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Lead, Mercury, and Cadmium Exposure and Attention Deficit Hyperactivity Disorder in Children

Stephani Kim[a], **Monica Arora**[b], **Cristina Fernandez**[c], **Joseph Caruso**[d], **Julio Landero**[d], and **Aimin Chen**[a]

[a]Division of Epidemiology and Biostatistics, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH, 45267 USA

[b]Department of Psychiatry, Creighton University School of Medicine, Omaha, NE, 68131, USA

[c]Department of Pediatrics, Creighton University School of Medicine, Omaha, NE, 68131, USA

[d]Metallomics Center, Department of Chemistry, University of Cincinnati, Cincinnati, OH, 45221 USA

Abstract

Background—There is limited research examining the relationship between lead (Pb) exposure and medically diagnosed Attention Deficit Hyperactivity Disorder (ADHD) in children. The role of mercury (Hg) and cadmium (Cd) exposures in ADHD development is even less clear.

Objectives—To examine the relationship between Pb, Hg, and Cd and ADHD in children living inside and outside a Lead Investigation Area (LIA) of a former lead refinery in Omaha, NE.

Methods—We carried out a case-control study with 71 currently medically diagnosed ADHD cases and 58 controls from a psychiatric clinic and a pediatric clinic inside and outside of the LIA. The participants were matched on age group (5–8, 9–12 years), sex, race (African American or Caucasians and Others), and location (inside or outside LIA). We measured whole blood Pb, total Hg, and Cd using Inductively Coupled Plasma Mass Spectrometry.

Results—Inside the LIA, the 27 cases had blood Pb Geometric Mean (GM) 1.89 μg/dL and the 41 controls had 1.51 μg/dL. Outside the LIA, the 44 cases had blood Pb GM 1.02 μg/dL while the 17 controls had 0.97 μg/dL. After adjustment for matching variables and maternal smoking, socioeconomic status, and environmental tobacco exposure, each natural log unit blood Pb had an odds ratio of 2.52 with 95% confidence interval of 1.07–5.92. Stratification by the LIA indicated similar point estimate but wider CIs. No associations were observed for Hg or Cd.

Conclusions—Postnatal Pb exposure may be associated with higher risk of clinical ADHD, but not the postnatal exposure to Hg or Cd.

Corresponding Author: Aimin Chen MD PhD, Division of Epidemiology and Biostatistics, Department of Environmental Health, University of Cincinnati College of Medicine, 3223 Eden Avenue, Cincinnati, OH 45267-0056, USA, Tel: 513-558-2129, Fax: 513-558-4397, aimin.chen@uc.edu.

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Keywords

attention deficit hyperactivity disorder; heavy metals; lead; mercury; cadmium; case-control study

1. Introduction

Attention deficit hyperactivity disorder (ADHD), characterized by inattention, impulsivity, distractibility, and hyperactivity, is the most commonly diagnosed neurobehavioral disorder in children (APA, 2000; CDC, 2010). The American Psychiatric Association (APA) estimates a childhood prevalence of 3 to 7% in the U.S. and these children are more likely to develop antisocial behavior, abuse drugs, and develop conduct disorder problems as adults (APA, 2000). The etiology of ADHD is complicated, and has a strong genetic component (Faraone et al., 2005; Smith et al., 2009). However, genetics cannot account for all ADHD cases and studies within the past decade have indicated that certain environmental factors, including exposure to environmental pollutants, prenatal substance exposure, and lifestyle, can play a role in ADHD etiology (Aguiar et al., 2010; Banerjee et al., 2007; Froehlich et al., 2011; Pennington et al., 2009; Schettler, 2001; Swanson et al., 2007).

Lead (Pb), mercury (Hg), and cadmium (Cd) are heavy metals naturally found in the environment and are also widely proliferated in the environment through human activity. Pb is a well-known neurotoxicant, especially harmful to child neurodevelopment. Many studies have shown the harmful effects of higher blood lead levels (BLL) (>10 μg/dL), however a growing body of evidence is showing adverse effects at lower BLLs (e.g., ≤5 μg/dL), suggesting no threshold of developmental neurotoxicity (Chiodo et al., 2004; Cho et al., 2010; Kim et al., 2010; Lanphear et al., 2005; Nigg et al., 2008; Wang et al., 2008). In early 2012 the Center for Disease Control and Prevention (CDC) Advisory Committee on Childhood Lead Poisoning Prevention recommended replacing the “blood lead level of concern” at 10 μg/dL with “reference value” at 5 μg/dL as a goal for lead exposure prevention in young children (CDC, 2012). Recent studies have associated blood Pb levels with medically diagnosed ADHD in children (Braun et al., 2006; Froehlich et al., 2009; Nigg et al., 2008; Nigg et al., 2010; Wang et al., 2008). While the Wang et al. study was in China and had mean BLL above 5 μg/dL in both ADHD cases and controls (Wang et al., 2008), the other studies were in the U.S. and the association between Pb exposure and ADHD diagnosis was observed at or below 2 μg/dL compared with even lower reference groups (Braun et al., 2006; Froehlich et al., 2009; Nigg et al., 2008; Nigg et al., 2010). The association at very low-level exposure, while with significant public health implications, needs to be examined in different populations.

Mercury comes in different forms, but children nowadays are mostly exposed to elemental Hg through dental amalgam and organic mercury (mainly methylmercury [MeHg]) through fish consumption(Caldwell et al., 2009; Ozuah, 2000). It has been suggested that contemporary use of dental amalgam may not be associated with adverse neurodevelopmental deficits in children (Bellinger et al., 2006; DeRouen et al., 2006). However, exposure to MeHg during prenatal period was associated with reduced cognitive function in school age children in a longitudinal study from Faroe Islands (Grandjean et al., 1997). Although similar association was not observed in another epidemiologic study from Seychelles Islands (Davidson et al., 2006), two recent studies, from Inuit population in Arctic Québec and New Bedford Massachusetts respectively, suggest an association between prenatal Hg exposure and child ADHD symptom score using behavioral rating scales (Boucher et al., 2012; Sagiv et al., 2012). Postnatal exposure to Hg was not consistently related to adverse neurodevelopment in both Faroese and Seychelles children (Debes et al., 2006; Myers et al., 2009), but a case control study in Hong Kong found a

significant association with medically diagnosed ADHD (Cheuk and Wong, 2006). The Hg levels in children of these three studies of postnatal exposure were significantly higher than the U.S. background exposure (Geometric Mean 0.4 μg/L among 6–11 year olds) (CDC, 2009). It is unclear whether current postnatal Hg exposure level in the U.S. children is related to ADHD.

Cadmium is of particular concern because of its known skeletal toxicity, nephrotoxicity, and carcinogenicity, but uncertainty remains about developmental neurotoxicity. Studies on prenatal and postnatal Cd exposure and child neurodevelopment are still limited and have had opposing results. A study using NHANES 1999–2000 data reported a weak association between blood Cd levels and attention deficit disorder (ADD) but after adjusting for persistent organic pollutants, the association disappeared (Lee et al., 2007). In a meta-analysis, the authors found only 2 studies from China that found associations between Cd levels and neurodevelopmental effects, but these were at very high levels and may not translate to lower exposures (Rodriguez-Barranco et al., 2013). Analysis of the National Health and Nutrition Examination Survey (NHANES) 1999–2004 data suggested a positive link between child urinary Cd and the prevalence of learning disability and special education among 6–15 year olds, however, a non-significantly lower prevalence of ADHD was related to the exposure (Ciesielski et al., 2012). Clearly more research is needed to examine the association with ADHD in children with postnatal exposure to Cd.

Overall, the U.S is seeing decreasing emission levels of various heavy metals and other chemicals, but the exposure report from the CDC shows low levels of metals and chemicals in biospecimens across the population (CDC, 2009). Across communities in the U.S., exposure to Pb, Hg, and Cd continues to be an important public health issue, in particular, the National Priorities Sites (aka Superfund sites) that have accumulated hazardous wastes from industries (Bellinger, 2004; Jarup, 2003). It is estimated that as of August 2000, 58% of children in the US live in counties with Superfund sites (Browner, 1996; EPA, 2000). In the scenario of Superfund sites, human exposure to a mixture of chemicals is not rare. On the Agency for Toxic Substances & Disease Registry (ATSDR) Substance Priority List of chemicals present at Superfund sites, lead, mercury, and cadmium ranked number 2, 3, and 7 respectively in 2011. The residents in the Superfund communities are vulnerable to these mixed exposures, however, few studies have examined combined exposures to heavy metals at these sites (Hu et al., 2007). It is becoming more common to investigate the mixture of metal exposures for child neurodevelopmental outcomes such as ADHD behavior score or medical diagnosis (Boucher et al., 2012; Ha et al., 2009; Nicolescu et al., 2010; Szkup-Jablonska et al., 2012; Yousef et al., 2011). Therefore, we conducted a case-control study of ADHD among children who live close to a current Superfund site to examine environmental exposure to Pb, Hg, and Cd.

2. Study subjects and methods

2.1 Study area

We performed a case-control study to investigate the association between heavy metal exposure and ADHD in Omaha, NE from August 2007 to December 2009. Omaha had been the site of a large lead refinery for about a hundred years before it closed in 1997. The plant emitted Pb and other metals into the atmosphere through smokestacks during its period of operation (EPA, 2009). The EPA and ATSDR designated the former refinery site (23 acres) and the surrounding 8,840 acres of land on the west bank of the Missouri River as the “Omaha Lead Initial Site Investigation Area”, or “Lead Investigation Area” (LIA) for short. The site, which covers a large proportion of downtown Omaha, was listed on the EPA’s National Priorities List (NPL) in 2003 because of increased lead levels in soil and children.

Considering the impact of the LIA on the blood lead levels in children, we enrolled ADHD cases and non-ADHD controls from both inside and outside the LIA.

2.2 Subject Enrollment

ADHD cases were recruited from two clinics at the Departments of Psychiatry and Pediatrics at Creighton University Medical Center (located within the LIA). The cases met the following inclusion criteria: 1) a medical diagnosis of ADHD by a physician based on Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV standard; 2) between 5- and 12-year old; and 3) living in Omaha city after birth. Children were excluded based on the following criteria: 1) having severe neurological or psychiatric problems such as cerebral palsy, mental retardation, schizophrenia; and/or 2) having severe birth defects such as chromosome disorders, congenital heart disease, and hereditary metabolic disorders. Non-ADHD controls were recruited from one study clinic at the Department of Pediatrics provided they satisfied the same criteria for enrollment barring the ADHD status. The study was designed to frequency match the cases and controls for age group (5–8 years, 9–12 years), sex (male, female), race (African American, White or Others), and residence (inside or outside the LIA). However, during enrollment we realized that we could not reach the residence matching because more children with ADHD living outside the LIA came to the university clinic for treatment than non-ADHD children living outside the site, therefore we relaxed the matching criterion.

After the parent or guardian provided informed consent and the child provided assent (if above age 7 years) to participate, we acquired information on sociodemographic factors, medical history, lead exposure, and prenatal and postnatal tobacco smoke exposure from questionnaires completed by the parents and collected whole blood samples from the child for heavy metal testing. In this study, a total of 71 ADHD cases and 58 non-ADHD controls had completed questionnaires and enough blood samples for Pb, Hg, and Cd testing. The study was initially approved by Institutional Review Board at Creighton University for enrollment and approved at the University of Cincinnati for metal assays and data analysis.

2.3 Heavy metal measurement and analysis

We measured blood Pb, total Hg, and Cd concentrations in the whole blood samples using an Agilent 7700x Inductively Coupled Plasma Mass Spectrometry (ICP-MS) equipped with a conventional Meinhard nebulizer, a Peltier-cooled spray chamber, and a shield torch under standard plasma conditions.

A plasma frequency-matching RF generator and an octopole collision/reaction system (ORS) were used to remove isobaric interferences. The microwave digestion was performed in a discover explorer microwave (CEM). We used doubly deionized water (DDW) 18 MΩ generated from a Milli-Q system (Bedford, MA, USA). Trace metal grade HNO_3, was obtained from Fisher Scientific (Pittsburg, PA, USA). Multi-elemental and internal standard 1000 μg/mL and 10 μg/mL stock solutions were obtained from Spex Certiprep (Metuchen, NJ, USA). The standard reference materials (SRM) DORM-3 were obtained from the NRC Institute for National Measurement (Ottawa, Canada).

In an acid washed glass digestion vial 0.2 mL of blood was digested, by adding 1 mL of 35% trace metal grade nitric acid, 100 μL of internal standard mix solution containing scandium, indium, yttrium, germanium and bismuth was added to a final concentration of 10 parts per billion (ppb). Five reagent blanks and 5 SRMs were used to correct and validate the results. A pre-digestion step was done in a heating block at 60°C overnight. Microwave digestion occurred in two steps. The sample vessels were first ramped to 100°C over 10 minutes and held for 5 minutes, the samples were then ramped to 160°C over 15 minutes

and held for 15 minutes before they were allowed to cool and subsequently vented. The digested solution was diluted to 10 mL with DDW and analyzed using the external calibration method using a calibration from 0.01 to 50 ppb in a metal free auto sampler by ICP-MS. The Limit of Detection (LOD) was 0.2 μg/dL for blood Pb, 0.05 μg/L for total Hg, and 0.01 μg/L for Cd. For blood metal concentrations below LOD (0% for Pb, 0% for total Hg, and 61% for Cd), the values were replaced with LOD divided by the square root of 2 (Hornung and Reed, 1990).

2.4 Statistical analyses

We compared the distribution of age group, race, sex, and residence between the cases and controls. In addition, we also assessed other covariates including maternal smoking (yes, no), maternal alcohol drinking (yes, no), socioeconomic status (SES: assessed by a question of economic hardship during pregnancy— not difficult, slightly difficult, moderate/very difficult to pay for basic needs), breastfeeding (yes, no), and environmental tobacco smoke (ETS: yes, no). We evaluated whether these covariates were related to blood levels of Pb, Hg, and Cd using t-test or analysis of variance. We estimated the odds ratio (OR) and 95% confidence intervals (CIs) of heavy metals using unadjusted and adjusted logistic regression models. We used natural log-transformed blood metal concentrations as well as the categorical blood Pb (cut off at 2 or 3 μg/dL, approximately the 90^{th} or 95^{th} percentile of the NHANES exposure in children 6–11 years), total Hg (cut off at 1 μg/L, approximately the 90^{th} percentile of the NHANES exposure), Cd (cut off at 0.2 μg/L, approximately the 90^{th} percentile of the NHANES exposure) as the independent variable in the regression models (CDC, 2009). We adjusted for *a priori* matching variables (age group, race, sex, and residence) in the multiple regression models. In addition, we adjusted for maternal smoking, maternal drinking, SES, and ETS because they were associated with ADHD status or lead exposure levels in this study and often considered contributing factors for ADHD in the literature (Froehlich et al., 2011).. Because the residence inside or outside the LIA is such a strong factor related to lead release in the past and blood lead levels in children, we stratified the analysis by residence to examine whether the associations remain both inside and outside of the LIA. To do this, we had to limit covariates to age group, race, sex, and ETS due to smaller sample size and unstable regression estimate for other covariates. All statistical analyses were carried out using SAS 9.2 (SAS Institute Inc., Cary, NC).

3. Results

Table 1 describes the maternal and child characteristics among cases and controls. ADHD cases and controls did not differ by sex, age group, and race, however, more cases were from outside the LIA, born from mothers who smoke or drink alcohol during pregnancy, with lower family SES, and exposed to postnatal ETS. The table also displays the geometric means (GMs) of blood concentration for each metal corresponding to the maternal and child characteristics. Blood Pb concentrations were higher in children age 5–8 years, African Americans, and children living inside the LIA. Blood total Hg and Cd concentrations were not statistically different by any of the covariates in the Table 1.

Table 2 displays the blood metal concentrations among ADHD cases and controls and the unadjusted and adjusted ORs and 95% CI. Blood Pb concentration was not related to ADHD in unadjusted analysis, but after consideration of covariates, high Pb concentration was associated with higher risk of ADHD. The pattern was similar if using categorical blood Pb (≥2 or ≥3 μg/dL). Among the covariates, living outside the LIA was a strong predictor of ADHD given the fact this was a matching variable but not fully compliant (data not shown). Low SES was significantly related to ADHD; maternal smoking, maternal alcohol drinking, and postnatal ETS were related to ADHD but did not reach statistical significance (data not

shown). Blood total Hg or Cd concentration was not related to ADHD in both unadjusted and adjusted logistic regression models. The correlation coefficient between blood Pb and total Hg was 0.03, between blood Pb and Cd was 0.02, both not significant. The correlation coefficient between blood total Hg and Cd was 0.31 ($p<0.05$), probably because of the high percentage of Cd <LOD. In a regression model with natural-log transformed blood Pb, total Hg, and Cd, the adjusted OR and 95% CI for Pb was 2.56 (1.07–6.17), for total Hg was 0.62 (0.31–1.23), and for Cd was 1.20 (0.90–1.62).

Because residence inside or outside the LIA was a strong predictor of blood Pb concentration and ADHD status, the results stratified by residence are shown in Table 3. With smaller number of subjects and limited covariates, the adjusted OR and 95% CI for a natural log unit of blood Pb was 2.28 (0.95–5.50) inside the LIA and 2.20 (0.64–7.56) outside the LIA, respectively. No associations were observed for blood total Hg and Cd.

4. Discussion

This study is one of a few case-control studies that examine a mixed metal exposure and ADHD in children, especially exposure related to the Superfund site or similar hazardous waste site. Our study was in line with many previous studies that found associations with blood Pb levels (< 5 μg/dL) and ADHD (Braun et al., 2006; Froehlich et al., 2009; Nigg et al., 2008; Nigg et al., 2010). The Braun et al. and the Froehlich et al. studies were analysis of the NHANES data in two different age groups (4–15, 8–15, respectively) and different periods (1999–2002, 2001– 2004, respectively), using slightly different case definition (self-reported medication use and physician diagnosis, Diagnostic Interview Schedule for Children [DISC] based on DSM-IV criteria, respectively) (Braun et al., 2006; Froehlich et al., 2009). The Nigg et al. studies involved children 6–17 years old and used DSM-IV criteria with Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-E) and Conners' ADHD rating scale (Nigg et al., 2008; Nigg et al., 2010). Our study corroborates the potential risk of Pb exposure at about 2 μg/dL or higher in relation to medically diagnosed ADHD in children of elementary school age. Other research studies did not investigate medical diagnosis of ADHD but used various ADHD rating scales and found an association of blood Pb concentrations <5 μg/dL with ADHD symptom score (Boucher et al., 2012; Cho et al., 2010; Ha et al., 2009; Kim et al., 2010; Szkup-Jablonska et al., 2012).

We did not find an association between concurrent blood total Hg or Cd and ADHD medical diagnosis. For Hg, one case-control study from Hong Kong found that children with ADHD had higher postnatal blood Hg concentration (GM 3.6 μg/L) than controls (GM 2.3 μg/L) and concentrations over 5.8 μg/L had a 9.69 times higher risk of ADHD after adjusting for confounding factors (Cheuk and Wong, 2006). This exposure level is about an order of magnitude higher than the current U.S. background exposure (CDC, 2009). However, in the Children's Health and Environment Research (CHEER) survey in the Republic of Korea, with similar Hg exposure (GM 2.4 μg/L), ADHD symptoms increased with increasing blood Pb levels but there was no significant association with blood Hg levels (Ha et al., 2009). Other research studies found only ADHD association with blood Pb, not with Hg in children from Romania (Nicolescu et al., 2010) or United Arab Emirates (Yousef et al., 2011). As new research studies suggest a possible role of prenatal Hg exposure on ADHD development (Boucher et al., 2012; Sagiv et al., 2012), the role of postnatal Hg exposure at background U.S. concentrations needs to be examined in larger studies. Our study of Hg and ADHD diagnosis was limited by smaller sample size and low exposure levels, research into higher exposure levels is also needed, especially in communities with high consumption of mercury contained fish species.

Recent analysis of urinary Cd and ADHD in the NHANES 1994–2004 suggested there was a possible non-significant decrease in ADHD risk in children who had urinary Cd levels above the first quartile, with OR of 0.50, 0.52, and 0.67 for the second, third, and fourth quartile (Ciesielski et al., 2012). We observed a close to null association between medical diagnosis of ADHD and either continuous or categorical blood Cd concentrations. It is not clear why the NHANES analysis revealed a significant positive association with learning disability and special education enrollment for the fourth quartile of urinary Cd but a potential lower risk with ADHD. Two recent studies examined associations between neurodevelopment and behavior disorders and levels of postnatal blood Cd, both found no statistically significant associations (Cao et al., 2009; Szkup-Jablonska et al., 2012). However, both study populations had higher levels of Pb than found in U.S. populations, including our own study population, so these results may not be translatable to the U.S. general population (Ciesielski et al., 2012). It should be noticed that in this study about 60% of subjects had blood Cd levels below LOD, which may affect the dose-response curve. We lacked statistical power in analyzing the association with Cd exposure, which might have prevented meaningful findings being detected. Nevertheless, the Cd exposure levels were low in this study and the results cannot predict higher exposure's effect. Additional study with moderately higher Cd exposure levels should be conducted to further the investigation of Cd exposure and child neurodevelopment. Urinary Cd is a better marker of the overall body burden concentration, however blood Cd is considered a better marker for recent exposure and a good marker for a body burden of long-term low-dose exposure (Jarup and Akesson, 2009). There is a need to investigate the association with ADHD using both urinary and blood Cd postnatal exposure.

The results showed an association between blood lead levels and ADHD but not with blood Cd or Hg, this may be explained by various interactions between the metals within the child's body. An animal study showed no difference in behavior between control rats and rats that were given both Pb and Cd in their diets, but they did report differences in the Pb only and Cd only rats (Nation et al., 1990). Although the Pb and Cd rats were given the same dosage as the single metal rats, the co-treated rats had lower levels of Pb in blood than the Pb-only rats, suggesting that Cd may have decreased the amount of Pb absorbed into the blood stream.

Our study has the strength of measuring multiples metals, which has been done in only a few case-control studies of ADHD. Also, we used physician diagnosed ADHD and reduced the likelihood of a misdiagnosis. Many studies report data from parent's or teachers' responses to behavior checklists that also vary from study to study, but ADHD is a comprehensive outcome to measure because it coexists with other neurobehavioral disorders and this may have resulted in misdiagnosis or bias. Additionally, this study involved study participants from a Superfund site, which has significant public health implications for similar hazardous waste sites. This study did also have several limitations, such as a small sample size and the absence of urinary Cd measure. We also had difficulty matching ADHD cases with non-ADHD controls living inside and outside the LIA. As a result, we enrolled more ADHD cases from outside the LIA. Even we considered this effect during data analysis, we had limited power to demonstrate the association both inside and outside the LIA. Nevertheless, the point estimates of adjusted odds ratios both inside and outside the LIA were similar, and may alleviate some concerns about variability in geographic area between cases and controls. Ideally research projects like this in a hazardous waste site should enroll cases and controls within close proximity to the site but still allow variations in exposure levels by personal experience.

In summary, we found that Pb exposure may be associated with higher risk of clinically diagnosed ADHD, even at low levels, in concert with previous studies and stressing the

importance of the actions needed to prevent childhood lead exposure from hazardous waste sites. Children who live near toxic waste sites are at greater risk of developing adverse neurodevelopmental outcomes therefore parents and guardians should take extra caution to limit the amount of exposure. Exposure to heavy metals, Pb in particular, can be reduced by taking a few simple steps in the home. Removing shoes before entering the home will decrease the amount of dust and soil brought in from outside. Mopping the areas around doors and windows will reduce the amount of dust in the home, which will in turn reduce the levels of Pb and other metals. Children should also wash their hands when they come in from playing outdoors and before every meal so that they do not ingest any residue that may be on their hands.

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Relevant Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
APA	American Psychiatric Association
ASARCO	American Smelting and Refining Company
ATSDR	Agency for Toxic Substances and Disease Registry
BLL	Blood Lead Level
Cd	Cadmium
CI	Confidence Interval
CDC	Centers for Disease Control and Prevention
CHEER	Children's Health and Environment Research
DDW	Double Deionized Water
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EPA	Environmental Protection Agency
ETS	Environmental Tobacco Smoke
GM	Geometric Mean
Hg	Mercury
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
LIA	Lead Investigation Area
LOD	Limit of Detection
NE	Nebraska
NHANES	National Health and Nutrition Examination Survey
NPL	National Priorities List
OR	Odds Ratio
Pb	Lead

ppb	Parts Per Billion
SES	Socioeconomic Status
SRM	Standard Reference Material

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Highlights

- Blood Pb levels are associated with ADHD diagnosis in children
- No association was found between blood Cd or Hg levels and ADHD
- Children living close to hazardous waste site need to reduce metal exposure

Table 1

Percentage of ADHD cases and controls and geometric mean blood Pb, Hg, and Cd concentrations by maternal and child characteristics

Characteristics	Cases (n=71) %	Controls (n=58) %	Blood Pb (μg/dL)	Blood Total Hg (μg/L) Geometric mean	Blood Cd (μg/L)
Sex					
Male	70	60	1.21	0.43	0.02
Female	30	40	1.52	0.38	0.02
Age group[b]					
5 to 8 years	39	45	1.67	0.40	0.02
9 to 12 years	61	55	1.10	0.42	0.02
Race[b]					
African American	39	38	1.56	0.41	0.02
Caucasian	61	62	1.17	0.41	0.02
Lead Investigation Area[a,b]					
Inside	38	71	1.65	0.42	0.02
Outside	62	29	1.01	0.41	0.02
Maternal smoking[a]					
Yes	43	14	1.41	0.37	0.01
No	57	86	1.31	0.43	0.02
Maternal alcohol drinking[a]					
Yes	17	3	1.65	0.41	0.02
No	83	97	1.33	0.41	0.02
Socioeconomic status[a] (mother paying for basic needs during pregnancy)					
No difficulty	32	67	1.30	0.41	0.02
Slightly difficult	30	19	1.32	0.46	0.02
Moderate/Very difficult	38	14	1.39	0.39	0.01
Singleton					
Yes	97	95	1.32	0.42	0.02
No	3	5	1.14	0.34	0.02
Low birth weight					

Characteristics	Cases (n=71) %	Controls (n=58) %	Blood Pb (μg/dL)	Blood Total Hg (μg/L) Geometric mean	Blood Cd (μg/L)
Yes	11	13	1.21	0.37	0.02
No	89	87	1.33	0.40	0.02
Preterm birth					
Yes	18	16	1.46	0.40	0.02
No	82	84	1.30	0.41	0.02
Breastfed					
Yes	45	52	1.21	0.38	0.02
No	55	48	1.42	0.45	0.02
Postnatal Environmental Tobacco Smoke[a]					
Yes	47	24	1.24	0.40	0.02
No	53	76	1.41	0.41	0.02

[a] $p<0.05$ between cases and controls

[b] $p<0.05$ for blood Pb levels

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Table 2

Blood Pb, total Hg, and Cd concentrations among ADHD cases and controls and odds ratios (OR) and 95% confidence intervals (CIs) of the natural log-transformed continuous or categorical metal exposures

Blood metal concentrations	Cases (n = 71)	Controls (n = 58)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Pb (μg/dL)				
Geometric mean (range)	1.29 (0.28–9.99)	1.33 (0.42–6.05)	0.94 (0.56–1.56)	2.52 (1.07–5.92)
% ≥2 μg/dL	27	28	0.96 (0.44– 2.09)	4.63 (1.36–15.72)
% ≥3 μg/dL	15	12	1.34 (0.48–3.70)	7.25 (1.66– 31.67)
Total Hg (μg/L)				
Geometric mean (range)	0.39 (0.08–2.9)	0.44 (0.09–2.59)	0.81 (0.49–1.32)	0.77 (0.41–1.46)
%≥1 μg/L	8	14	0.58 (0.19–1.77)	0.39 (0.08– 1.82)
Cd (μg/L)				
Geometric mean (range)	0.02 (0.007–4.04)	0.02 (0.007–8.69)	1.08 (0.87–1.35)	1. 18 (0.89–1.56)
% ≥0.2 μg/L	11	14	0.79 (0.28–2.26)	0.87 (0.24–3.18)

*Adjusted for age, sex, race, mother smoking during pregnancy, mother drinking during pregnancy, exposure to postnatal environmental tobacco smoke, socioeconomic status, and residence (living inside or outside the LIA).

Table 3

Metal concentrations in ADHD cases and controls, odds ratios (OR) and 95% confidence intervals (CIs) of natural-log transformed continuous exposures stratified by location: Inside or outside of the lead investigation area (LIA)

Location		Cases Geometric mean (range)	Controls Geometric mean (range)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Inside LIA	N	27	41		
	Pb (μg/dL)	1.89 (0.54–9.99)	1.51 (0.56–6.05)	1.67 (0.79– 3.51)	2.28 (0.95– 5.50)
	Total Hg (μg/L)	0.35 (0.08–2.29)	0.47 (0.09–2.60)	0.56 (0.28–1.14)	0.60 (0.30–1.21)
	Cd (μg/L)	0.02 (0.01–0.41)	0.02 (0.01–8.69)	1.06 (0.77– 1.45)	1.12 (0.80– 1.56)
Outside LIA	N	44	17		
	Pb (μg/dL)	1.02 (0.28–5.76)	0.97 (0.42–2.88)	1.14 (0.45– 2.91)	2.20 (0.64–7.56)
	Total Hg (μg/L)	0.43 (0.08–2.90)	0.37 (0.16–1.25)	1.44 (0.58–3.56)	1.15 (0.42–3.15)
	Cd (μg/L)	0.02 (0.01–4.04)	0.02 (0.01–0.46)	1.03 (0.73–1.44)	0.94 (0.64– 1.39)

*Adjusted for age, sex, race, and exposure to postnatal environmental tobacco smoke.