefore we combined the two treatment groups for analysis. The geometric mean for Hg at age 7 years was close to that at age 2 years, but a child's concentrations at the 2 time points were only weakly correlated with each other (Pearson correlation coefficient = 0.15).

Developmental outcomes

The overall performance of the TLC cohort on neurobehavioral measures is presented in Table 3. The cohort was lower functioning with respect to Full-Scale IQ (86.7, SD = 13.3). However, means on assessments of academic skills (reading), memory, attention, neuromotor skills and behavior were mostly within normal parameters.

Associations between MeHg and endpoints

Figure 1 displays the scatter plots between MeHg concentration at age 7 years and selected endpoints: Full Scale IQ, CVLTC-Learning Slope index T scores, Teacher-Rating Adaptive Skills T score and School Problems T score. The scores were adjusted for the covariates noted above and the blood MeHg concentrations below the LOD were excluded.

The regression coefficients for test scores for Cognition, Learning and Memory are shown in Table 4. There are no marked collinearities and results are similar with or without outliers. Coefficients (β) shown in Table 4 are from models using the method of MLE. Blood MeHg concentration is positively and significantly associated with Full Scale IQ (p=0.02). For a 1 unit increase in MeHg concentration (μg/L), there is a 2.1 (95% CI: 0.4, 3.8) point increase in Full Scale IQ. MeHg concentration at age 2 years showed a non-significant positive association with Full Scale IQ but its magnitude was lower than that at age 7 years. As expected, children with higher blood Pb concentration had lower Full Scale IQ. Results from models excluding MeHg concentrations below the LOD were quite similar. The coefficient for MeHg and Full Scale IQ was 2.1 (95% CI: 0.3, 3.9; p=0.02). In addition, there was also a slight increase in CVLTC-Learning Slope index T scores with increasing MeHg concentration (β=0.2, 95% CI: 0.02, 0.4, p=0.02). Models excluding concentrations below LOD yielded the same results. For other endpoints, MeHg at age 7 years also showed a positive trend with scores on Broad Reading and CVLTC- List A Memory, but coefficients were not statistically significant.

Regression coefficients for MeHg concentration and test scores on Behavior and Neuromotor Speed are shown in Table 4. There are non-significant linear trends for better scores with higher MeHg on teacher rating Adaptive Skills, fewer teacher rating School

Problems, and fewer parent rating Externalizing Problems. MeHg has no significant adverse effect on Neuromotor Speed indicators. Models excluding influential data points yielded similar results and were not additionally reported.

Discussion

We found that postnatal MeHg exposure at US background levels has no detectable adverse effect on neuropsychological and behavioral development among children enrolled in TLC at age 7 years. Instead, children with higher blood MeHg concentration had significantly higher IQ and CVLTC-Learning Slope index T scores, and the association was robust to different approaches to deal with MeHg concentrations below the LOD.

Two longitudinal studies that examined postnatal MeHg exposure, in the Faroe Islands (Debes et al. 2006; Grandjean et al. 1999; Grandjean et al. 1997) and the Seychelles (Davidson et al., 2010; Davidson et al., 1998; Myers et al., 2003), had subjects with high seafood consumption. The Faroe Islands population mainly consumed pilot whale meat (Grandjean et al., 1992), while the Seychelles children consumed finfish similar to those found in the US market (Davidson et al., 1998). As noted above, exposure in these investigations was about 30-fold higher than US preschool children; however, neither study found any consistent adverse effects of postnatal exposure on neurodevelopment. In addition, the Seychelles study used several metrics to reflect cumulative postnatal exposure, but no consistent findings on neurodevelopment were observed (Myers et al., 2009). In our study, we have blood MeHg concentrations as our exposure metric. The geometric mean for MeHg, 0.57 μg/L, is close to the 0.56 (95% CI: 0.44–0.67, μg/L) for black children in National Health and Nutrition Examination Survey (NHANES) (Schober et al., 2003). We previously reported that there were no negative associations between blood MeHg concentrations at age 2 years among children enrolled in TLC and the neuropsychological endpoints at age 2, 5 and 7 years (Cao et al., 2010). The present study provides more evidence that postnatal MeHg exposure, at the low background MeHg levels of the general US children, does not produce any detectable adverse effects on those aspects of neurodevelopment performance tested.

We did observe significant positive associations between MeHg concentrations and WISC-III Full Scale IQ and the CVLTC Learning Slope index T scores, which reflect verbal learning and memory. A similar beneficial association was also reported in the Seychelles study. At age 66 months, children’s arithmetic scores (measured by Applied Problem Subtest of the Woodcock-Johnson Tests of Achievement) were higher as Hg exposure increased (Davidson et al., 1998). In addition, a cross-sectional study in the US with exposures similar to ours showed positive trends with increasing Hg concentration for Full Scale IQ and most other test scores, even after for adjusting for fish consumption (Surkan et al., 2009). The “beneficial” effect may represent the effect of nutrients from fish consumed by the US children. Studies on maternal consumption of fish during pregnancy have found that children whose mothers consumed more fish during pregnancy have higher developmental test scores (Daniels, Longnecker, Rowland, & Golding, 2004; Hibbeln et al., 2007; Mendez et al., 2009; Oken et al., 2008). Furthermore, the Seychelles study found that the beneficial effects of polyunsaturated fatty acids can impede identification of adverse effects of prenatal MeHg exposure (Stokes-Riner et al., 2011; Strain et al., 2008). NHANES III data showed that school-age children with higher dietary intake of polyunsaturated fatty acids had higher scores on a test of short term memory, the Digit Span Test (Zhang, Herbert, & Muldoon, 2005). The above results suggest that, in the current diet of US children, the beneficial effect of fish consumption may be predominant. To further examine this hypothesis, we are investigating the feasibility of testing the n-3 unsaturated fatty acids in stored samples from TLC.

Although EPA's fish advisories (US Environmental Protection Agency, 2004) for pregnant women are based on sound data, the extension to children, especially school-aged children, might be questioned. In NHANES data, children with geometric mean hair Hg concentration of 0.21 μg/g (mean blood Hg concentration was 0.34 μg/L) consumed fish 1 or 2 times in the past 30 days (Schober et al., 2003). This degree of exposure is similar to what the children in our study experienced. Based on our findings, it may be worth discussing whether children eat enough fish to get the optimal amount of fatty acids.

An important strength of our study is the longitudinal measures of MeHg blood concentrations. Exposure was measured at two different stages of childhood. The findings at age 7 are consistent with, but more precise than, the findings using exposure at age 2. Another strength is the quality and breadth of our neuropsychological testing. Since the CDC laboratory for the TLC study is also laboratory for NHANES, our results are readily compared with the NHANES national results.

A potential limitation in our study is that the TLC samples are from a clinical trial treating mildly Pb-poisoned children. It is possible that the Pb-exposed children's responses to further challenge are different from those of other children. Another limitation is that the TLC tests were selected to capture the effects of Pb-related impairment, and the domains were selected primarily to gather evidence for a Pb effect. However, the TLC protocol provided a comprehensive survey of the neurodevelopmental status of children in the first years of elementary education.

In conclusion, we found that in this unique study of inner-city children exposed to lead a positive association between MeHg and IQ and Learning Slope T scores in children at age 7 years. MeHg exposure in the U.S. is largely from dietary fish consumption, and fish are rich in fatty acids that are important for brain development. Longitudinal studies that measure MeHg, fish consumption, and micronutrients favoring brain development are needed to better understand trade-offs and help refine the current recommendations for fish consumption.

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Abbreviations

BASC-PRS	Behavioral Assessment System for Children-Parent Rating Scale
BASC-TRS	Behavioral Assessment System for Children-Teacher Rating Scale
CDC	the Centers for Disease Control and Prevention
CI	Confidence Interval
CPT	Conners' Continuous Performance Test
CVLTC	California Verbal Learning Test for Children
EPA	The US Environmental Protection Agency
FDA	The US Food and Drug Administration
Hg	Mercury
LOD	Limit of Detection
MeHg	Methyl Mercury
MLE	Maximum Likelihood Estimation
NEPSY	A Developmental Neuropsychological Assessment
NESS	Neurological Examination for Subtle Signs
NHANES	National Health and Nutrition Examination Survey
Pb	Lead
TLC	The Treatment of Lead-exposed Children Trial
WISCIII	Wechsler Intelligence Scale for Children-III

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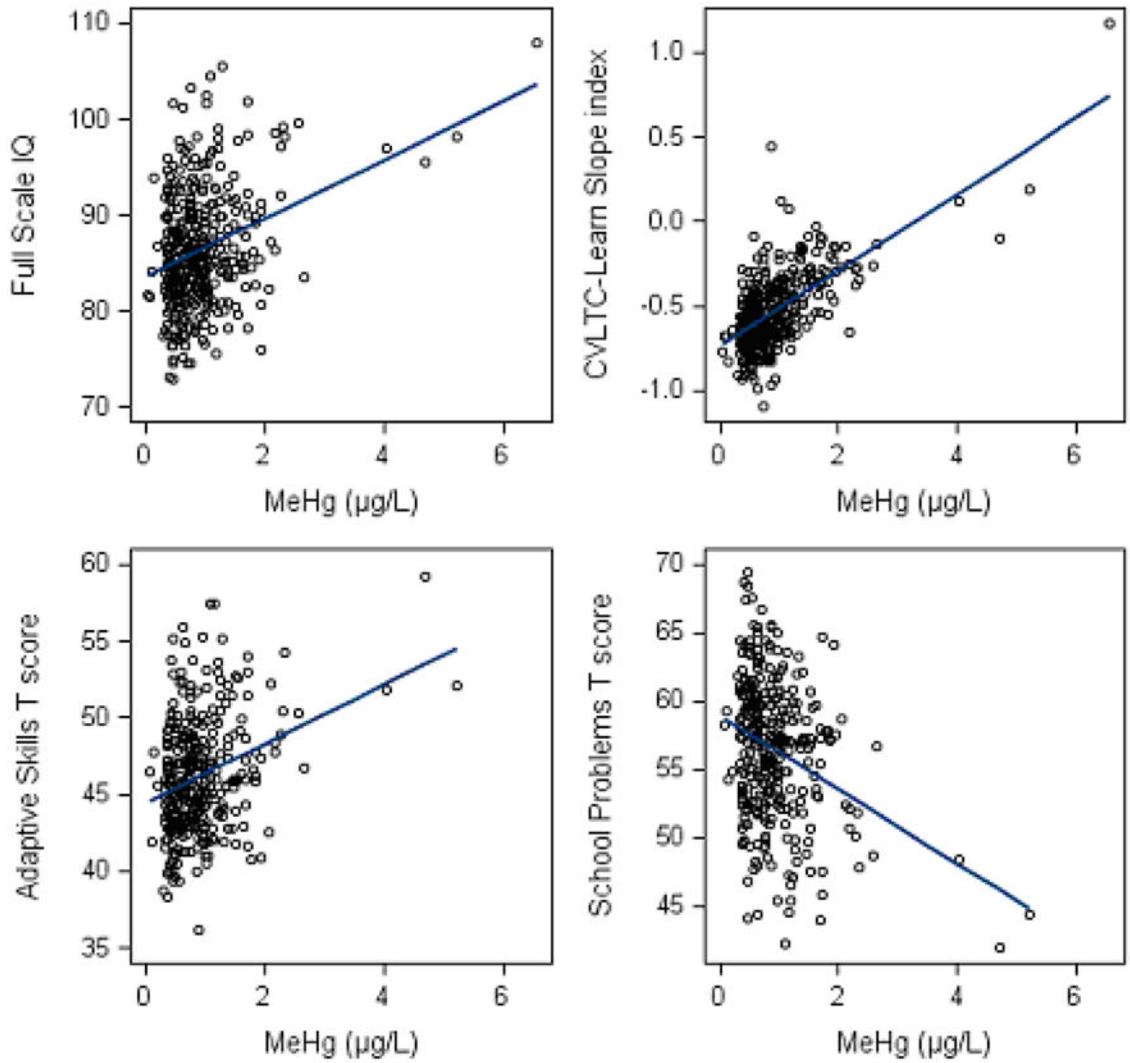

Figure 1.

Scatter plots between blood MeHg concentrations at age 7 and selected endpoints. The endpoints were WISC-III Full Scale IQ, CVLTC-Learning Slope index T scores, teacher-rating Adaptive Skills T score and School Problems. Each plot was adjusted for relevant covariates and excluded MeHg concentrations below LOD. Abbreviations: WISC-III, Wechsler Intelligence Scale for Children, CVLTC, California Verbal Learning Test for Children; LOD, Limit of Detection.

Table 1

TLC Neuropsychological Domains and Instruments at Age 7 Years

Neuropsychological Domains	Instruments (Scales)
Cognition, Learning, and Memory	
Intellectual Attainment	Wechsler Intelligence Scale for Children -III (Verbal IQ, Performance IQ, and Full Scale IQ)
Overall Reading Ability	Woodcock Language Proficiency Battery-Revised (Broad Reading score)
Verbal Learning and Memory	California Verbal Learning Test for Children (CVLTC-List A Memory and Learning Slope index T scores)
Attention/Executive Functions	NEPSY-A Developmental Neuropsychological Assessment (Attention and Executive Function Core Domain standard score) Conners' Continuous Performance Test (CPT-d- Prime T score: perceptual sensitivity or the ability to discriminate targets from non-targets)
Behavior	
Emotional and Behavioral Conduct	Behavioral Assessment System for Children-Parent Rating Scale (BASC-PRS-Externalizing Problems and Internalizing Problems T score)
Behavioral and Academic Conduct	Behavioral Assessment System for Children-Teacher Rating Scale (BASC-TRS-Adaptive Skills T score and School Problem T score; BASC-TRS- Externalizing Problems and Internalizing Problems T score)
Neuromotor	
Neurological Function	Neurological Examination for Subtle Signs (NESS - Rapid Sequential Movements Time index)
Motor Speed	Conners' Continous Performance Test (CPT-Hit Reaction Time T score: an index of psychomotor processing speed for the correct response)

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Table 2

Geometric Mean of Blood MeHg Concentrations (μg/L) at Age 7 Years by Characteristics of Subjects

Variables	**N**	**Geometric Mean (95% CI)**	***P***
Clinical Center			<0.001
Baltimore	113	0.64 (0.57,0.73)	
Newark	199	0.68 (0.61,0.75)	
Philadelphia	138	0.52 (0.46,0.59)	
Cincinnati	168	0.41 (0.35,0.47)	
Gender			0.24
Male	338	0.53 (0.48,0.58)	
Female	280	0.59 (0.54,0.64)	
Race/Ethnicity			<0.001
White	68	0.32 (0.25,0.41)	
Black	475	0.59 (0.55,0.63)	
Other	75	0.63 (0.52,0.76)	
Treatment			0.27
Succimer	308	0.54 (0.49,0.59)	
Placebo	310	0.58 (0.53,0.63)	
Language spoken at home			0.51
English	581	0.55 (0.52,0.59)	
Spanish	37	0.60 (0.44,0.80)	
Parents' education			0.99
<12 yr	242	0.56 (0.51,0.62)	
>=12 yr	375	0.55 (0.51,0.60)	
Either parent working			0.23
No	356	0.57 (0.53,0.62)	
Yes	260	0.53 (0.48,0.59)	
Living with single parent			0.42
No	172	0.53 (0.46,0.60)	
Yes	437	0.57 (0.53,0.61)	
Total	618	0.56 (0.52, 0.59)	

Abbreviations: CI, confidence interval.

Table 3

Mean (SD) of Neuropsychological Endpoints

Endpoints	N	Mean (SD)
Intellectual Attainment		
Full-scale IQ	644	86.7 (13.3)
Verbal IQ	644	84.1 (13.9)
Performance IQ	646	88.7 (13.7)
Reading		
Broad Reading score	600	94.4 (18.4)
Verbal Learning and Memory		
Listing A Memory	645	43.6 (11.6)
Learning Slope	645	−0.43 (1.16)
Attention/Executive Functions		
NEPSY standard score	593	87.2 (17.1)
Conners' CPT d-Prime T score	572	55.7 (9.8)
Teacher-Rating BASC		
Adaptive Skills T score	531	46.3 (9.4)
School Problems T score	542	56.2 (12.2)
Externalizing Problems T score	542	52.4 (10.1)
Internalizing Problems T score	540	55.2 (13.0)
Parent-Rating BASC		
Externalizing Problems T score	648	50.1 (12.1)
Internalizing Problems T score	648	58.0 (15.4)
Neuromotor Speed		
Sequential Movements Time	565	1.0 (1.3)
CPT Hit reaction time	572	42.7 (12.9)

Abbreviations: SD, standard deviation.

Table 4

Linear Regression Coefficients (β) and 95% CI for Associations between Blood MeHg Concentrations and Neuropsychological Endpoints at Age 7 Years

Endpoints	Unadjusted β (95 % CI) [a]	Adjusted β (95 % CI) [a, b]
Intellectual Attainment		
Full-scale IQ	3.1 (1.1, 5.0)	2.1 (0.4, 3.8)
Verbal IQ	2.8 (0.8, 4.9)	2.2 (0.3, 4.0)
Performance IQ	2.9 (0.8, 4.9)	1.8 (−0.1, 3.7)
Reading		
Broad Reading score	2.2 (−0.7, 5.1)	0.9 (−1.9, 3.7)
Verbal Learning and Memory		
Listing A Memory	0.9 (−0.8, 2.7)	1.3 (−0.3, 2.9)
Learning Slope	0.2 (0.1, 0.4)	0.2 (0.03, 0.4)
Attention/Executive Functions		
NEPSY standard score	1.8 (−0.9, 4.4)	1.3 (−1.1, 3.6)
Conners' CPT d-Prime T score	−1.6 (−3.2, 0.03)	−1.5 (−3.1, 0.1)
Teacher-Rating BASC		
Adaptive Skills T score	1.9 (0.1, 3.7)	1.1 (−0.6, 2.8)
School Problems T score	−2.7 (−5.0, −0.4)	−1.9 (−4.0, 0.3)
Externalizing Problems T score	−0.8 (−3.2, 1.5)	−0.2 (−2.6, 2.2)
Internalizing Problems T score	0.0 (−1.9, 2.0)	0.5 (−1.4, 2.5)
Parent-Rating BASC		
Externalizing Problems T score	−2.8 (−5.3, −0.3)	−1.7 (−4.2, 0.7)
Internalizing Problems T score	−0.04 (−1.9, 1.9)	0.5 (−1.4, 2.4)
Neuromotor Speed		
Sequential Movements Time	−0.1 (−0.3, 0.1)	−0.1 (−0.3, 0.1)
CPT Hit reaction time	0.3 (−1.6, 2.3)	0.2 (−1.8, 2.2)

Abbreviations: CI, confidence interval.

[a] Coefficients were from linear regression models in which blood MeHg concentrations below LOD were taken as censored data.

[b] Models adjusted for age at test, blood MeHg concentrations at age 2 years, caregiver's IQ, blood lead at age 7 years, race, clinical center, language at home, single parent, treatment, and either parent working.