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Prenatal lead exposure and childhood executive function and behavioral difficulties in project viva

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ABSTRACT

Background: Lead is an established neurotoxicant and early life exposure to lead is associated with detrimental impacts on IQ and several neurobehavioral domains. Less is known, however, about effects of prenatal lead exposure below 5 μg/dL on executive function and on social, emotional and self-regulatory behaviors in childhood.

Objectives: To examine the association between prenatal lead exposure and childhood executive function and social, emotional and self-regulatory behaviors.

Methods: We included 1006 mother-child pairs from the Project Viva prospective pre-birth cohort. We measured prenatal maternal lead in second-trimester erythrocytes. In mid-childhood (median 7.7 years), parents and teachers rated executive function related behaviors using the Behavior Rating Inventory of Executive Function (BRIEF) and behavioral difficulties using the Strengths and Difficulties Questionnaire (SDQ). We used multivariable linear regression models adjusted for maternal, paternal, and child characteristics and metal co-exposures.

Results: Mean maternal erythrocyte lead concentration was 1.2 μg/dL (interquartile range [IQR] 0.8–1.5 μg /dL), equivalent to approximately 0.4 μg/dL in whole blood. In adjusted models, associations with parent and teacher-rated scales were largely null, although effect estimates were consistently positive, suggesting worse scores with increasing lead levels. For an IQR increase in lead, BRIEF Global Executive Composite (GEC) was 0.73 (95% CI: -0.06, 1.52) points higher for parent-rated scores and 0.42 (95% CI: -0.39, 1.23) points higher for teacher-rated scores. Associations were strongest for parent-rated BRIEF plan/organize (β = 0.85; 95% CI: 0.12, 1.59) and shift (β = 0.88; 95% CI: 0.01, 1.75) subscales, as well as the SDQ emotional problems subscale (β = 0.18; 95% CI: 0.03, 0.33).

Discussion: In this cohort with lead levels commonly experienced by U.S. women, there were few statistically significant associations with childhood executive function and behavior. However, there was a trend of worse neurobehavioral scores with increasing prenatal lead concentrations, in particular for childhood emotional problems and capacity to plan/organize and shift. Our results highlight the importance of continuing efforts to eliminate lead exposure in the general population.

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1. Introduction

Lead is a neurotoxic metal that is ubiquitous in the environment (ATSDR, 2007; Sanders et al., 2009). Although the U.S. ban of leaded gasoline and paint reduced population lead levels and resulted in major health benefits (CDC, 2010; Schwartz et al., 1985; Silbergeld, 1997), the ubiquity of environmental lead from past industrial usage has made total eradication of exposure difficult. In pockets of urban and rural America, adverse neurological effects of lead remain a heavy burden since there is no known safe level of exposure (CDC, 2018a). Additionally, recent research has shown detrimental neurological impacts of childhood lead concentrations below the CDC reference level for children (5 μg/dL) that are still commonly observed among children today. Furthermore, the prenatal period is a vulnerable time of rapid neurodevelopment (ATSDR, 2007; CDC, 2010; World Health Organization (WHO, 2017). Lead crosses the placenta and exposure to the developing fetus represents an even greater dose of lead per unit of body weight than childhood exposure (ATSDR, 2007; CDC, 2010; World Health Organization (WHO, 2017). Lead in maternal bone can also be mobilized during pregnancy, acting as an endogenous source of lead (CDC, 2010; Gulson et al., 2003; Manton et al., 2003). An estimated 79% of fetal lead exposure is from mobilized maternal bone lead (Gulson et al., 2003). Lead can also cross the blood-brain barrier and penetrate fetal brain tissue (CDC, 2010; Goyer, 1990), raising concerns about the neurological health of offspring following in utero lead exposure, even at current population levels.

Epidemiologic research has demonstrated associations between prenatal lead exposure and worse performance in childhood tests of central nervous system function, including childhood IQ and tasks of infant and toddler development and child cognition (Bellinger et al., 1990; Dietrich et al., 1987; Hu et al., 2006; Kim et al., 2018; Liu et al., 2014; Ris et al., 2004; Schnaas et al., 2006; Shen et al., 1998; Wasserman et al., 2000). Effects in children have also been reported in multiple behavioral domains, including attention, cognitive efficiency, social behavior, visual-motor reasoning, visuoconstruction in adolescence and executive function-related behaviors (Berent and Albers, 2010; Chiodo et al., 2004; Mazzocco and Ross, 2007; Ris et al., 2004). Executive function (EF) refers to a set of cognitive processes that facilitate regulation of behavior and achievement of goals (Espy et al., 2011; Skogan et al., 2016). These processes support goal motivated behaviors and are essential for successful response to shifting life demands (Rinsky and Hinshaw, 2011).

For previous studies of lead and EF, standardized performance-based tests have more typically been used to assess aspects of EF, including working memory (Chiodo et al., 2004; Min et al., 2007; Ris et al., 2004; Surkan et al., 2007), inhibition (Chiodo et al., 2004; Kordas et al., 2006; Stewart et al., 2006), cognitive flexibility (Canfield et al., 2003; Chiodo et al., 2004; Surkan et al., 2007), and planning (Canfield et al., 2003; Chiodo et al., 2004; Surkan et al., 2007). Performance-based tests are conducted under standardized conditions and optimal performance situations (Toplak et al., 2013). These tests are different from EF rating scales, which are typically completed by parents or teachers about the child's behaviors in their everyday environment. Rating scales allow for the evaluation of multiple EF domains comprehensively to assess overall executive function related behaviors. They measure the extent to which individuals pursue goals under typical performance situations and unstructured conditions in daily life (Toplak et al., 2013) and may therefore add a dimension to our understanding of lead's impact on EF problem-solving processes and behavioral manifestations of EF in the real world (Gioia et al., 2002; Goldberg and Podell, 2000). Moreover, previous literature exploring the association between lead and childhood EF-related behaviors using rating scales (Barg et al., 2018; Roy et al., 2009) has mainly examined lead exposure in childhood and at levels that exceed US population averages and are therefore not generalizable to the current population (CDC, 2017).

Our study evaluates the association of prenatal lead at levels relevant to current U.S. population averages with parent and teacher observations of EF-related tasks in the child's everyday environment and social, emotional and self-regulatory behaviors. We investigated this relationship in Project Viva, a prospective pre-birth cohort in Massachusetts. We hypothesized that higher prenatal lead levels would be associated with worse EF-related behaviors and social, emotional and self-regulatory behaviors in mid-childhood, even at prenatal exposure levels that commonly occur in U.S. women, while simultaneously accounting for other neurotoxic metals (mercury, manganese). Additionally, we evaluated potential sex-specific associations of lead with EF and with behavioral difficulties given evidence from previous studies (Llop et al., 2013).

2. Materials and methods

2.1. Study participants

Study participants were mother-child pairs from Project Viva, a prospective, pre-birth cohort study. Details of Project Viva have been described previously (Oken et al., 2015). Briefly, pregnant women were recruited from eight clinical facilities (Atrius Harvard Vanguard Medical Associates) across eastern Massachusetts during their first prenatal visit from 1999-2002. Eligibility criteria included ability to understand English, less than 22 weeks gestation at the first prenatal visit, singleton births, and having no plans to move from the geographic area prior to delivery. The Harvard Pilgrim Health Care Institutional Review Board approved the recruitment procedure, and mothers provided written informed consent at recruitment and follow-up. A total of 2128 live births were enrolled in Project Viva. Second trimester blood was collected from 1617 enrolled mothers. Of those, we included 1006 children with a mid-childhood assessment (at the 7-year visit) in the final sample for this analysis.

2.2. Measurement of lead

We collected venous erythrocyte blood from pregnant women at the second trimester visit (median 27.9 weeks gestation). Lead was measured in erythrocytes as a secondary analysis, because the original study aims were related to gestational nutrition, birth outcomes and neurodevelopment, and we did not retain whole blood but did retain erythrocytes. More than 99% of lead in whole blood is found in the erythrocytes and this portion can be used to estimate lead exposure (Smith et al., 1998). Samples were collected in ethylenediaminetetraacetic acid vacutainer tubes and stored on ice for 24 h before being sent to the Trace Metals Laboratory at Harvard T.H. Chan School of Public Health in Boston, MA. Samples were then centrifuged to separate plasma and erythrocytes, and erythrocytes were stored in -80 °C freezers. Erythrocyte samples were prepared by digesting in nitric acid (HNO_3) and hydrogen peroxide (H_2O_2) and then diluting with deionized water (Perkins et al., 2014). The concentration of lead in erythrocytes was measured as described previously using a dynamic reaction cell-inductively coupled plasma mass spectrometer (ICP-MS) (Perkins et al., 2014) (Elan DRC II, Perkin Elmer, Norwalk, CT). The limit of detection for lead in this study was 0.2 ng/ml in erythrocytes and one lead sample was below this LOD (0.1%). Quality control measures were analyzed with the calibration verification standards, procedural blanks, 1-ppb lead standard, and QC standard (Wu et al., 2017). Lead measurements were computed as the mean of five replicates (Wu et al., 2017). Recovery of the QC standard and spiked samples by this procedure was 90–110% (Perkins et al., 2014).

2.3. Neurobehavioral assessment

Parents and teachers completed two neurobehavioral rating scale assessments about child participants in mid-childhood (median

7.7 years): the Behavior Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ). Mothers completed neurobehavioral assessments at the mid-childhood visit. We asked mothers for permission to contact their child's teacher and mailed these assessments to the teacher if permission was granted. The BRIEF is a validated questionnaire designed to evaluate behaviors related to EF in children ages 5–18 years based on observer reporting (Gioia et al., 2000). The BRIEF questionnaire for parent- and teacher-rated scales consists of 86 items separated into eight subscales: emotional control, shift, inhibit, initiate, working memory, plan/organize, organization of materials, and monitor. Two indices are created by summing across subscales: (1) Behavioral Regulation Index, which is the sum of emotional control, shift, and inhibit subscale scores; and (2) Metacognition Index, which is the sum of initiate, working memory, plan/organize, organization of materials, and monitor subscale scores. Finally, an overall EF-related behaviors outcome, the Global Executive Composite (GEC) score, is created by summing the raw scores of all subscales (Sullivan and Riccio, 2007). All scores (subscales, indices, and GEC) are converted to T-scores (mean = 50, SD = 10) and represent age- and sex-standardized scores. Higher BRIEF scores indicate more executive function related behavioral dysfunction (Sullivan and Riccio, 2007), with T-scores greater than 65 considered to be clinically significant for executive dysfunction (McCandless and O' Laughlin, 2007). Test-retest reliability correlations across scales for the normative sample range from 0.83-0.92 for teacher-rated and 0.76-0.85 for parent-rated scales (Gioia et al., 2000). Internal consistency was measured using Cronbach's alpha and ranged from 0.80 and 0.98 (Gioia et al., 2000).

The SDQ is a screening questionnaire on which parents and teachers rate behavioral difficulties in children aged 4–16 years (Goodman and Goodman, 2009). The SDQ incorporates five scales: peer relationship problems, hyperactivity, emotional problems, conduct problems, and prosocial behavior, which are scored from 0 to 10 points. Higher scores indicate worse performance on all scales except the prosocial behavior scale, which is scored in the opposite direction. The total difficulties score is a composite SDQ score that is calculated by summing the scales of peer, hyperactivity, emotional, and conduct problems to obtain a maximum of 40 points (Goodman and Goodman, 2009). SDQ scores greater than the 90th percentile are considered to be within the clinically abnormal range (Goodman, 1997; Kremer et al., 2015; Mellor, 2005), corresponding to a score of 16 points or more for the US population (Bourdon et al., 2005; Goodman, 1997). The SDQ website (www.sdqinfo.com) provides the SDQ normative data and scoring information for the U.S. Test-retest correlations for the SDQ subscales on the test's normative sample ranged from 0.65 to 0.76 for parent-rated scales and 0.72 to 0.85 for teacher-rated scales (Stone et al., 2015, 2010). Internal consistency for the normative sample was measured using Cronbach's alpha, ranging from 0.53 to 0.89 (Stone et al., 2015, 2010).

2.4. Covariates

We collected information on demographics (maternal age, annual household income, education status, marital status), maternal smoking status during pregnancy, and date of last menstrual period (LMP) through interviews and self-administered questionnaires in pregnancy. Data on maternal parity, date of delivery, birthweight, and hemoglobin clinical lab values were abstracted from medical records. We calculated length of gestation in days by subtracting the date of LMP from date of delivery. If gestational age according to the second trimester ultrasound differed from the LMP calculation by greater than 10 days, we used the ultrasound result to determine gestational duration. Gestational age was then converted from days to weeks. Child race/ethnicity was reported by the mother during early childhood. We measured manganese (μg/L) and mercury (ng/g) concentrations in erythrocytes from the same second trimester maternal blood samples used for lead measurements. Manganese was measured using ICP-MS (Elan DRC II, Perkin Elmer, Norwalk, CT) following the same method as described above for lead. The limit of detection for manganese was 2.0 μg/L, with one sample (0.1%) below this LOD. Mercury concentrations were analyzed using the Direct Analyzer 80 (Milestone Inc., Monroe, CT) as previously published (Oken et al., 2016). The detection limit for mercury was 0.5 ng/g of sample, and percent recovery for QC standards was 90–110% (Oken et al., 2016), with 31 samples (3.1%) below the LOD. We used the reported instrument values for all samples below the LOD.

At the mid-childhood visit, the Kaufman Brief Intelligence Test (KBIT-2) was administered to mothers as a measure of maternal IQ (Kaufman and Kaufman, 2004). We also administered the Home Observation Measurement of the Environment short form (HOME-SF). The HOME-SF assesses the emotional support and stimulation in a child's home environment, with higher scores indicating more positive outcomes (Frankenburg and Coons, 1986).

2.5. Statistical analysis

Summary statistics and distributional plots were examined for all variables. We evaluated distributions of metals and neurobehavioral scores for normality by testing model residuals using histogram inspection and Shapiro-Wilk testing. Model residuals were approximately normally distributed. In addition, we computed Spearman rank correlation coefficients between parent and teacher ratings for each neurobehavioral scale.

We evaluated associations between prenatal lead levels and neurobehavioral outcomes using multivariable regression. We assessed potential nonlinear associations between lead and neurobehavioral outcomes using generalized additive models with penalized splines restricted to four knots. Based on visual inspection of splines, most associations appeared approximately linear; therefore, lead concentrations were modeled as continuous linear terms and scaled by the interquartile range (IQR) to compare the 75th with the 25th percentile.

In constructing multivariable models, baseline models controlled for age and sex (BRIEF scores are age- and sex-standardized; models of SDQ were adjusted for age and sex as covariates). Additionally, the main model was adjusted for the following covariates, based on prior literature and directed acyclic graphs (Hernán et al., 2002): maternal IQ, maternal smoking during pregnancy (self-reported as former or during pregnancy vs. never), nulliparity (yes vs. no), maternal and paternal education (college graduate yes vs. no), prenatal mercury (ng/g), prenatal manganese (μg/L), child race/ethnicity (black, Hispanic, Asian, other vs. white), HOME-SF score and household income modeled as an ordinal variable (≤$40,000; > $40,000–70,000; > $70,000). We examined sex-specific effects of lead by 1) stratifying models by child sex, and 2) including cross-product terms between lead and child sex in the models.

Data were missing on several important covariates (*Table S1*). We therefore imputed missing values using multiple imputation by chained equations, assuming data were missing at random (MAR) (Horton and Kleinman, 2007; White et al., 2011). We conducted multiple imputation using the MI procedure in SAS, generating 50 imputed datasets. All participants (n = 2128) were included in the imputation, and all variables that might be related to the process causing missingness were included. These imputed datasets were then pooled using the *MI analyze* procedure in SAS. Primary data analysis was performed on the multiply imputed (MI) data, with mother-child pairs that had second trimester blood drawn and mid-childhood data (n = 1006). In two separate sensitivity analyses, we (1) compared the MI results to the complete case analysis (n = 625) and (2) adjusted for hemoglobin as a proxy for iron status. Data analysis was performed using SAS Version 9.4 and R Version 3.1.3 (R Foundation for Statistical Computing, Vienna).

3. Results

Of the 1006 mothers, the mean age at enrollment was 32.5 years,

Table 1
Characteristics of study participants, overall and by maternal 2nd trimester lead level (n = 1006).

Characteristics	All participants[a]	Participants with lead level < median [a,b]	Participants with lead level > = median [a,b]
Maternal Characteristics			
Age at Enrollment (Years) (1999-2002), Mean ± SD	32.5 ± 5.0	31.8 ± 5.0	33.1 ± 4.8
College graduate, %	72.1	72.1	72.2
Nulliparous, %	48.6	50.2	47.0
Married or cohabitating, %	93.6	93.8	93.5
Smoking Status, %			
Never	71.4	74.4	68.5
Former	19.5	17.3	21.8
Smoked During Pregnancy	9.1	8.4	9.8
Maternal combined KBIT score from age 7 visit, Mean ± SD	107.9 ± 15.0	108.5 ± 15.0	107.4 ± 15.0
Child Characteristics			
Female, %	49.3	48.6	50.0
Gestational age (weeks)	39.6 ± 1.6	39.7 ± 1.6	39.6 ± 1.6
Race/Ethnicity, %			
Asian	3.2	1.8	4.6
Black	13.5	11.4	15.7
Hispanic	3.3	3.6	2.9
White	69.3	72.7	65.9
Other	10.7	10.6	10.9
Paternal Characteristics			
College graduate, %	66.9	65.8	68.0
Household Characteristics			
Household income reported on early pregnancy questionnaire (annual), %			
≤$40k	14.7	14.3	15.2
> $40-70K	22.1	21.1	23.1
> $70K	63.2	64.6	61.7
HOME-SF score, Mean ± SD	18.4 ± 2.1	18.5 ± 2.1	18.4 ± 2.2
Metals (2nd Trimester)			
Lead (Pb) concentration (μg/dL), Median (IQR)	1.1 (0.6)	0.8 (0.3)	1.5 (0.6)
Manganese (Mn) concentration (μg/L), Median (IQR)	33.1 (11.8)	32.2 (12.2)	33.9 (11.7)
Mercury (Hg) concentration (ng/g), Median (IQR)	3.1 (3.4)	3.0 (3.3)	3.3 (3.4)
Neurobehavioral Assessments			
Parent BRIEF Global Executive Composite (GEC) score, Mean ± SD	48.6 ± 9.1	48.2 ± 9.0	49.1 ± 9.1
Teacher BRIEF GEC score, Mean ± SD	50.6 ± 9.9	50.5 ± 9.9	50.7 ± 9.9
SDQ Parent Total Difficulties score, Mean ± SD	6.5 ± 4.6	6.2 ± 4.6	6.7 ± 4.7
SDQ Teacher Total Difficulties score, Mean ± SD	6.3 ± 5.8	6.2 ± 5.7	6.3 ± 5.8
Child Age at Neurobehavioral Assessment (Years), Mean ± SD	7.8 ± 0.8	7.8 ± 0.8	7.8 ± 0.8

[a] Includes participants with multiply imputed variables.
[b] Median lead level in this sample is 1.1 μg/dL.

72.1% were college graduates and 71.4% were never smokers (Table 1). Most women were married or cohabitating (93.6%) and about half were nulliparous before the current pregnancy (48.6%). Mean (SD) gestational age of the infants at birth was 39.6 (1.6) weeks, 69.3% were white and 49.3% were female. Relative to mothers with second trimester lead concentrations below the median (1.1 μg/dL in erythrocytes), mothers with lead concentrations at or above the median were more likely to be former smokers (21.8% vs. 17.3%) or to have smoked during pregnancy (9.8% vs. 8.4%). Children in the higher lead group were also more likely to be black than children in the lower lead group (15.7% vs. 11.4%). Distributions of other characteristics were similar between lead groups (Table 1). Distributions of characteristics, including prenatal metals concentrations, were also similar between boys and girls (*Table S2)*. Characteristics of the imputed dataset were comparable to the characteristics of the complete case dataset with data on prenatal lead exposure and a neurobehavioral assessment in mid-childhood (*Table S3*).

The median (IQR) prenatal lead concentration was 1.1 (0.8 to 1.5) μg/dL in erythrocytes, which is roughly equivalent to 0.4 (0.3 to 0.5) μg/dL in whole blood, given that lead concentrations in erythrocytes are approximately three times higher than lead levels in whole blood during pregnancy (Perkins et al., 2014). Lead levels ranged from below the LOD to 9.8 μg/dL, with a standard deviation of 0.7 μg/dL. The mean ± SD (range) parent- and teacher-rated GEC BRIEF scores were 48.6 ± 9.1 (30–88) points and 50.6 ± 9.9 (30–100) points, respectively (Table 1). The mean ± SD (range) parent- and teacher-rated total difficulties SDQ scores were 6.5 ± 4.6 (0–30) points and 6.3 ± 5.8 (0–34) points, respectively (Table 1). Spearman rank correlations between parent and teacher ratings were moderate and positive (e.g., BRIEF: GEC, $r = 0.33$; subscales, $r = 0.20$-0.40; SDQ: total difficulties, $r = 0.43$; subscales, $r = 0.24$-0.53).

3.1. Associations between prenatal lead and mid-childhood BRIEF scores

In multivariable regression models, associations between prenatal lead levels and BRIEF scores were consistently positive, particularly for

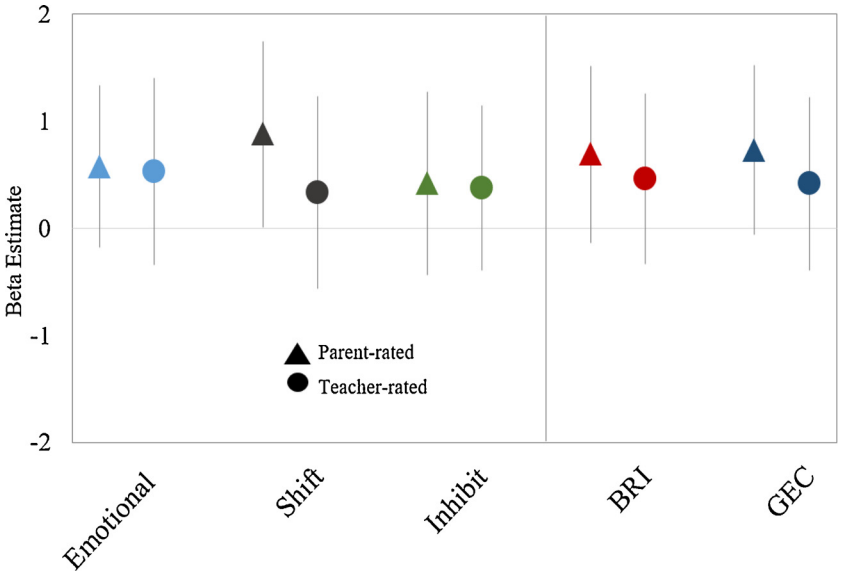

Fig. 1. Associations of maternal 2nd trimester blood lead levels with Behavioral Regulation Index (BRI) BRIEF scores in mid-childhood. Coefficients represent change in score for an IQR increase in maternal erythrocyte lead (0.6 μg/dL). Outcomes standardized for child age and sex; models adjusted for maternal 2nd trimester mercury and manganese levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income; and child race/ethnicity.

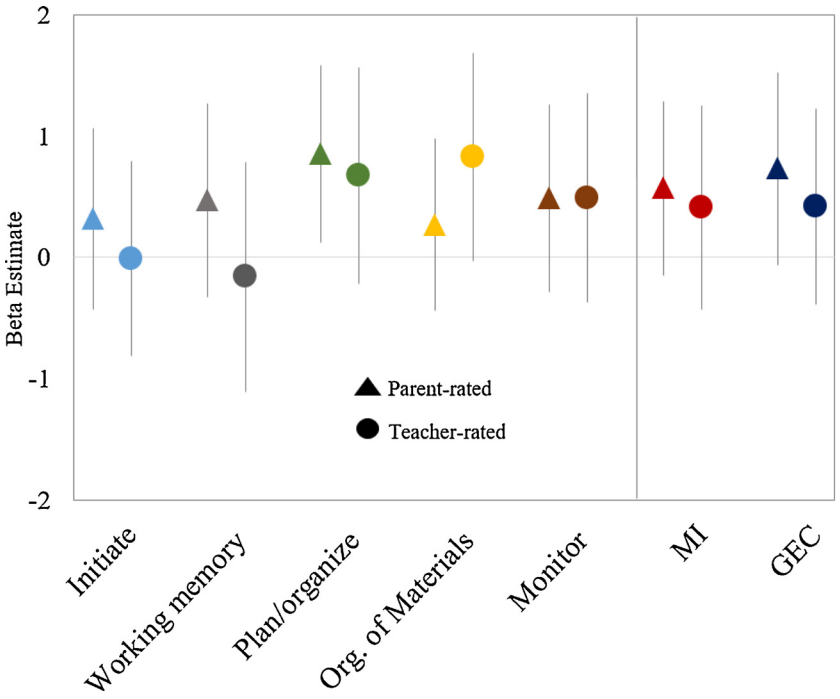

Fig. 2. Associations of maternal 2nd trimester blood lead levels with Metacognition Index (MI) BRIEF scores in mid-childhood. Coefficients represent change in score for an IQR increase in maternal erythrocyte lead (0.6 μg/dL). Outcomes standardized for child age and sex; models adjusted for maternal 2nd trimester mercury and manganese levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income; and child race/ethnicity.

the parent-rated BRIEF scales (Figs. 1 and 2). In the baseline model (i.e, age- and sex-adjusted) for parent-rated BRIEF scores, each IQR increase (0.6 μg/dL) in erythrocyte lead concentration was associated with a 0.75 (95% CI: -0.02, 1.52) point higher overall GEC score (*Table S4*). In the fully adjusted model, associations remained similar: each IQR increase (0.6 μg/dL) in erythrocyte lead was associated with a 0.73 (95% CI: -0.06, 1.52) point higher parent-rated GEC score and a 0.85 (95% CI: 0.12, 1.59) point higher plan/organize subscale score (Table 2). Higher lead levels were also associated with worse performance on the parent-rated shift subscale: an IQR (0.6 μg/dL) increase in lead was associated with a nearly 1-point increase, or a 0.10 standard deviation increase, in shift subscale score (β = 0.88; 95% CI: 0.01, 1.75). Effect estimates from models of teacher-rated BRIEF subscales were smaller in magnitude to models of parent ratings, and all confidence intervals included the null value (Table 2).

We also explored possible sex-specific effects in these data. In fully adjusted models stratified by sex, associations between lead and BRIEF scores were stronger among girls than boys on most subscales. For example, each IQR increase (0.6 μg/dL) in erythrocyte lead concentration was associated with a 1.17 (95% CI: 0.06, 2.28) point higher (worse) parent-rated GEC score among girls, while the association was weaker among boys (β = 0.47; 95% CI: -0.58, 1.51) (Table 3). Similarly, higher lead levels were associated with worse performance for girls on the parent-rated Behavioral Regulation Index (β = 1.03, 95% CI: 0.01, 2.04) and plan/organize scale (β = 1.05, 95% CI: 0.11, 1.98); among boys, these associations were weaker. However, in models including cross-product terms between lead and sex, there was little evidence that associations with BRIEF scores varied by sex (i.e., interaction p-values ranged from 0.37-0.99) (*Table S5)*. Associations with teacher-rated BRIEF subscales were generally in the same direction as parent-rated subscales, but most were smaller in magnitude, particularly when comparing across scores for girls.

Table 2
Associations of maternal 2nd trimester blood lead levels with BRIEF scores in mid-childhood (n = 1006).

	Adjusted Model[a] β (95% CI)
Parent-rated BRIEF Scales	
Behavioral Regulation Index	0.69 (−0.13, 1.51)
Emotional control	0.58 (−0.18, 1.34)
Shift	0.88 (0.01, 1.75)
Inhibit	0.42 (−0.44, 1.28)
Metacognition Index	0.57 (−0.15, 1.29)
Initiate	0.31 (−0.44, 1.06)
Working memory	0.47 (−0.33, 1.27)
Plan/organize	0.85 (0.12, 1.59)
Organization of materials	0.27 (−0.44, 0.98)
Monitor	0.49 (−0.29, 1.26)
General Executive Composite	0.73 (−0.06, 1.52)
Teacher-rated BRIEF Scales	
Behavioral Regulation Index	0.46 (−0.34, 1.26)
Emotional control	0.53 (−0.34, 1.41)
Shift	0.34 (−0.56, 1.23)
Inhibit	0.38 (−0.39, 1.14)
Metacognition Index	0.41(−0.43, 1.25)
Initiate	−0.01 (−0.81, 0.79)
Working memory	−0.16 (−1.11, 0.78)
Plan/organize	0.67 (−0.22, 1.57)
Organization of materials	0.82 (−0.03, 1.68)
Monitor	0.49 (−0.38, 1.35)
General Executive Composite	0.42 (−0.39, 1.23)

Note: Coefficients represent change in score for an IQR increase in maternal erythrocyte lead (0.6 μg/dL).

[a] Outcomes standardized for child age and sex. Model adjusted for maternal 2nd trimester mercury and manganese levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income; and child race/ethnicity.

Table 3
Associations of maternal 2nd trimester blood lead levels with BRIEF scores in mid-childhood, by sex.

	Girls [a] β (95% CI)	Boys [a] β (95% CI)
Parent-rated BRIEF Scales		
Behavioral Regulation Index	1.03 (0.01, 2.04)	0.51 (−0.63, 1.66)
Emotional Control	1.04 (−0.002, 2.08)	0.36 (−0.70, 1.42)
Shift	0.77 (−0.23, 1.77)	0.87 (−0.35, 2.10)
Inhibit	0.78 (−0.38, 1.93)	0.21 (−0.92, 1.34)
Metacognition Index	0.89 (−0.06, 1.85)	0.36 (−0.63, 1.35)
Initiate	0.90 (−0.14, 1.94)	−0.002 (−1.02, 1.02)
Working memory	0.83 (−0.27, 1.92)	0.25 (−0.82, 1.32)
Plan/organize	1.05 (0.11, 1.98)	0.70 (−0.34, 1.74)
Organization of materials	0.49 (−0.46, 1.45)	0.12 (−0.81, 1.05)
Monitor	0.62 (−0.36, 1.60)	0.39 (−0.68, 1.45)
General Executive Composite	1.17 (0.06, 2.28)	0.47 (−0.58, 1.51)
Teacher-rated BRIEF Scales		
Behavioral Regulation Index	0.56 (−0.68, 1.81)	0.45 (−0.54, 1.44)
Emotional control	0.83 (−0.53, 2.19)	0.40 (−0.65, 1.46)
Shift	0.45 (−0.91, 1.82)	0.30 (−0.84, 1.44)
Inhibit	0.24 (−0.93, 1.41)	0.47 (−0.50, 1.45)
Metacognition Index	0.54 (−0.78, 1.87)	0.41 (−0.69, 1.50)
Initiate	0.09 (−1.19, 1.37)	−0.02 (−1.06, 1.03)
Working memory	−0.02 (−1.45, 1.41)	−0.16 (−1.40, 1.08)
Plan/organize	0.81 (−0.59, 2.21)	0.65 (−0.49, 1.80)
Organization of materials	0.96 (−0.41, 2.32)	0.80 (−0.29, 1.89)
Monitor	0.62 (−0.79, 2.03)	0.49 (−0.57, 1.54)
General Executive Composite	0.53 (−0.75, 1.82)	0.41 (−0.60, 1.43)

Note: Coefficients represent change in score for an IQR increase in maternal erythrocyte lead (0.6 μg/dL).

[a] Outcomes standardized for child age and sex; models adjusted for maternal 2nd trimester mercury and manganese levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income; and child race/ethnicity.

3.2. Associations between prenatal lead and mid-childhood SDQ scores

Associations between prenatal lead and SDQ subscales contributing to total difficulties scores were consistently positive, suggesting adverse effects of lead on both parent- and teacher-rated SDQ scales, although most confidence intervals included the null (Fig. 3). In baseline models of parent-rated SDQ scores adjusted for age and sex only, each IQR increase (0.6 μg/dL) in maternal erythrocyte lead concentration was associated with a 0.18 (95% CI = 0.04, 0.32) point higher emotional problems subscale score and a 0.40 (95% CI = 0.01, 0.79) point higher total difficulties SDQ score (*Table S6*). In the fully adjusted model, associations were similar to the baseline model: an IQR increase (0.6 μg/dL) in lead was associated with a 0.18 (95% CI = 0.03, 0.33) point higher parent-rated SDQ emotional problems score, and a 0.36 (95% CI: -0.04, 0.77) point higher parent-rated total difficulties score, corresponding to a 0.08 standard deviation increase per IQR increase in lead (Table 4). Although associations with teacher ratings were similar in direction and trend as parent ratings, confidence intervals were generally wider and all crossed the null (Table 4).

In sex-stratified models, positive (i.e. adverse) associations were stronger among girls than boys on SDQ parent- and teacher-rated subscales. For example, each IQR increase (0.6 μg/dL) in erythrocyte lead concentration was associated with a 0.72 (95% CI: 0.16, 1.27) point higher parent-rated total difficulties score among girls; in boys, this association was closer to null (β = 0.16; 95% CI: -0.38, 0.70) (Table 5). In addition, higher lead levels were associated with worse performance on parent-rated emotional problems (β = 0.31, 95% CI: 0.11, 0.52) and hyperactivity (β = 0.18, 95% CI: -0.09, 0.45) scales for girls, but this association was attenuated for boys (Table 5). Confidence intervals for associations with teacher-rated subscales all included the null. There was little evidence for effect modification by sex based on interaction terms (interaction p-values ranged from 0.30 to 0.95), with the exception of parent-rated total difficulties (p = 0.16) and emotional subscale (p = 0.10) (*Table S7)*.

In sensitivity analyses, results generated by complete case analysis models (n = 625) showed consistency in direction when compared with MI models for most subscales *(Table S8-S9)*. Adjusting the model further for hemoglobin levels did not change the results of this analysis.

4. Discussion

In this cohort of school-age children, most associations between prenatal erythrocyte lead and EF-related behaviors in childhood were null. However, there was a consistent, positive trend in the associations across BRIEF and SDQ subscales for both parent- and teacher-reported outcomes, suggesting poorer childhood EF with increased prenatal lead exposure. In particular, higher average prenatal erythrocyte lead levels predicted poorer childhood ability to plan/organize and shift tasks and more emotional problems, as rated by parents responding to the BRIEF and SDQ assessments.

While effect estimates are modest, these data nonetheless suggest that lead exposure at levels even lower than NHANES average population levels (2013–2014 median for women: 0.73 μg/dL) may have the capacity to alter the developing brain, findings which underline prior reports of the lack of a detectable threshold for adverse effects of lead on neurobehavioral outcomes (Lanphear, 2017; Lanphear et al., 2005; Shefa and Héroux, 2017). The Project Viva cohort is a largely suburban population with mean erythrocyte lead levels equivalent to ~0.40 μg/dL in whole blood. These results suggest that higher exposure to lead during the prenatal period is modestly associated with poorer childhood neurobehavioral performance on specific subscales, even in a suburban population not thought to be at high risk of lead exposure and with blood lead levels that are commonly experienced by U.S. women today.

Previous research on lead exposure and EF-related behavioral assessment rating scales has predominantly focused on exposure during

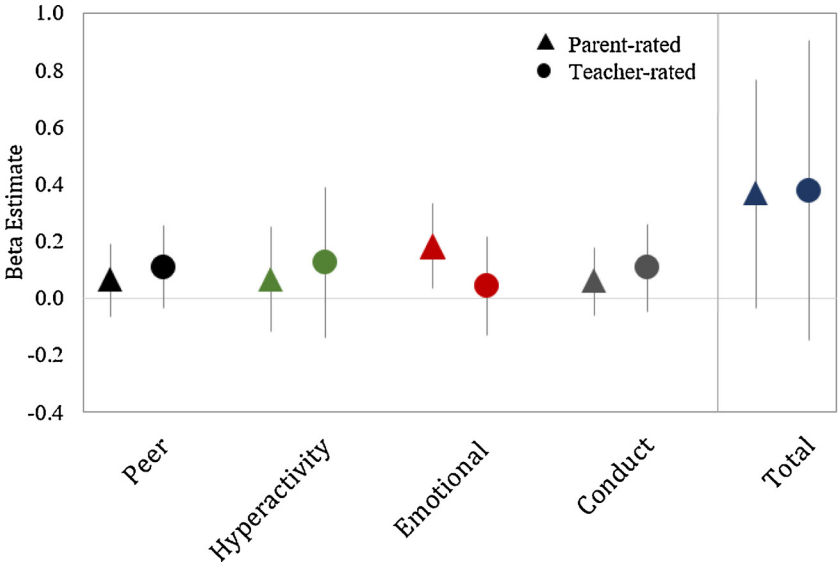

Fig. 3. Associations of maternal 2nd trimester blood lead levels with SDQ scores in mid-childhood. Coefficients represent change in score for an IQR increase in maternal erythrocyte lead (0.6 μg/dL). Total Difficulties is calculated by summing the scales of emotional problems, conduct problems, hyperactivity, and peer relationship problems. Adjusted for child age, sex and race/ethnicity; maternal 2nd trimester mercury and manganese levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income.

Table 4
Associations of maternal 2nd trimester erythrocyte lead levels with SDQ scores in mid-childhood (n = 1006).

	Adjusted Model [a] β (95% CI)
Parent-rated SDQ Scales	
Total Difficulties	0.36 (−0.04, 0.77)
Peer	0.06 (−0.06, 0.19)
Hyperactivity	0.06 (−0.12, 0.25)
Emotional	0.18 (0.03, 0.33)
Conduct	0.06 (−0.06, 0.18)
Prosocial	−0.08 (−0.21, 0.05)
Teacher-rated SDQ Scales	
Total Difficulties	0.38 (−0.15, 0.91)
Peer	0.11 (−0.04, 0.25)
Hyperactivity	0.12 (−0.14, 0.39)
Emotional	0.04 (−0.13, 0.21)
Conduct	0.11 (−0.05, 0.26)
Prosocial	−0.12 (−0.30, 0.06)

Note: Coefficients represent change in score for an IQR increase in maternal erythrocyte lead (0.6 μg/dL); Total Difficulties is calculated by summing the scales of emotional problems, conduct problems, hyperactivity, and peer relationship problems; Higher scores indicate worse performance on all scales with the exception of the prosocial behavior scale. The prosocial behavior scale is scored in the opposite direction.

[a] Model adjusted for child age, sex, and race/ethnicity; maternal 2nd trimester mercury and manganese levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income.

Table 5
Regression coefficients for associations of maternal 2nd trimester erythrocyte lead levels with SDQ scores in mid-childhood, by sex.

	Girls[a] β (95% CI)	Boys [a] β (95% CI)
Parent-rated SDQ Scales		
Total Difficulties	0.72 (0.16, 1.27)	0.16 (−0.38, 0.70)
Peer	0.15 (−0.003, 0.30)	0.01 (−0.16, 0.19)
Hyperactivity	0.18 (−0.09, 0.45)	0.002 (−0.25, 0.26)
Emotional	0.31 (0.11, 0.52)	0.10 (−0.10, 0.30)
Conduct	0.08 (−0.08, 0.24)	0.04 (−0.11, 0.19)
Prosocial	−0.12 (−0.32, 0.07)	−0.06 (−0.24, 0.13)
Teacher-rated SDQ Scales		
Total Difficulties	0.51 (−0.19, 1.20)	0.29 (−0.43, 1.02)
Peer	0.16 (−0.03, 0.36)	0.06 (−0.15, 0.27)
Hyperactivity	0.17 (−0.16, 0.50)	0.11 (−0.26, 0.48)
Emotional	0.07 (−0.18, 0.33)	0.01 (−0.20, 0.22)
Conduct	0.10 (−0.07, 0.28)	0.11 (−0.10, 0.32)
Prosocial	−0.23 (−0.50, 0.05)	−0.06 (−0.31, 0.20)

Note: Coefficients represent change in score for an IQR increase in maternal erythrocyte lead (0.6 μg/dL); Total Difficulties is calculated by summing the scales of emotional problems, conduct problems, hyperactivity, and peer relationship problems. Higher scores indicate worse performance on all scales with the exception of the prosocial behavior scale. The prosocial behavior scale is scored in the opposite direction.

[a] Model adjusted for child age and race/ethnicity; maternal 2nd trimester mercury and manganese levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income.

childhood, whereas our study was able to evaluate lead levels during the prenatal period. Notwithstanding this difference in the exposure timeframe, our EF results show consistent directionality with those from a study in India in which childhood lead levels (mean whole blood lead: 11.4 μg/dL) were studied in relation to the BRIEF questionnaire (Roy et al., 2009). This finding lends support to the idea that the prenatal period is an important window of susceptibility to lead with respect to EF, even in a population with relatively higher SES. Roy et al. (2009) exclusively measured teacher-rated GEC for the BRIEF and estimated that each 1 μg/dL increase in log blood lead was associated with a 0.42 point higher (worse) age- and sex-standardized GEC score (β = 0.42; 95% CI: 0.18, 0.65) (Roy et al., 2009). Another study from Uruguay evaluating childhood blood lead (mean whole blood lead: 4.2 μg/dL) and BRIEF teacher-rated executive function related behaviors reported poorer ability to inhibit inappropriate behaviors with higher lead levels (prevalence ratio = 1.01; 95% CI: 1.00, 1.03) (Barg et al., 2018). Barg et al. (2018) also found slightly worse overall behavioral regulation in girls when compared to boys, similar to our findings of stronger adverse associations for girls. We are unaware of any previous studies on lead exposures during prenatal development that evaluated EF-related behavioral assessment rating scales. Our findings were also similar to some studies that utilized EF performance-based tests, such as the Wisconsin Card Sorting Test (WCST) to evaluate cognitive flexibility (set shifting) (Chiodo et al., 2004; Surkan et al., 2007) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) Stockings of Cambridge (SOC) subtest to evaluate planning (Canfield et al., 2004). These studies reported that higher lead levels were associated with worse EF performance. In contrast to our results, a previous New England study found no association between blood lead and scores on tests of shifting as assessed by the Stroop Color-Word test and the Trail Making Test B, or with planning evaluated using the

WISC-III Mazes subtest (Surkan et al., 2007). This analysis, however, was performed on a smaller sample (n < 400) and was cross-sectional. Importantly, none of these previous studies examined associations of EF with *prenatal* lead. In all of the aforementioned studies, mean lead levels in whole blood ranged from 2.3 to 11.5 μg/dL (Barg et al., 2018; Canfield et al., 2004; Chiodo et al., 2004; Roy et al., 2009; Surkan et al., 2007), which are higher than levels in our study (mean and median equivalent to 0.40 and 0.36 μg/dL, respectively, in whole blood) and higher than the average U.S. lead levels reported in the most recent NHANES 2013–2014 data (geometric mean for women: 0.75 μg/dL; median for women: 0.73 μg/dL) (CDC, 2017).

Our results are also similar to those reported in previous literature on lead exposure and behavioral difficulties as assessed by the Strengths and Difficulties Questionnaire (SDQ). A longitudinal study in a Flemish cohort found that the odds of having an abnormal SDQ total difficulties score were 5.08 times higher for children in the highest prenatal lead concentration tertile (95% CI: 1.36, 19.18) compared to children in the lowest tertile (median lead level: 1.4 μg/dL) (Sioen et al., 2013). Additionally, a cross-sectional study of 6–11 year old Canadian children reported positive (i.e., adverse) associations between blood lead levels (geometric mean: 0.90 μg/dL) and total difficulties on the SDQ (Arbuckle et al., 2016). Lead levels in this study were more comparable to current U.S. population levels, but lead was measured during childhood and not prenatally.

In our study, the effect estimates were similar in direction for parent- and teacher-rated assessments, but slightly attenuated in most models of teacher-rated scores. Our findings were different from many, but not all, studies that have used both raters (Chandramouli et al., 2009; Chen et al., 2007; Nigg et al., 2010) and found associations with teacher ratings to be stronger than parent ratings. Behavioral ratings completed by parents may diverge from teachers' ratings for several reasons, including the variation of child behaviors in different settings (i.e. contextual differences in school vs. home) (Rettew et al., 2011; Vitoratou et al., 2019). Teachers evaluate children relative to other classmates of the same age, although it is plausible that subtle behavioral differences are not as distinguishable given that the child spends less time in school than at home. Additionally, teachers observe children in settings that necessitate sitting quietly over long periods of time in a structured classroom setting, which is often different from the home setting. In both cases, outcome misclassification is possible and is a limitation of our study. Parents and teachers may rate students differently based on factors other than the child's behavior, such as parental stress or classroom stress, allowing for potential rater bias (Dekker 2017; Stone 2010). Parents with higher lead exposure may themselves have cognitive impairments that affect their parenting behaviors and the assessment of their child's EF and behavioral difficulties. This bias is a limitation of rating scales, but these rating scales permit us to assess another dimension of the lead-EF landscape in the real world, rather than assessing lead effects with controlled performance-based tests alone. Finally, HOME score was similar between high and low lead groups (Table 1), indicating comparability of the home environment and the potential for similar parental influence, despite differences in lead exposure level.

Although effect estimates were at magnitudes that may be considered subclinical for individual children, these results are important at the population level. In our study, 4.6% and 5.6% of children were above the clinical cut-point for the BRIEF and SDQ, respectively. The estimated increase of 0.73 points on the parent-rated GEC score and 0.36 points on the parent-rated total difficulties score per IQR increase in lead contributes to distributional shifts in the proportion of adverse neurobehavioral outcomes. These shifts can increase the percent of children in the population who meet the clinical threshold for behavioral dysfunction.

Potential implications of poor EF performance are far-reaching. EF is mediated by frontal lobe brain systems and regulates higher order cognitive functions, including working memory, planning and organization, capacity to inhibit inappropriate responses, initiation of activity, monitoring of behavior and cognitive flexibility (set shifting) (Otero and Barker, 2014). Childhood EF deficits have been associated with poorer academic achievement (Biederman et al., 2006; Diamantopoulou et al., 2007; Miller and Hinshaw, 2010) and social functioning (Miller and Hinshaw, 2010) that can continue through later childhood and adolescence (Miller and Hinshaw, 2010). EF can also be diminished in attention deficit hyperactivity disorder (ADHD), the most common neurobehavioral disorder in childhood, with an estimated prevalence of 5–10% (Aguiar et al., 2010; Eubig et al., 2010). Deficits in EF are significantly more common for individuals with ADHD and are considered a comorbidity of the disorder (Biederman et al., 2006; Nigg et al., 2005). Furthermore, prior research has described both ADHD and poor EF as predictors of subsequent delinquent behaviors (Burton et al., 2016; Fletcher and Wolfe, 2009; Savolainen et al., 2010; Wright et al., 2008). Shifting our attention to the prenatal period for elimination of early life EF risk factors, such as fetal lead exposure even at low levels, is therefore important for reducing later life impacts.

Though effect estimates for sex-specific cross-product terms were not statistically significant, we estimated stronger adverse associations between lead and neurobehavioral outcomes among girls across most subtests when compared with boys. The results suggest greater susceptibility to prenatal lead exposure among girls for these behavioral outcomes, but these findings should be confirmed by additional studies. Sex-specific differences in the effects of *in utero* lead exposure have been reported in previous toxicological studies (Bunn et al., 2001; Ronis et al., 1998; Virgolini et al., 2008) as well as epidemiologic studies of childhood IQ, attention, visuoconstruction, visuomotor performance, and internalizing behaviors (Llop et al., 2013). The direction of these sex-specific associations has been inconsistent, however, and findings have differed across domains. Many studies have suggested higher sensitivity to lead among boys (related to IQ, cognitive function, visuoconstruction, visuomotor performance, externalizing behavior, and psychometric and objective neuro-radiological indices of brain development) (Cecil et al., 2008; Dietrich et al., 1987; Jedrychowski et al., 2009; Ris et al., 2004; Taylor et al., 2017; Tong et al., 2000; Vermeir et al., 2005) and may be explained by lower levels of estradiol in boys, which is neuroprotective (Vahter et al., 2007). Estrogen regulates brain function and there are sex specific differences in density and location of brain estrogen receptors, especially during the developmental period (Vahter et al., 2007). Fewer studies have suggested higher sensitivity to lead among girls (related to IQ and internalizing behavior) (Burns et al., 1999; Tong et al., 2000).

One potential explanation for our finding of higher lead sensitivity among girls may relate to ADHD prevalence and the use of medications in the U.S. The U.S. prevalence of ADHD in boys is about twice that of girls (Pastor et al., 2015), and an estimated 69% of 6–11 year old children with an ADHD diagnosis are taking medications (CDC, 2018b). Thus, we might expect that if more boys have an ADHD diagnosis and currently take ADHD medications to treat behavioral and/or EF difficulties than girls, it is possible that lead appears less harmful among boys because a larger proportion are receiving benefits from ADHD medications compared to girls. However, the prevalence of reported ADHD diagnosis here is low (6.1%; 4.8% boys, 1.3% girls); therefore, the use of ADHD medications is not likely to explain the sex differences we estimated. Our findings of potential sex-specific associations between lead with executive function related behaviors and behavioral difficulties are hypothesis-generating and should be investigated further as part of future research.

There are several limitations to our study. We lack information on postnatal lead levels, which precludes us from determining if observed associations are due to prenatal versus postnatal lead exposure, as is the case for all longitudinal studies with a single exposure timepoint. Participants were mostly white, highly educated, middle class women with health insurance who did not smoke. Although this homogeneity may limit generalizability of our findings, it also reduces the potential

for residual confounding. Exposure to lead was estimated in erythrocytes for this study, a method that is less common than measuring lead in whole blood. While not customary, this erythrocyte biomarker is nonetheless valid for ranking exposure and thus the observed associations are relevant and valid. Additionally, the literature demonstrates that 99% of whole blood lead is contained in erythrocytes and erythrocyte lead is highly correlated with whole blood lead ($r = 0.998$) (ATSDR, 2007; Chen et al., 2014). We converted lead concentrations in erythrocytes to lead concentrations in whole blood to allow for comparability and generalizability, with our median lead levels roughly equivalent to 0.4 μg/dL in whole blood (Perkins et al., 2014). Finally, selection bias from differential loss to follow-up over the seven-year period is possible if, for example, children with higher prenatal lead exposure also had behavioral difficulties that made it challenging to participate in the follow-up visits. This scenario would bias findings toward the null, because we would not be capturing participants with high lead exposure that experienced adverse neurobehavioral outcomes, and the true association may actually be stronger. Baseline characteristics of participants included in the analysis were similar to the characteristics of the entire cohort overall.

Our study has many strengths. It is among the first to evaluate the relationship between EF rating scales and prenatal lead exposure at levels that are more reflective of current-day exposure in the U.S. Our rich covariate data allowed us to control for many important potential confounding variables. Furthermore, observed associations were robust to confounder adjustment, as additional adjustment of baseline models by maternal IQ, nulliparity, smoking during pregnancy, maternal education, 2nd trimester mercury and manganese levels, paternal education, HOME composite score, household income, and child race/ethnicity did not substantially change effect estimates. Additionally, our sample (n = 1006) was larger than other studies of lead and EF rating scales. Moreover, the prospective design with extended follow-up at 7 years of age permitted us to assess long-term EF-related behavior and behavioral difficulties associated with lead exposure from as early as the second trimester.

5. Conclusion

Although population lead levels continue to decrease over time, exposure to lead at health relevant levels persists. Our research focused on prenatal lead exposure and executive function, which may be a more sensitive endpoint than IQ, in a suburban, relatively affluent cohort. While our findings for most subscales were null, the direction of association was consistently positive and linear, with strongest associations on the subtests of childhood emotional problems and capacity to plan/organize and shift. Our findings suggest lead's continued impact on neurobehavior, even at levels that are a full order of magnitude below the current childhood CDC reference level of 5 μg/dL, and at population relevant concentrations. This work highlights the importance of sustained efforts to eliminate lead exposure across the population.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

Dr. Bellinger reports personal fees from several legal firms outside the submitted work; Dr. Oken reports grants from NIH, during the conduct of the study; Dr. Wise reports grants from National Institutes of Health outside the submitted work; Dr. Wright reports grants from National Institutes of Health, during the conduct of the study; Dr. Claus Henn reports grants from National Institutes of Health, during the conduct of the study;

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neuro.2019.09.006.

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