A Prospective Birth Cohort Study on Early Childhood Lead Levels and Attention Deficit Hyperactivity Disorder: New Insight on Sex Differences

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Objective To investigate the prospective associations between early childhood lead exposure and subsequent risk of attention deficit hyperactivity disorder (ADHD) in childhood and its potential effect modifiers.

Study design We analyzed data from 1479 mother–infant pairs (299 ADHD, 1180 neurotypical) in the Boston Birth Cohort. The child's first blood lead measurement and physician-diagnosed ADHD was obtained from electronic medical records. Graphic plots and multiple logistic regression were used to examine dose–response associations between lead exposure and ADHD and potential effect modifiers, adjusting for pertinent covariables.

Results We found that 8.9% of the children in the Boston Birth Cohort had elevated lead levels (5-10 μg/dL) in early childhood, which was associated with a 66% increased risk of ADHD (OR, 1.66; 95% CI, 1.08-2.56). Among boys, the association was significantly stronger (OR, 2.49; 95% CI, 1.46-4.26); in girls, the association was largely attenuated (*P* value for sex-lead interaction = .017). The OR of ADHD associated with elevated lead levels among boys was reduced by one-half if mothers had adequate high-density lipoprotein levels compared with low high-density lipoprotein, or if mothers had low stress compared with high stress during pregnancy.

Conclusions Elevated early childhood blood lead levels increased the risk of ADHD. Boys were more vulnerable than girls at a given lead level. This risk of ADHD in boys was reduced by one-half if the mother had adequate high-density lipoprotein levels or low stress. These findings shed new light on the sex difference in ADHD and point to opportunities for early risk assessment and primary prevention of ADHD. *(J Pediatr 2018;■■:■■-■■).*

Lead is a recognized environmental toxin.[1-5] Lead exposure has decreased significantly over the past decades since the removal of lead from paints and gasoline and the adoption of other environmental safety measures,[6] However, exposure to low lead levels continues to be widespread in the general US population, particularly in urban low-income populations.[7]

To date, critical questions remain regarding the role of early life lead exposure in the development of attention deficit hyperactivity disorder (ADHD).[8-10] Existing studies used cross-sectional designs,[2,3,5] and lead measurement occurred either simultaneous to or after the ADHD diagnosis; thus, the temporal relationship between lead exposure and ADHD could not be established. Despite the well-observed greater likelihood of ADHD in boys compared with girls, few studies have investigated if lead affects boys and girls differently.[2] Additionally, most studies on ADHD examined lead exposure late in childhood (mean age of measurement ranging from 7 to 14 years).[10] Last, prior studies did not consider potential modifiers of the lead-ADHD association, which is necessary both in terms of understanding the etiology of ADHD and informing intervention strategies.[11]

In this study, we sought to examine the association between early childhood lead exposure and the development of ADHD using a prospective birth cohort design. We were particularly interested in identifying early life factors that could modify lead-ADHD associations in a predominantly urban low-income minority population in the US. We hypothesized that there is a significant association

ADHD	Attention deficit hyperactivity disorder
BBC	Boston Birth Cohort
BMC	Boston Medical Center
CDC	Centers for Disease Control and Prevention
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EMR	Electronic medical record
HDL	High-density lipoprotein
ICD	*International Classification of Diseases*
MLR	Multivariate logistic regression
NT	Neurotypical

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between early childhood blood lead levels and the risk of developing ADHD. Motivated by findings from our previous work,[12] we further hypothesized that this association might be modified by prenatal factors, including child sex, maternal high-density lipoprotein (HDL) levels, and degree of stress during pregnancy. The conceptual framework of these hypotheses is illustrated in **Figure 1** (available at www.jpeds.com).

Methods

This study analyzed data from the Boston Birth Cohort (BBC), which has recruited mother-infant pairs at birth from Boston Medical Center (BMC) since 1998, using a rolling enrollment. Details of the BBC recruitment have been published previously.[13,14] Eligible mothers were those who delivered a single live birth at BMC. Pregnancies resulting from in vitro fertilization, multiple gestation pregnancies, deliveries induced by maternal trauma, or newborns with substantial congenital disabilities were not eligible for enrollment. BBC mother-infant pairs who continued to receive pediatric primary care at BMC were enrolled in a postnatal follow-up study.[13,15,16] The Institutional Review Board of Boston University Medical Center and The Institutional Review Board of Johns Hopkins Bloomberg School of Public Health approved the BBC study. Informed consent was obtained from each participant under the Institutional Review Board approved protocol.

There were 3098 mother-infant pairs enrolled in the postnatal follow-up study at BMC at the time of the study. Our study sample excluded participants who had missing data for lead measurements and key covariates. We further excluded those with lead measurement after ADHD diagnosis, incorrect lead measurement dates, lead measurement age older than 4 years, and a lead level higher than 10 μg/dL (to focus on the effects in the low lead exposure range). Because many neurodevelopmental disorders may have common risk factors, we excluded those with neurodevelopmental disorder diagnoses other than ADHD (**Figure 2**; available at www.jpeds.com). Our final analyses consisted of 1479 mother-infant pairs (299 children with ADHD and 1176 neurotypical [NT] children) who were enrolled at birth from 1998 to 2013 and followed-up prospectively until the end of 2016 (**Figure 2**).

After recruiting mothers within 24-72 hours after delivery, a standard questionnaire interview was used to collect data on maternal demographic characteristics, smoking status, and stress during pregnancy. Stress during pregnancy was defined according to the response to the following question: "How would you characterize the amount of stress in your life during pregnancy?" The possible responses to the question included not stressful, average stressful, and very stressful. A medical abstraction form was used to review participants' medical records and collect clinical-related data including parity, pregnancy-related complications, intrauterine infection, and birth outcomes such as gestational age and birthweight. Since 2003, electronic medical records (EMRs) were implemented for routine clinical data collection at BMC, including both well-child and specialty medical visits. For each primary care visit, the EMRs contain the primary and secondary diagnoses from the *International Classification of Diseases, Ninth Revision* (ICD-9) (before October 1, 2015) and ICD-10 (after October 1, 2015). In this study, we extracted EMR data until the end of 2016.

Maternal plasma HDL levels and lead levels in red blood cells were measured using nonfasting blood samples obtained between 24 and 72 hours after delivery. The child postnatal blood lead levels (as part of routine pediatric screening) were obtained from the EMRs. The low detection limit of lead was 2 μg/dL; 659 children had blood lead levels below this threshold. The below threshold lead level was coded as 1 μg/dL when lead was analyzed as a continuous variable. For each child with repeated measurements of lead levels, the level measured at the earliest age was selected for analysis in this study.

In our study, the ADHD group was defined as having any of the following ICD-9 codes: 314.0, 314.00, 314.01, 314.1, 314.2, 314.8, and 314.9, or any of the following ICD-10 codes: F90.0, F90.1, F90.2, F90.8, and F90.9 as documented in the child's EMRs. The NT group was defined as not having any diagnosis of autism spectrum disorder, ADHD, conduct disorders, developmental delays, intellectual disabilities, failure to thrive, and/or congenital anomalies. **Table I** (available at www.jpeds.com) lists the ICD-9 and ICD-10 codes for these neurodevelopmental disorders diagnoses.

The characteristics of the study sample for the ADHD and the NT groups were compared using *t* tests for continuous variables and χ^2 tests for categorical variables. Variables with a $P < .05$ were included in the subsequent multivariate logistic regression (MLR) analyses as covariates. The key predictor analyzed in this study was the child's lead level, which was natural log-transformed to approximate the normal distribution. Lead level was also analyzed as a binary (5 μg/dL as the cutoff) and categorical variable (<2, 2-4, and 5-10 μg/dL) based on cutpoints used in previous studies and Centers for Disease Control and Prevention (CDC) guidelines.[2,8] Maternal HDL levels were analyzed as a binary variable cut at the median (60.7 mg/dL).[12] Maternal stress during pregnancy was converted from a 3-category variable (not stressful, average, very stressful) into a binary variable (not stressful vs stressful) for analysis.[17]

We conducted MLR to examine the dose-response association between early childhood lead level and the risk of having ADHD, both categorically and continuously, adjusting for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight. Sex-stratified analyses and the joint effect of the child's sex with lead levels on the risk of ADHD diagnosis were tested using MLR, and adjusted for the same covariates except for child's sex. The interaction between child's sex and lead level on the risk of ADHD was then tested using MLR and adding the interaction term into the model while adjusting for the same covariates. We further tested the joint associations among maternal HDL level, maternal stress during pregnancy, and early childhood lead level with the risk of ADHD diagnosis both across and within the child's sex groups, adjusting for the same covariates except for child's sex. For the sensitivity analyses,

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