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Identifying periods of heightened susceptibility to lead exposure in relation to behavioral problems

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Abstract

Background: Lead exposure is associated with behavioral problems in children, but the age(s) of greatest susceptibility to low-level lead exposure is unknown.

Objective: We evaluated the association of repeated blood lead concentrations with parent-reported behaviors to identify periods of heightened susceptibility during infancy and childhood (HOME Study; Cincinnati, Ohio; 2003–2006; n=244).

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ETHICAL APPROVAL: The institutional review boards (IRB) of Cincinnati Children's Hospital Medical Center (CCHMC) and the participating prenatal clinics and delivery hospitals approved the HOME Study. Brown University deferred to the CCHMC IRB as the IRB of record. Women provided written informed consent for themselves and their children after research assistants explained study protocols during face-to-face visits.

COMPETING INTERESTS: JMB's institution was financially compensated for his services as an expert witness for plaintiffs in litigation related to PFAS-contaminated drinking water; these funds were not paid to JMB directly. BPL has served as an expert witness for plaintiffs in litigation related to lead poisoning prevention cases, but he received no personal payments for his services. His institution was financially compensated for some of those cases. The other authors declare they have no actual or potential competing financial interests.

Methods: We quantified lead in whole blood samples (ages 1-,2-,3-,4-,5-, and 8-years) and assessed behavior using the Behavioral Assessment System for Children-2 (BASC-2; ages 2-,3-,4-,5-, and 8-years). We used multiple informant models and modified Poisson regression to estimate covariate-adjusted associations of ln-transformed blood lead concentrations with continuous BASC-2 T-scores and the relative risk of behavior scores classified as at-risk or clinically significant, respectively.

Results: We observed trends indicating that higher blood lead concentrations at all ages were adversely associated with scores on behavioral scales. On the Externalizing Problems and Adaptive Skills scales, these associations were strongest for blood lead concentrations at age 8-years (β=3.1-point; 95%CI=0.7, 5.4 and β=−2.2-point; 95%CI= −4.9, 0.5, respectively) compared with other ages. Overall, higher blood lead concentrations were associated with elevated risk of behavior scores classified as at-risk or clinically significant on the Adaptive Skills, Behavioral Symptom Index, and Externalizing Problems scales.

Keywords

lead; children’s health; behavior; periods of heightened susceptibility

INTRODUCTION

Lead is a recognized neurotoxicant with no safe level of exposure (1). Studies have reported adverse associations of higher blood lead concentrations with cognition, cardiovascular health, and kidney function in adulthood (2–5). Primary prevention is the preferred solution to eliminate the burden of lead-related neurobehavioral consequences including diminished intellectual and academic abilities in childhood, as well as hyperactivity and attention problems — the primary features of attention-deficit-hyperactivity (ADHD) disorder (1,2).

Current practices to protect children from lead toxicity focus on blood lead screening, surveillance, and secondary prevention during the first two years of life (6). Furthermore, the Centers for Disease Control and Prevention (CDC) emphasizes a higher risk for children less than six years old (7). The biological processes underlying rapid neurodevelopment during this period may result in heightened susceptibility to lead toxicity (8). Current efforts have also targeted this life stage because of the recognition that developmentally appropriate behaviors can increase lead exposure from lead-based paint, lead-contaminated water, house dust, and soil. These practices, however, are primarily informed by studies of children with higher blood lead concentrations than contemporary children (9–12). Thus, it is unclear whether heightened susceptibility to lead exposure extends beyond early childhood into later childhood, particularly in populations with low-level exposure from a variety of sources that would require more extensive primary prevention interventions.

The objective of this study was to evaluate the association of blood lead concentrations collected during the first 8-years of life with longitudinal measures of behaviors in a contemporary cohort and identify periods of heightened susceptibility to low-level lead exposure.

SUBJECTS AND METHODS

Health Outcomes and Measures of the Environment (HOME) Study Recruitment

Between 2003 and 2006, HOME Study research staff recruited pregnant women living in the Cincinnati, Ohio metropolitan area from nine local prenatal clinics (13). Eligibility criteria included: English fluency; 18 years of age or older; 16 ± 3 weeks gestation; plan to continue prenatal care and deliver at collaborating clinics and hospitals; residence in a home built in or prior to 1978 which was not a mobile or trailer home; plan to live in the greater Cincinnati metropolitan area for at least one year; HIV-negative; not taking medications for seizures or thyroid disorders; not diagnosed with diabetes, bipolar disorder, schizophrenia, or cancer. We targeted women living in homes built before 1978, the year residential lead paints were banned in the United States, and we oversampled women self-identifying as non-Hispanic Black because of their children's increased risk of lead exposure. A residential lead hazard intervention study was conducted as part of the HOME Study (14). For participants randomly assigned to receive the residential lead hazard intervention, we implemented a series of measures to remove or reduce lead hazards in paint, dust, water, and bare soil in and around the homes of pregnant women prior to delivery of the infant. We maintained the interventions for the first three years of childhood. If a participant moved prior to age 21 months, we attempted to implement the intervention in the new residence. For the control group, we installed injury prevention devices, including stair gates, cabinet locks, and smoke detectors, as well as made residential modifications to prevent injury (14,15).

Of the 355 women who participated in the intervention, eligible participants for this analysis included singletons born without a congenital abnormality to women who identified as non-Hispanic Black or non-Hispanic White and completed at least one study visit after baseline (n=271). We included participants who had the outcome measures or whole blood samples collected during at least one study visit and complete covariate information (n=244). The institutional review boards (IRB) of Cincinnati Children's Hospital Medical Center (CCHMC) and the participating prenatal clinics and delivery hospitals approved the HOME Study. Brown University deferred to the CCHMC IRB as the IRB of record. Women provided written informed consent for themselves and their children after research assistants explained study protocols during face-to-face visits.

Blood Lead Concentrations

We collected whole blood samples from children at ages 1-, 2-, 3-, 4-, 5-, and 8-years using collection materials that were prescreened for lead contamination. We stored blood samples at −80°C until shipment to the CDC laboratory for analysis. Blood lead concentrations were quantified using inductively coupled plasma mass spectrometry (Limit of Detection=0.07 μg/dL for samples quantified at age 8 years and 0.25 μg/dL for samples from earlier ages)(16). All batches included reagent blanks and quality control samples (coefficient of variation, <3.5%).

Behavioral Assessment System for Children-2

At ages 2-, 3-, 4-, 5-, and 8-years, caregivers rated their children's behavior using the Behavioral Assessment System for Children-2 (BASC-2), a valid and reliable caregiver-

reported measure of child behavior (17). We analyzed the four composite scales - Adaptive Skills, Behavioral Symptoms Index (BSI), Externalizing Problems, and Internalizing Problems. The Adaptive Skills composite score reflects adaptability, social skills, as well as leadership, and the BSI score is a rating of the child's overall level of problem behaviors. The Externalizing Problems score assesses disruptive behaviors such as aggression, conduct problems and hyperactivity, while the Internalizing Problems score reflects inwardly directed behaviors, such as anxiety, depression, and somatization.

We used U.S. population-based normative referent data to calculate combined sex normalized T-scores (mean: 50, standard deviation [SD]: 10) for each scale. Lower scores on the Adaptive Skills scale indicate less adaptive behaviors and higher scores on the BSI, Externalizing Problems, and Internalizing Problems scales indicate more problem behaviors. We further explored relations of blood lead concentrations with the Externalizing Problems subscales related to: Aggression, Hyperactivity, and Conduct Problems (age 8-years only) because lead has previously and consistently been associated with these ADHD-related behavioral features (18,19). We assessed all composite scores and subscales as continuous measures, and also dichotomized BASC-2 scores using thresholds recommended by the test developer to identify at-risk or clinically significant behavior problems (Adaptive Skills score ≤ 40 on original scale and BASC-2 scores ≥ 60 for other scales).

Participant Characteristics

At baseline (around 20-weeks' gestation), trained research staff administered standardized interviews to collect information on maternal race and ethnicity, household income, maternal education, and residential ownership status (own – yes/no). We extracted the construction year for the residence from housing assessors' databases. We assessed maternal IQ using the Wechsler Abbreviated Scale of Intelligence- WASI (20) and, at the one-year study visits, we assessed the children's caregiving environment using the Home Observation for Measurement of the Environment (HOME) Inventory Score (21). To estimate gestational and childhood tobacco smoke exposure, we averaged maternal cotinine concentrations in serum samples collected at 16- and 26-weeks' gestation, as well as children's cotinine concentration quantified in serum samples collected at ages 1-, 2-, 3- and 4-years (22). At each study visit, we administered the Beck Depression Inventory-II to the mother to assess maternal depressive symptoms (23).

Statistical Analysis

We characterized the distributions of blood lead concentrations at each visit. We calculated the intraclass correlation coefficient (ICC) for blood lead concentrations at ages 1-, 2-, 3-, 4-, 5-, and 8-years to assess the reproducibility within children over time. Based on the distribution of the blood lead concentrations, we used the natural logarithm (ln) to transform blood lead concentration to reduce the influence of outliers. We also examined the distribution of the BASC-2 scores over time and calculated the ICC for composite and subscale scores.

We used a multiple informant approach with generalized estimating equations (GEE) to jointly evaluate the relations of ln-transformed blood lead concentrations at ages 1-, 2-,

3-, 4-, 5-, and 8-years with repeated continuous BASC-2 scores at ages 2-, 3-, 4-, 5-, and 8-years. This model assumes that the predefined exposure periods have the same timing for all participants, the exposure effect is homogenous within each exposure period, and there is at least one exposure sample per participant (24). Furthermore, the model assumes that data are missing completely at random. In these models, we assessed the relation of blood lead concentrations at each timepoint with the BASC-2 scores reported at both the concurrent and subsequent timepoints. For example, when estimating the relation of blood lead concentrations quantified at age 3-years with BASC, we included BASC-2 scores at ages 3-, 4-, 5-, and 8-years. Using this approach, we also assessed if the relation of blood lead concentrations with BASC-2 scores varied at one age, relative to other ages, using a lead by exposure period product term (24). We considered a heterogeneity product term p-value < 0.20 to be suggestive of potential differences in these associations by exposure period. We used this approach, instead of separate regression models for each exposure timepoint, to statistically compare the associations between blood lead and behavior across timepoints.

Next, we used modified Poisson regression to examine relations of repeated ln-transformed blood lead concentrations at ages 2-, 3-, 4-, 5-, and 8-years with the relative risk of having BASC-2 scores classified as at-risk or clinically significant at ages 2-, 3-, 4-, 5-, and 8-years. The resulting beta coefficients from this analysis represent the cross-sectional and longitudinal association of repeated blood lead concentrations and repeated behavior measures.

We selected covariates *a priori* based on the literature and adjusted all models for the child's age (months) at BASC-2 assessment, child sex (categorical), household income (continuous), residential intervention group (categorical), maternal race/ethnicity (categorical), maternal depressive symptoms at time of evaluation (continuous), and child's average serum cotinine concentration (continuous) (25,26).

In secondary analyses, we evaluated if the periods of heightened susceptibility to lead varied by sex. First, we used the multiple informant model and assessed the heterogeneity p-value for a sex by blood lead by exposure period product term; we considered p-values < 0.20 to be suggestive of potential sex differences in the periods of heightened susceptibility to lead toxicity. This analysis specifically evaluates if the pattern of associations between repeated blood lead concentrations and BASC-2 scores varies by child sex. When we identified sex differences, we further examined these in adjusted sex-stratified models. We evaluated heterogeneity in the association between blood lead concentrations at each exposure period and BASC-2 scores using the lead by exposure period product term p-value within each sex strata.

We evaluated sex differences in the associations between repeated blood lead concentrations and repeated BASC-2 scores by adding a sex by blood lead product term to fully-adjusted modified Poisson regression models. In these models, we considered product term p-values < 0.05 as evidence of potential sex-differences in the association between blood lead and risk of having BASC-2 scores classified as at-risk or clinically significant.

Sensitivity Analyses

We conducted a series of sensitivity analyses to evaluate the robustness of our results to several assumptions. First, we adjusted our main models for maternal average serum cotinine instead of average serum cotinine during childhood. We also adjusted for both prenatal and childhood cotinine in the models. Prior research suggests that prenatal tobacco smoke exposure could be related to childhood behavior (18). Second, to evaluate the robustness of models, we also adjusted models for maternal IQ scores, HOME Inventory Scores, and maternal education. Third, we assessed results from the multiple informant analyses in the injury prevention and lead hazard intervention groups separately because the lead hazard intervention had previously been associated with lower blood lead concentrations and subtle improvements in children's neurobehavioral outcomes (14). We also evaluated our results after removing the residential intervention variable from adjusted models. Finally, we conducted additional analyses using only the 8-year BASC outcomes in the multiple informant models. While using repeated BASC-2 measures reduces within-person variation in our outcome, it is possible that variation in the exposure-outcome association across exposure timepoints could be due to heightened susceptibility to lead or latency in the manifestation of behavioral outcomes. Because we previously observed that BASC-2 scores had fair to good reproducibility over childhood (27), we hypothesized that the results would not meaningfully differ when we only used the 8-year BASC scores.

RESULTS

Relations of Blood Lead and BASC-2 Scores with Participant Characteristics

The distributions of blood lead concentrations were similar at ages 1 and 2 years (Figure 1; median blood lead concentration at age 1-year = 1.5 μg/dL; 25^{th}, 75^{th}= 1.0, 2.3). Blood lead concentrations tended to gradually decline for subsequent visits, with the lowest concentrations occurring at age 8-years (median blood lead concentration at 8-years= 0.5 μg/dL; 25^{th}, 75^{th}= 0.4, 0.9). Repeated blood lead concentrations had good reproducibility (ICC= 0.59). Children of mothers who self-identified as non-Hispanic Black, had a high school diploma or less, and a household income less than $45,000 tended to have higher blood lead concentrations compared with other groups (Table 1). On average, children who lived in older rental housing units had higher blood lead concentrations compared with those living in a newer and caregiver-owned residence.

BASC-2 scores had fair to good reproducibility over childhood (ICC ranging from 0.48 to 0.59; Table S1). Compared with males, females tended to have scores indicative of fewer behavioral problems on most scales. BASC-2 scale scores did not strongly vary by other demographic characteristics. The characteristics of participants who completed the study visit at age 8-years were similar to participant characteristics of the full sample at baseline (Table S2). However, a higher proportion of participants at baseline had a mother who was a college graduate compared to the characteristics of participants who were included from the 8-year study visit.

Differences in the Relations of Blood Lead Concentrations Across Ages with Childhood Behavior

In general, we found trends suggesting positive associations between blood lead concentrations during all ages and higher scores on the BSI and Externalizing Problems scales (Figure 2 and Table S3). We found modest evidence that the associations between blood lead concentrations and the Externalizing Problems scores varied by exposure period (heterogeneity p-value=0.20). Specifically, blood lead concentrations at 8-years (β=3.1-point per unit increase; 95% CI=0.7, 5.4) was more strongly associated with higher Externalizing Problems scores compared to other exposure periods. We also found slight evidence of an adverse association between higher blood lead concentrations and Adaptive Skills scores that was stronger at age 8-years (β= −2.2-point per unit increase; 95% CI= −4.9, 0.5) years compared with other exposure periods (heterogeneity p-value=0.22). In contrast, we did not find evidence to suggest that associations of blood lead concentrations with BSI and Internalizing Problems scores varied by exposure period (heterogeneity p-values= 0.45 and 0.89, respectively).

When we further examined the association between blood lead concentrations and Externalizing Problems subscales we found evidence suggesting that higher blood lead concentrations across all ages were associated with more aggressive and hyperactive behaviors, as well as conduct problems. We did not find strong evidence to suggest that these relations varied by exposure period for the Aggression and Conduct subscales (Figure 3 and Table S4). We did, however, find some evidence suggesting that the association between blood lead concentrations and Hyperactivity scores varied by exposure period (heterogeneity p-value=0.25). Similar to patterns observed for the Externalizing Problems scale, blood lead concentrations at age 8-years (β=3.2-point per unit increase; 95% CI=0.6, 5.8) was more strongly associated with higher Hyperactivity scores compared with other exposure periods.

Blood Lead Concentrations and Relative Risk of BASC-2 Scores Classified as At-risk or Clinically Significant

Adjusted for covariates, higher repeated blood lead concentrations were associated with higher risk of having scores classified as at-risk or clinically significant on the Adaptive Skills, BSI, and Externalizing Problems scales (Table 2). Furthermore, higher blood lead concentrations were associated with higher risk of having at-risk or clinically significant Hyperactivity, Aggression, and Conduct Problems scores.

Secondary Stratified Analyses

Our results suggested that the pattern in the association between blood lead concentrations at each exposure period and Adaptive Skills scores varied by sex (sex by blood lead by exposure period heterogeneity p-value=0.02). For females, the association between blood lead concentrations and Adaptive Skills scores varied by exposure period (blood lead by exposure period heterogeneity p-value=0.15); higher blood lead concentrations at age 8-years, compared with other exposure periods, were associated with lower Adaptive Skills scores (β=4.8-point per unit decrease; 95% CI=0.6, 5.8). For males, we found slight evidence suggesting the association between blood lead concentrations and Adaptive

Skills scores may vary by exposure period (blood lead by exposure period heterogeneity p-value=0.25). However, the confidence intervals for the effect estimates at all exposure periods included the null. Patterns of associations between blood lead concentrations across exposure periods and the other BASC-2 scales were similar among females and males (Figure 4 and Figure S1). Overall, we did not find evidence to suggest that associations between higher repeated blood lead concentrations and the risk of having BASC-2 scores classified as at-risk or clinically significant varied by sex (Table S5, sex by blood lead p-values=0.19–0.94).

Sensitivity Analyses

In sensitivity analyses, our main results did not meaningfully change when we included maternal cotinine, instead of childhood cotinine, in models or adjusted for both maternal and childhood cotinine (Table S6 and S7). Our results also did not meaningfully change when we adjusted for HOME Inventory scores, maternal IQ, or maternal education (Table S8 and S9). Furthermore, the results did not meaningful change when we stratified by residential intervention group (Figure S2) or when we removed residential intervention as a covariate in the fully-adjusted models (Table S10).

When we used only 8-year BASC-2 scores in multiple informant models, the magnitude of the associations at each timepoint did not meaningfully differ. However, for the Externalizing Problems scale, the associations were more homogenous for blood lead measures between ages 1- and 5-years than our main results (Table S10). We also observed more heterogeneity in the associations of blood lead concentrations with Adaptive Skills scores (heterogeneity p-value=0.05). Higher blood lead concentrations at 8-years (β= −2.2; 95% CI= −4.8, 0.5) were more strongly associated with poorer adaptive skills at age 8-years.

DISCUSSION

Our results indicated that higher blood lead concentrations during the first 8-years of life were associated with elevated risk of several ADHD-related behaviors, specifically aggression, conduct problems, and hyperactivity. We observed trends indicating that higher blood lead concentrations between ages 1- and 8-years were associated with these behaviors; however, we found consistent evidence indicating that higher blood lead concentrations at age 8-years was more strongly associated with these behaviors than at other ages. We found similar results when we restricted our analysis to 8-year BASC-2 scores, the timepoint that is potentially most relevant to long-term behavioral outcomes. In secondary analyses, we found evidence of adverse associations between higher blood lead concentrations at age 8-years and adaptive skills among females, but not males. Overall, our results suggest that the relatively low blood lead levels quantified among contemporary pediatric populations may increase risk for the behavioral features of ADHD.

Our results are consistent with decades of literature indicating that lead exposure at higher levels relative to our contemporary population is associated with cognitive impairments and higher risk of ADHD-related behavioral problems (1,18,28–31). Lead exposure may be directly related to ADHD-related behavior problems during childhood, but it may also indirectly contribute to these behaviors by impairing cognition (32). Froehlich et al (2009)

previously estimated that approximately 1 in 5 cases of ADHD among US children ages 8 to 15 years may be attributable to lead exposure.

The removal of lead from gasoline and residential paint has resulted in dramatic declines in blood lead levels for the general US population since earlier studies of lead toxicity. Still, the geometric mean blood lead level during our study period was 1.3 μg/dL (2007–2010) and 0.6 μg/dL (2011–2016) among US children ages 1–5 and 6–11 years, respectively (33). Moreover, structural inequalities disproportionately expose Black Americans and low-income communities to higher levels of lead (33–35). In our study, the geometric mean blood lead concentrations among children ages 1–5 years was 1.3 μg/dL, suggesting that blood lead concentrations, at levels below the CDC reference value of 5 μg/dL, are associated with ADHD-related behaviors. Our results confirm again that there is no safe level of lead exposure, and indicate that susceptibility to lead toxicity extends into middle childhood.

Earlier investigations of lead neurotoxicity suggested that peak blood lead concentrations typically occur around age two years and these concentrations are most strongly associated with childhood cognitive deficits (9,36,37). However, as prospective cohort studies extended later into childhood, growing evidence indicates that blood lead concentrations among school-aged children may be more strongly associated with cognition, as well as associated with gray matter volume in adulthood (31,38–44). We are not aware of any prior studies that have directly compared relations of sequential blood lead concentrations over early life developmental periods with childhood behavior. Prior research conducted by Horton et al used dentine biomarkers to identify periods of heightened susceptibility to lead exposure between 3-months gestation and 1-year postnatally. Results from this analysis identified heightened susceptibility to lead beginning postnatally after 8 months when higher dentine lead concentrations were associated with externalizing behaviors, especially hyperactivity, assessed using the BASC-2 at ages 8–11 years (45).

Overall, the magnitude of differences in age-specific associations was small relative to overall effect sizes and we did not find strong evidence that the association between blood lead concentrations and behavioral profiles varied by exposure timing. We did, however, find consistent evidence indicating that higher blood lead concentrations at age 8-years were associated with more ADHD behavioral features. It is possible that susceptibility to lead toxicity varies during childhood due to time-specific developmental processes. For example, mid-childhood and adolescence could be a period of heightened susceptibility to lead exposure due to structural changes that occur in the frontal cortex and other areas of the brain that control dimensions of attention, self-regulation, and social cognition (46–48). However, it is also plausible that blood lead concentrations at these ages provide more stable estimates of lead body burden, and thus, could be more predictive of lead-related neurobehavioral outcomes (41). Blood lead concentrations primarily reflect recent exposure over the previous months in adults, but blood lead concentrations are also influenced by the release of accumulated lead stored in bones (2). Recent evidence suggests the half-life of blood lead varies by age, with a blood lead half-life equal to approximately 6.9 and 19.3 days for children between the ages of 1 to 3 and from 3 to 14, respectively (49). Furthermore, the relation between lead intake and blood lead concentration differs with age

due to variation in gastrointestinal absorption (2,50). Thus, it is plausible that blood lead screening conducted during the first several years of life fails to identify some school-aged children who have higher blood lead concentrations in mid-childhood and are at-risk for lead-related behavioral problems later in life.

Guided by the early lead toxicity studies among toddlers, blood lead screening and prevention programs have heavily focused on the first two years of life (6). The CDC Childhood Lead Poisoning Prevention Program also depicts children less than six years as having heightened susceptibility to lead (7). Our analysis leverages novel statistical methods and repeated blood lead measures to directly compare relations of behavioral profiles with blood lead concentrations during multiple developmental periods (24). We did not find strong evidence to suggest that the first two to six years of life represents a unique period of heightened susceptibility to lead toxicity among children with low-level exposure. Instead, our results suggest that lead exposure at any time during childhood may negatively impact behavior. Because school-aged children spend more time outside of the home and have different time-activity patterns compared to toddlers, it is plausible that the primary exposure sources contributing to blood lead concentrations vary across these developmental periods. Future research could examine if primary prevention, as well as secondary interventions for school-aged children diagnosed with conduct or externalizing behavioral problems can help reduce the burden of lead-related cognitive and behavioral impairments. Our results also highlight the need to identify and reduce additional sources of lead exposure among infants and school-aged children.

Our results indicating that blood lead at age 8 years was associated with poorer adaptive skills among females, but not males, is consistent with some prior epidemiologic and animal studies (12,51). For example, in studies of the Port Pirie cohort, investigators reported a pattern across studies suggesting that females may be more at-risk for lead-related effects on cognition and mental health outcomes in childhood, adolescence, and adulthood (12). Yet, results from studies have also reported no sex-differences or have suggested that males may be more susceptible than females to lead-related cognitive and neurodevelopmental effects (for example: (18,52–55). Our results suggest that inconsistencies in sex-specific associations reported across studies may be due to differences in the timing of the exposure and blood lead concentrations, but this area warrants further investigation in larger studies. During mid-childhood and adolescence, periods of heightened susceptibility to lead exposure may be sex-specific due to differences in the timing and underlying biology of structural changes in regions of the brain controlling self-regulation and social cognition (46,56,57).

Our analysis included a relatively small number of participants with blood lead concentrations above the CDC reference values and consisted primarily of non-Hispanic White participants. Therefore, while we were able to quantify the relations of low blood lead levels with behavioral profiles, the results may not be generalizable to more diverse populations with higher levels of exposure or additional risk factors for ADHD-related behaviors.

Our study had some limitations. First, other socioeconomic and behavioral factors that we did not consider in adjusted models could contribute to residual confounding. However, we report consistent trends in associations between blood lead concentrations and BASC-2 scores across several sensitivity analyses with different covariates. Second, it is possible that data used in the multiple informant models are not missing completely at random, which could bias our results. Furthermore, there is slight variation in exact age of blood lead measurement at each study visit, which may lead to misclassification of the exposure timing that could bias our results. This variation in exposure timing was smaller at younger ages (e.g., at 2-year visit age range≅ 0.6 years) than the 8-year visit (e.g., age range≅ 2.5 years). However, we adjusted all models for exact age (months) of BASC-2 assessment. Third, our sample size may have limited our ability to detect associations, especially in sex stratified analyses of periods of heightened susceptibility to lead toxicity.

Our study also had several strengths. We used repeated measures of blood lead concentrations along with the repeated measures of the validated and reliable BASC-2 instrument across infancy and childhood. Additionally, the HOME Study collected other information about behavioral and mental health data that we considered as covariates in our analyses.

In conclusion, our results suggest that contemporary levels of lead exposure during childhood are associated with ADHD-related behaviors, specifically hyperactivity, aggression, and conduct problems. Understanding how blood lead concentrations across childhood relate to behavior problems can guide public health policy focused on reducing lead-related behavioral effects for all children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY:

Data are available upon reasonable request. The HOME Study Principal Investigators welcome new collaborations with other investigators and have actively engaged in collaborative data sharing projects. Interested investigators should contact Drs Joseph M. Braun (joseph_braun_1@brown.edu) and Kimberly Yolton (kimberly.yolton@cchmc.org) to obtain additional information about The HOME Study, discuss collaborative opportunities, and request a project proposal form. The HOME Study Protocol Review Committee reviews

proposed research projects to ensure that they do not overlap with extant projects and are an efficient use of scarce resources (eg, biospecimens).

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Significance:

Contemporary levels of lead exposure during the first 8-years of life were associated with ADHD-related behaviors, specifically aggression, hyperactivity, and conduct problems.

Impact Statement:

Our results highlight the importance of primary lead prevention across childhood.

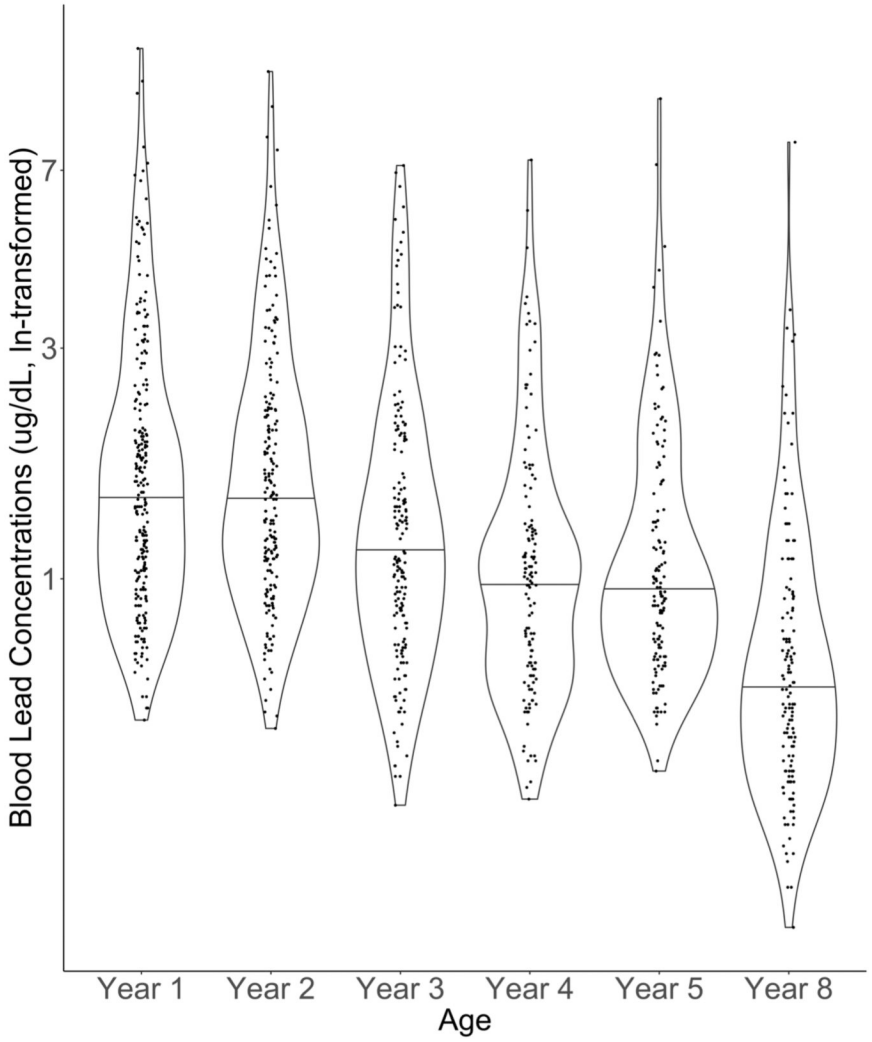

Figure 1. Distribution of children's blood lead concentrations by study visit at ages 1, 2, 3, 4, 5, and 8 years (The HOME Study; Cincinnati, OH).

Solid line indicates median of each distribution. Jittered dots are individual observations. Smoothed lines are density functions. Labels on the y-axis have been back-transformed. Observations: Year 1= 229; Year 2 = 203; Year 3= 182; Year 4= 133; Year 5 = 140; Year 8= 147.

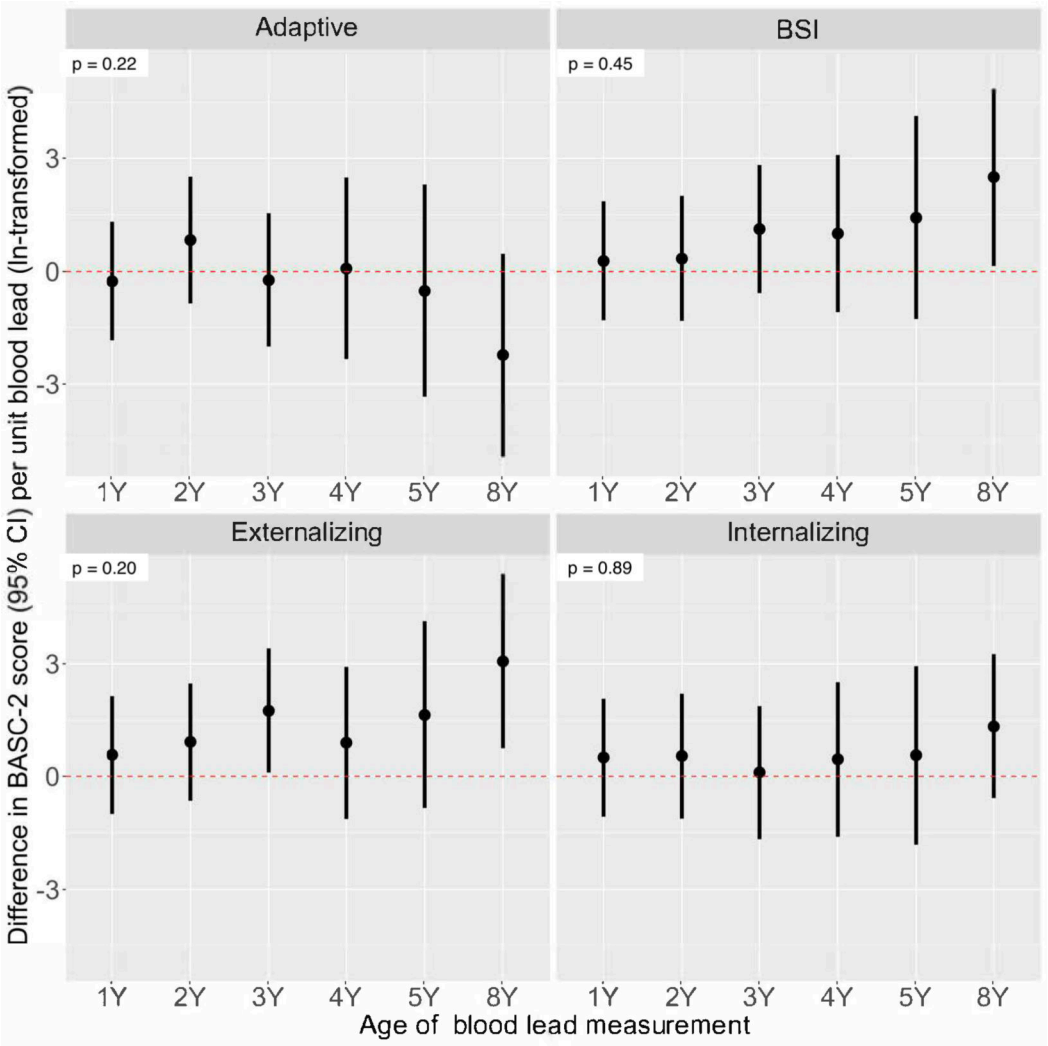

Figure 2. Adjusted difference in repeated BASC-2 scores at ages 2–8 years per unit increase in ln-transformed blood lead concentration at ages 1, 2, 3, 4, 5, and 8 years.

Model adjusted for child's age, sex, intervention group, household income, maternal race, maternal depressive symptoms, child's serum cotinine. Total participants = 244 (BASC observations: 2Y = 222; 3Y = 210; 4Y = 151; 5Y = 164; 8Y = 171). Heterogeneity p-values included to indicate difference in lead-BASC associations by child's age at blood lead measurement.

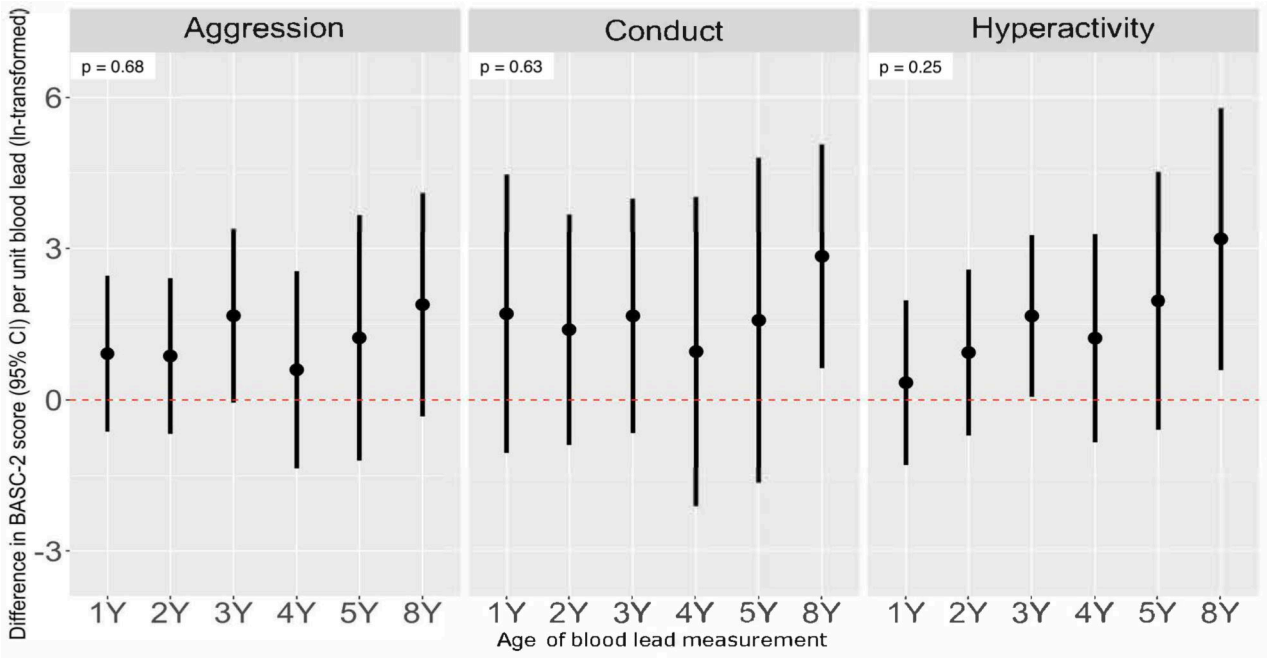

Figure 3. Adjusted difference in repeated BASC-2 Externalizing Subscale scores at ages 2–8 years per unit increase in ln-transformed blood lead concentration at ages 1, 2, 3, 4, 5, and 8 years.

Model adjusted for child's age, sex, intervention group, household income, maternal race, maternal depressive symptoms, child's serum cotinine. Total participants for Aggression and Hyperactivity Subscales = 244 (BASC observations: 2Y = 222; 3Y = 210; 4Y = 151; 5Y = 164; 8Y = 171). Conduct models include blood lead concentrations at age 1, 2, 3, 4, 5 and 8 years and BASC-2 scores at age 8 years only (participants n=147). Heterogeneity p-values included to indicate difference in lead-BASC associations by child's age at blood lead measurement.

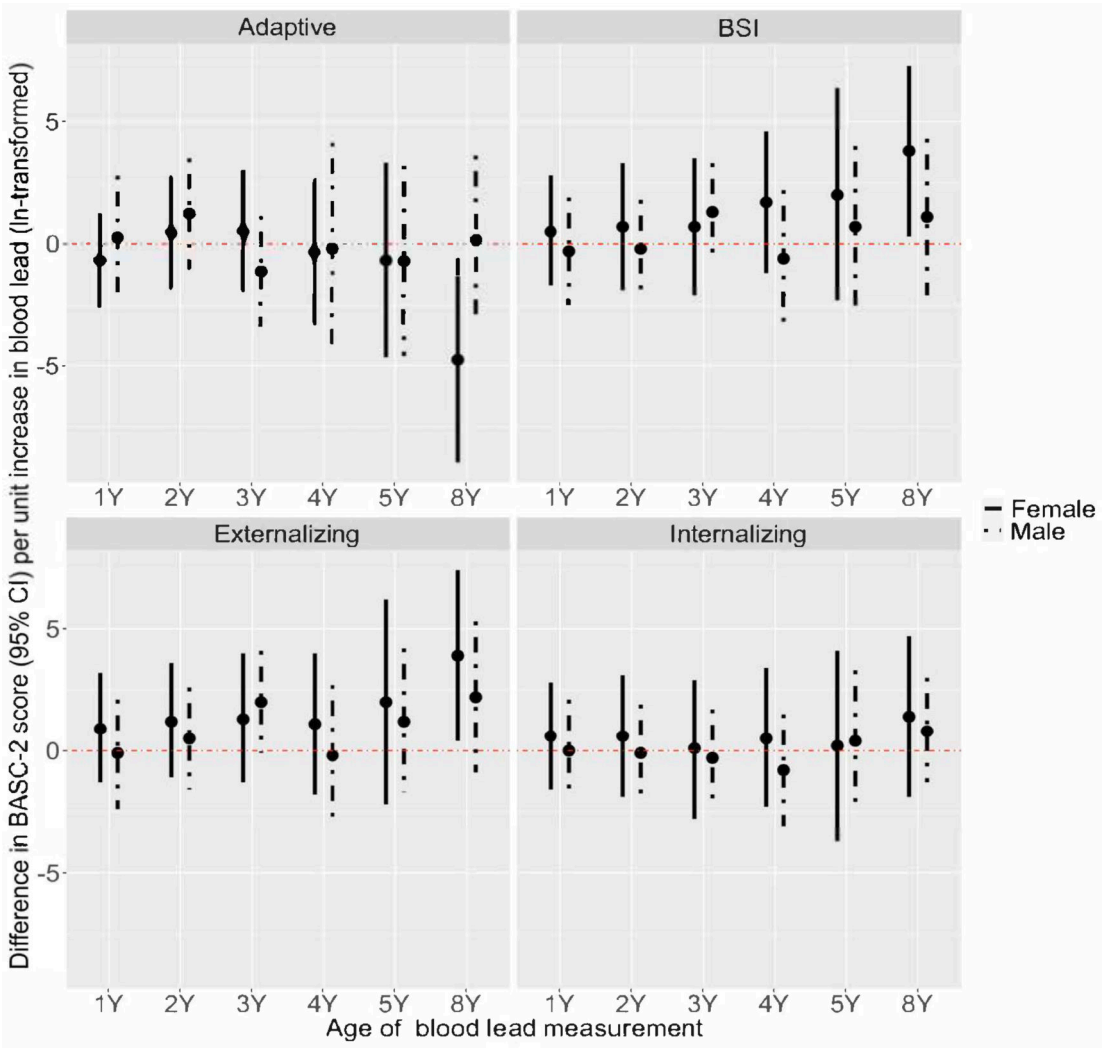

Figure 4. Adjusted difference in repeated BASC-2 composite scores at ages 2–8 years per unit increase in ln-transformed blood lead concentration at ages 1, 2, 3, 4, 5, and 8 years by sex.

Model adjusted for child's age, household income, maternal race, maternal depressive symptoms, child's serum cotinine, intervention group. Total participants = 244 (BASC observations: 2Y = 222; 3Y = 210; 4Y = 151; 5Y = 164; 8Y = 171). Female (n=132) Heterogeneity p-value: Adaptive = 0.15; BSI = 0.39; Externalizing = 0.42; Internalizing = 0.95; Male (n=112) Heterogeneity p-value: Adaptive = 0.25; BSI = 0.21; Externalizing = 0.18; Internalizing = 0.84.

Table 1.

Participant characteristics, BASC-2 Composite Scale Scores, and blood lead concentrations (first observation only).

Characteristic	Total	Adaptive Skills	Behavioral Symptom Index	Externalizing Problems	Internalizing Problems	Blood Lead (μg/dL)
	n (%)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Median (25th, 75th)
Total	244 (100)	43 (7.8)	50 (7.3)	48 (7.8)	46 (8.4)	1.5 (1.0, 2.3)
Child Sex						
Male	112 (46)	42 (7.3)	51 (7.0)	49 (7.1)	45 (6.7)	1.4 (1.0, 2.3)
Female	132 (54)	45 (8.0)	50 (7.4)	47 (8.2)	46 (9.5)	1.5 (1.0, 2.5)
Maternal Race/Ethnicity						
non-Hispanic White	189 (77)	43 (6.9)	50 (6.5)	48 (7.2)	45 (6.8)	1.3 (0.9, 1.9)
non-Hispanic Black	55 (23)	45 (10)	51 (9.6)	49 (9.5)	48 (12)	2.6 (1.7, 3.6)
Intervention						
Injury	125 (51)	44 (8.1)	51 (7.7)	49 (8.3)	47 (9.3)	1.6 (1.0, 2.5)
Lead	119 (49)	43 (7.5)	50 (6.7)	47 (7.2)	45 (7.3)	1.4 (1.0, 2.0)
Maternal Education						
High School or Less	37 (15)	44 (8.8)	53 (9.7)	51 (10)	50 (14)	3.1 (2.0, 3.8)
Some College	59 (24)	43 (8.8)	49 (7.1)	47 (8.1)	44 (7.2)	1.7 (1.1, 2.4)
College Graduate	148 (61)	43 (7.2)	50 (6.6)	47 (6.7)	46 (6.6)	1.2 (0.9, 1.8)
Household Income						
< $45,000	70 (28)	45 (9.3)	52 (8.8)	50 (9.5)	48 (11)	2.4 (1.6, 3.6)
$45,000–75,000	92 (38)	42 (7.9)	50 (6.4)	46 (6.3)	44 (6.7)	1.3 (0.9, 1.9)
>$75,000	82 (34)	43 (6.2)	50 (6.6)	48 (7.4)	46 (6.4)	1.2 (0.9, 1.9)
Average Maternal Serum Cotinine (ng/mL)						
<0.015	100 (41)	42 (6.9)	50 (6.9)	48 (7.0)	46 (6.6)	1.3 (0.9, 1.9)
0.015 to 3.0	122 (50)	44 (8.5)	50 (7.7)	48 (8.3)	46 (9.6)	1.5 (1.0, 2.7)
>3.0	22 (9)	42 (7.5)	51 (6.9)	50 (8.5)	45 (8.1)	3.2 (1.2, 3.8)
Average Child' Serum Cotinine (ng/mL)						
<0.02	61 (25)	43 (6.3)	50 (6.9)	48 (7.2)	45 (7.0)	1.2 (0.9, 1.7)
0.02 to 0.22	123 (50)	43 (7.5)	49 (6.3)	47 (6.8)	45 (6.7)	1.4 (1.0, 2.0)
>0.22	60 (25)	44 (9.7)	52 (9.0)	51 (9.4)	49 (12)	2.8 (1.4, 3.6)
Year Residence was Built[a]						
=<1924	76 (31)	43 (7.5)	51 (8.3)	48 (8.9)	48 (10)	2.2 (1.5, 3.4)
>1924 to 1955	97 (40)	44 (8.2)	50 (6.7)	47 (7.3)	46 (7.3)	1.3 (1.0, 1.9)
>1955 – 1978	70 (29)	43 (7.6)	50 (6.8)	48 (7.3)	44 (7.2)	1.2 (0.9, 1.9)
Residential Ownership[a]						
No	61 (25)	45 (9.0)	51 (8.9)	49 (9.3)	48 (12)	2.6 (1.5, 3.7)
Yes	182 (75)	43 (7.4)	50 (6.7)	47 (7.1)	45 (6.5)	1.3 (0.9, 1.9)

[a]Missing participant data (n=1)

Table 2.

Adjusted relative risk of BASC-2 scores classified as at-risk or clinically significant at ages 2–8 years per ln-unit increase in blood lead concentrations.

BASC-2 Scale	Observations[a] / Total	Adjusted RR (95% CI)
Adaptive Skills	151/790	1.31 (0.98, 1.80)
Behavioral Symptom Index (BSI)	86/790	1.60 (1.03, 2.48)
Internalizing	73/790	0.96 (0.53, 1.72)
Externalizing	94/790	1.56 (0.95, 2.56)
Hyperactivity	114/790	1.48 (1.08, 2.02)
Aggression	80/790	1.72 (1.19, 2.51)
Conduct	17/147	1.73 (0.97, 3.07)

[a]The number of observations that met the threshold for being considered at- risk for clinically significant problematic behaviors. Total refers to the total number of observations.

Adjusted model includes child's age, sex, intervention group, household income, maternal race, maternal depressive symptoms, child's serum cotinine.

Adaptive Skills, BSI, Internalizing, and Externalizing Composite, as well as Hyperactivity and Aggression Subscale models include time-varying blood lead concentrations (ages 2–8 years) and time-varying BASC-2 score category (participants n=232).

Conduct models include blood lead concentrations at age 8 years and BASC-2 scores at age 8 years only (participants n=147).

At-risk for clinically significant problematic behaviors indicated by Adaptive Skills scores ≤ 40, or BSI, Internalizing, as well as Externalizing composite and subscale scores ≥ 60.