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When are fetuses and young children most susceptible to soil metal concentrations of arsenic, lead and mercury?

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Abstract

This study was designed to analyze when, during pregnancy and early childhood, the association between soil metal concentrations of arsenic (As), lead (Pb) and mercury (Hg) and the outcome of intellectual disability (ID) is statistically significant. Using cluster analysis, we identified ten areas of land that contained a cluster of ID and areas of average risk for ID. We analyzed soil for As, Pb, and Hg and estimated the soil metal concentration at the residential sites where the woman and children lived during pregnancy and early childhood using a Bayesian Kriging model. Arsenic concentrations were associated with ID during the first trimester of pregnancy and Hg was associated with ID early in pregnancy and the first two years of childhood. The covariates that remained in the final models were also temporally associated with ID.

Keywords

intellectual disability; arsenic; lead; mercury; Bayesian Kriging; spatial clusters; epidemiology

1.Introduction

Intellectual disability (ID; previously classified as mental retardation) is a lifelong disability that is defined as “Significant sub-average intellectual functioning (2 standard deviations below the mean on standardized tests of intelligence) existing concurrently with deficits in adaptive behavior, and manifest during the developmental period” (Luckasson, et al., 2002). The known causes include genetic and chromosomal abnormalities, infections, chemical exposures, and intentional and unintentional injuries. Many cases of ID do not have a known

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cause although the insult to the brain is evident by brain hemorrhage, prematurity, and abnormal structures in the brain.

Arsenic (As), lead (Pb) and mercury (Hg) are developmental toxicants that have been associated with ID even at low levels of exposure (Bellinger, 2006; Goldman and Koduro, 2000; Miodovnik, 2011; Schroeder, 2000; Sullivan and Krieger, 2001). There is substantial evidence that metals cross the placenta and accumulate in fetal tissue (Miodovnik, 2011). The major exposure route for the pregnant woman has been identified as dermatologic (handling arsenic and lead), and oral (hand-to-mouth consumption of lead, and consumption of fish with mercury) (Baghurst, et al., 1992; Counter, Buchanan, et al, 2002; Davidson et al, 2006; Mielke, et al, 2007; Patel et al, 2005; Tong et al, 1998; Wasserman, et al., 1994; Wasserman, et al., 1997; Zakharova et al., 2002). There is also evidence that there is a statistically significant association between soil and blood concentrations of Pb and As in children through hand-to-mouth contamination (Axelrad et al., 2007; Bellinger and Needleman, 2003; Goldman and Koduro, 2000; Lanphear et al., 2005; Rosado, et al., 2007; Wang, et al., 2007). Numerous reports document elevated soil metal concentrations in urban areas from industrial and transportation sources and elevated rural soil concentrations of metals from natural geologic sources, pesticides, and industrial facilities (Aelion et al, 2008; Davis et al, 2009; Li et al, 2004). The exact mechanism whereby soil metal concentrations affect neurodevelopmental outcomes in children is not known.

The US EPA sets two acceptable levels for human exposures to soils containing metals. The more stringent human health residential soil screening level (RSSL) is to protect against a cancer risk at 1×10^{-6} . The EPA also sets a higher soil screening level to protect against non-cancer effects (Environmental Protection Agency, 2000). It has been suggested that longitudinal studies that begin prenatally, are needed to identify the low level effects of metals on intellectual performance and the adverse outcome of ID (Goldman and Koduro, 2000).

Most studies of metal exposures during pregnancy have explored As, Pb, and Hg, one at a time, and there are numerous reports of associations with ID and reduced neurological development of children (Factor-Litvak et al, 1999; Murata et al, 2007; Patel et al, 2005; Vahter, 2009; Wasserman, et al., 2004). Our research team has identified an association between As in soil and the combined outcome of ID and developmental delay (DD), and we have shown the combination of As and Pb is associated with an enhanced risk for ID and ID/DD (Liu, et al, 2010; McDermott et al, 2011). The approach used in the current study elaborates our previous work that utilized spatial statistical methods (geocoding of maternal residences during pregnancy, measurement of soil metals on a uniform grid system located throughout the study areas, and Bayesian Kriging to estimate residential soil metal concentrations at residential addresses) to find associations with ID and DD. We used Medicaid data to capture the residential location experience of low-income mothers and children, since it has been reported that children in poor neighborhoods are disproportionately impacted by environmental pollution and the outcome of ID.

The purpose of this study was to answer the question: When are fetuses and young children most susceptible to soil metal concentrations of As, Pb and Hg? This question builds on the strong association of As, Pb, and Hg during pregnancy and ID in the literature and in our previous work. Since ID is usually not diagnosed until a child fails to meet developmental milestones the association between in utero exposures and child outcomes has always skirted the issue of when the exposure occurs, before or after birth. Our study is one approach to answer this question of timing.

2. Methods

2.1. Study population

This is a retrospective cohort study of pregnant women who were insured by South Carolina Medicaid from 1996 through 2002 and resided in ten residential study areas during pregnancy and early childhood. The design of the study includes individual characteristics of mothers and children, neighborhood characteristics, and measures of soil metals which are extrapolated to their home address. The residences of the women were available through pregnancy and early childhood using a GIS coded address for each month of pregnancy and at four follow-ups before age 2 years. The children were followed in Medicaid and public school records for at least 8 years to identify the outcome of ID.

The study was granted exempt status for human subjects research by the University of South Carolina Institutional Review Board based on procedures that assured confidentiality of the individuals. After actual soil sampling and estimates of concentrations at residences were obtained, the geocoded coordinates of the homes were shifted. There were no maps showing the actual location of homes and the data were de-identified during analyses. This allowed us to maintain confidentiality but still find associations between concentrations of metals in soil during specific months and the outcome.

All the mother child pairs were insured by Medicaid, an insurance plan for people living under the federal poverty level. In order to maintain their insurance coverage addresses were verified during each month of pregnancy and at six-month intervals during early childhood. As a result we had up to 14 addresses for each mother-child pair, depending on when the mother enrolled in Medicaid during pregnancy and how long she remained income-eligible. In South Carolina pregnant women living below 185% of poverty were eligible for Medicaid. The federal poverty guideline for eligibility for a family of four is an annual income of \$22,050, and the pregnancy guideline for eligibility for a family of four is an annual income of \$40,792, and this accounts for 50% of the births in South Carolina.

2.2. Identification of Cases of unknown cause ID

We started with a statewide data set that included 105,931 pregnant women insured by Medicaid during the period January 1, 1996- December 31, 2002. Since the study was designed to identify risk factors for unknown cause ID we excluded 245 babies with the following known causes of ID: Trisomy 13, 16-18, other chromosomal aberrations, Prader-Willi Syndrome, Rett's Syndrome, phenylketonuria, Fragile X Syndrome, postnatal injury, prenatal rubella, meningitis, encephalitis, and Fetal Alcohol Syndrome, using ICD9 codes (Centers for Disease Control and Prevention (CDC) and Centers for Medicare and Medicaid Services (CMS), 2007).

In order to identify children with unknown cause ID we merged the Medicaid reimbursement files for the mothers and children, birth certificates and the public school and disability agency records for early intervention and children's services for ID through March 2011. As a result we had 6.7 years of follow-up time to identify codes for ID.

2.3. Selection of Study Areas and Geocoding of Maternal Residences

We identified ten areas that contained a cluster of unknown cause ID using cluster analysis as described by Zhen et al (2008). We could not collect and analyze soil samples throughout the state so we selected ten areas that each contained a risk gradient for ID (including an area of high prevalence and areas of average prevalence) and each sampling area was approximately 105 km² in size. We then identified 12,798 mother-child pairs who lived in these ten land areas during at least one month of pregnancy, and carried out soil sampling.

The study areas were dispersed throughout South Carolina, in rural and urban communities. In Figure 1A we show a section of the state and the identification of a statistically significant cluster, and the variation around the cluster of different levels of risk for ID. The darker colored areas have high prevalence of ID and the light colors are below the state average prevalence for ID. There is an area of highest risk identified in the red box in Figure 1A and this area is one sampling area in Figure 1B. In Figure 1B we show a sampling area and the actual location of cases of ID and the normal births, using maternal residences during the sixth month of pregnancy.

Addresses were obtained from a Medicaid eligibility file for each month of pregnancy through age 2 years for the child. Since women entered the dataset when they enrolled in Medicaid and they left the dataset when their child was born we do not have addresses for every month of pregnancy for every woman. We used the months for which we had data and did not impute missing addresses. We also had the addresses during the first two years of life, as reported to the Medicaid office for eligibility, for families who stayed on Medicaid. Some families left Medicaid during their child's early childhood due to increase in income, so the childhood addresses were only available for the subset that remained on Medicaid. These addresses were geo-coded using ArcGIS version 9.3. In order to maintain the confidentiality agreement the soil sampling was done according to a grid throughout a residential area. The intersection of the grid lines were sampling locations, referred to as grid nodes, and were not the actual residential addresses.

2.4. Soil Sampling and Metal Analysis

The latitude and longitude of the four corners of the ten rectangular areas that contained a cluster of ID were identified, and a uniform grid was overlaid at locations 1.0-3.0 km apart. The coordinates for each area were mapped and Global Positioning System (GPS) latitudes and longitudes were taken at each sampling location with a handheld GPS device (Garmin Etrex, Olathe, KS) (Aelion et al, 2008). Soil was collected at 5-cm depths from each node (Aelion et al, 2009; Aelion et al, 2009); where nodes were inaccessible (e.g., on building locations or water bodies), soil samples were collected as close to the grid node as possible. Duplicate samples were collected at 10% of the sampling locations for quality assurance and quality control purposes. The mean sampling sites in each study area is 115 with standard deviation of 5. After sampling, soil was analyzed for As, Pb and Hg by an independent analytical laboratory (Pace Analytical, Huntersville, NC). We then explored the associations of the Kriged values of the metals at each pregnancy and early childhood address using data from a total of 1092 sample sites.

2.5. Kriging to assign chemical concentration at each residence

Since there was misalignment between concentrations at soil sample sites and the geocoded location of the homes, we used the Bayesian Kriging model proposed by Diggle and Ribeiro (Diggle et al 1998; Diggle and Ribeiro, 2002; Diggle and Ribeiro, 2007) to get unbiased estimates for addresses. Since the metal concentrations were highly asymmetric we used the Box-Cox transformation of these variables and we used Kriging methods to produce maps of the estimated concentration of metals at each known address (Banerjee et al, 2004). The parameters used for Box-Cox transformations were not highly variable; e.g. for As half of the parameters were zero and the others ranged from -0.4 to -0.1. The model parameters were sampled from their posterior distributions with proper priors using the `Krige.bayes` function of "geoR" in R. Once transformed, we validated the ability of the Kriging approach using the "leave-one-out" cross validation method (Cressie, 1993). This was achieved by fitting the Kriged model to the residential points, estimating a missing point from the fitted model, and examining the mean error (ME) and mean square deviation ratio (MSDR) (Webster and Oliver, 2001). The MSDR and ME were close to reference levels

after transformation, indicating that Box-Cox transformation yielded a good approximation. To test the validity of the Kriged estimates we sequestered 20% of measurement data from samples to evaluate correlation between observed and predicted at each point (location of sequestered samples). There was a statistically significant correlation (Pearson correlation coefficient > 0.8, p-value < 0.01) for the kriged value based on 20% of the measured data compared with the krige value based on the rest of data.

During the Kriging process, soils measured below the reportable concentrations were assigned a value of half of the minimum detectable limit according to the EPA Guidance for data Quality Assessment (Environmental Protection Agency, 2000), since the non-detected rate was less than 15% for most of the metals. The detection limit for As and Pb was 0.5 mg kg⁻¹, and 0.00055 mg kg⁻¹ for Hg.

2.6. Statistical Analysis

The hypothesis for this study was ID in the child was associated with maternal exposure to elevated soil concentrations of As, Pb, and Hg during the first trimester of pregnancy or during the first two years of childhood. The covariates included in the analyses included infant, maternal and neighborhood characteristics, as shown in Table 1. The child and mother characteristics were obtained from the birth certificate, which was linked to the Medicaid billing file. The infant characteristics were sex (male, female), and weeks of gestation. The maternal covariates were maternal age (in years). Maternal race was dichotomized as non-Hispanic black or others. The number of prior births (parity) was categorized as 0, 1, 2, and 3 or more, and tobacco and alcohol use was categorized as yes or no. Finally, we added two neighborhood characteristics for each mother to capture the density per square mile and the median age of housing in the block group of the residence. The cohort dataset was prepared based on the monthly following up information for the mother and child from Medicaid. Then the monthly dataset used in our study was selected within the ten areas based on the coordinates.

We explored the association between the concentration of each metal with the risk of ID using separate generalized additive mixed models (GAMM) for each month of pregnancy and for four follow-up times during the first two years of childhood only based on complete dataset. We used forward selection to include the statistically significant independent variables. Based on the observed nonlinear effects for the metals we used spline functions for As, Pb and Hg. The other variables were modeled to have linear effects. The “mgcv” package in R with automatic smoothness selection was used for GAMM model fitting (Wood, 2006).

The binary response variable ID versus no ID is assumed to follow a Bernoulli distribution with probability (ID=1) = p . The covariates ($\{X_j\} \ j=1, \dots, m$) include both mother and child demographic information and the Kriged concentration for soil chemicals. A semi-

parametric model, $\text{logit}(p_i) = \alpha_0 + \sum_{j=1}^s \alpha_j x_{ij} + \sum_{j=s+1}^m s_j(x_{ij}) \quad i=1, \dots, n, j=1, \dots, m$, was considered, where $s(\cdot)$ is a smooth and possible nonlinear function, n is the sample size, m is the total number of predictors, and the first s predictors are assumed to be linearly associated with $\text{logit}(p)$ by parameter α (parametric terms), and the remaining predictors are nonlinearly associated with response (smooth terms). All the candidate models were assessed via $\Delta\text{AIC} > 2$ entry criteria.

3. Results

The characteristics of the study group are shown in Table 1. When compared to the children with ID and children with no ID, those with ID were significantly more likely to be male,

less than 28 weeks of gestation at birth, less than 1500 grams in birthweight, and small for gestational age. Maternal risk factors included being over 34 years old, a race other than non-Hispanic white, and parity greater than or equal to one. The median year of housing for the mother-child pairs with ID was 1962 compared to 1965 for those without ID. In addition, the soil concentration for Pb and Hg were significantly associated with ID.

In order to know who had the ID outcome we had to follow the mother child pairs, in the electronic records since ID is not usually diagnosed until school age. The mean (and standard deviation) for years of follow-up for the pairs was 6.7 (2.6) years. We also explored the follow-up for mother-child addresses based on when during pregnancy the mother enrolled. The proportions with follow-up addresses through the first two years of life was over 75% for those who enrolled in Medicaid during the 4th through the 8th month of pregnancy. It was lower for those enrolled very early and very late in pregnancy.

The Kriged metal concentrations from soil samples for residential sites in the 10 areas are shown in Table 2. For As there was no statistically significant difference between the mean As values at the nodes compared to the mean Kriged values for eight of the areas. In two areas the mean Kriged values were statistically significant higher (2.6 versus 2.1 for Area 2 and 1.3 versus 1.1 for Area 3). Different residential patterns probably account for these differences. The EPA soil screening level to protect against non-cancer effects for As is 22 mg kg⁻¹, for Pb it is 400 mg kg⁻¹, and for Hg it is 23 mg kg⁻¹. The EPA soil screening level to protect against cancer is 0.39 mg kg⁻¹ for As and 400 mg kg⁻¹ for Pb, and for Hg it is 23 mg kg⁻¹ (Environmental Protection Agency, 2009). All of the soil samples were below the EPA Regional Soil Screening Level (RSSL) for non-cancer hazard index for the metals. Arsenic and Pb were the only chemicals that exceeded EPA Preliminary Remediation Goals (PRG) residential soil sample limit (RSSL) for carcinogenic target risk, 99.2% of the residential sites had higher soil As levels than the EPA PRG-RSSL level, 0.4 mg kg⁻¹ and 2.2% of the residential sites had higher soil Pb levels than the EPA PRG-RSSL level of 400 mg kg⁻¹.

The analysis of the adjusted association of As, Pb and Hg with ID is shown in Table 3. Arsenic concentrations were associated with ID only during the first trimester and Hg was associated with ID during the first trimester and the first two years of childhood. The covariates were also temporally associated with ID. Premature birth and male sex were associated with ID throughout pregnancy and early childhood. Higher parity was associated with ID through month 9 of pregnancy and during the first two follow-up during infancy and maternal self report of alcohol use was associated with ID during month 1-3 of pregnancy. Mothers who identified as black race were more likely to have a child with ID based on residence during month 6-9 of pregnancy. Finally older homes were associated with ID outcomes only during early childhood.

4. Discussion

We believe this is the first study to investigate the association of soil metal concentrations proximal to maternal residence during each month of pregnancy and during early childhood. It is known that As, Pb and Hg, are absorbed into the maternal bloodstream and cross the placenta and the blood-brain barrier thereby accessing the fetal brain (Miodovnik, 2011). Lead neurotoxicity has been shown to have a substantial impact on the developing brain even at very low exposures. Likewise recent studies of methylmercury exposure at low concentrations have been associated with reduced IQ scores (Grandjean and Landrigan, 2006). Arsenic's impact on subclinical neurodevelopmental neurotoxicity is also emerging (Wasserman, et al., 2004; Wright et al, 2006). The evidence from our study is consistent

with the accumulated knowledge about the individual effects and it suggests more studies need to focus on the timing of exposures.

The key finding is that soil arsenic concentration is associated with significantly increased odds of ID in the first trimester of pregnancy, and mercury was associated with ID early in pregnancy (and during Month 9) and during early childhood. These associations are present when controlling for gestational weeks at birth, birth weight, parity, alcohol use, mean residential building age in the neighborhood, and maternal race. It should be noted that age of the residences was statistically significantly associated with ID only after birth, although Pb in the soil was not statistically significant associated with the outcome. Many of the mother child pairs lived in neighborhoods where the typical house was built and painted with lead-based paint, which was banned in 1978 (Landrigan, 1992; US Consumer Product Safety Commission: 16 coder of Regulations CFR 1303).

This study has a number of limitations. First, it is limited to Medicaid-funded births in South Carolina and findings in this population may not be fully generalizable to middle and upper income families or to other geographic areas outside of the southern United States. A second limitation is our reliance on administrative data for ascertainment of some of the independent and the dependent variables. For the outcome of ID we relied on Medicaid diagnoses, public school records, and receipt of services from the SC Department of Disabilities and Special Needs (DDSN). The public school system and DDSN require a formal psychological assessment with IQ testing before a child is eligible for special education classes or ID-related services. We did not always have information on the factors underlying a diagnosis of ID in the Medicaid billing records, although when a known cause was coded the case was excluded since we were studying unknown cause cases only. Finally, in terms of our methodology for estimating the soil concentration at maternal residences, we used a Kriging approach that accounted for standard error of measurement but could not account for measurement error. Thus, we do not have validation of the accuracy of the soil concentrations.

One of the strengths of this study is the large sample size, which provides ample power for the analyses; our cohort included 12,798 children after exclusions, 746 with a diagnosis of ID. The sample size did vary month by month but it was large enough to identify some statistically significant differences. And we excluded children with birth defects, chromosomal conditions, or other diagnoses known to be causes of ID, so our findings are directly relevant for the approximately 50% of cases of ID that do not have known causes. Another strong point was our soil testing for metals in areas where pregnant women and young children resided and our use of Kriging of the concentrations for each maternal and child address. This is an innovative way to estimate exposure. Our analytic method allowed us to take into account potential nonlinearity in the relationships between soil metal concentrations and the outcome ID, which is important since we do not anticipate a linear relationship between these potential exposures and odds of ID. Finally, we controlled for a number of potentially important factors so we can be confident that the associations between the soil metal concentrations and ID are not due to those factors.

Additional epidemiologic study in different geographic and socioeconomic groups is needed to assess the generalizability of our findings to these groups. It is important to understand the time during pregnancy and early childhood when exposure to soil containing As and Hg is most associated with the ID outcome, since these findings could suggest families remove their shoes before entering their homes during pregnancy and early childhood.

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REFERENCES

- Aelion CM, Davis HT, McDermott S, Lawson AB. Metal concentrations in rural topsoil in South Carolina; Potential for human health impact. *Sci Total Environ*. 2008; 402(2-3):149–156. [PubMed: 18538375]
- Aelion CM, Davis HT, Liu Y, Lawson AB, McDermott S. Validation of Bayesian kriging of arsenic, chromium, lead and mercury in surface soils based on internode sampling. *Environ Sci Technol*. 2009; 43(152):4432–4438. [PubMed: 19603658]
- Aelion CM, Davis HT, McDermott S, Lawson AB. Soil metal concentrations and toxicity: Associations with distances to industrial facilities and implications for human health. *Sci Total Environ*. 2009; 407(7):2216–2223. [PubMed: 19155049]
- Axelrad DA, Bellinger DC, Ryan LM, Woodruff TJ. Dose-response relationship of prenatal mercury exposure and IQ: an integrative analysis of epidemiologic data. *Environ Health Perspect*. 2007; 115(4):609–615. [PubMed: 17450232]
- Baghurst PA, McMichael AJ, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ, et al. Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study. *N Engl J Med*. 1992; 327:1279–1284. [PubMed: 1383818]
- Banerjee, PA.; Gelfand, AE.; Carlin, BP. Hierarchical modeling and analysis for spatial data. Chapman & Hall/CRC; Boca raton: 2004.
- Bellinger DC, Needleman HL. Intellectual impairment and blood lead levels. *N Engl J Med*. 2003; 349:500–502. [PubMed: 12890850]
- Bellinger, DC. Human Developmental Neurotoxicology. Taylor & Francis; New York: 2006.
- Burnham, KP.; Anderson, DR. A Practical Information-Theoretic Approach. Springer-Verlag; New York: 2002. Model Selection and Multimodel Inference..
- Centers for Disease Control and Prevention (CDC). Centers for Medicare and Medicaid Services (CMS). The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) sixth ed. National Center for Health Statistics; Washington, D.C.: 2007.
- Counter SA, Buchanan LH, Ortega F, Laurell G. Elevated blood mercury and neurootological observations in children of the Ecuadorian gold mines. *J Toxicol Environ Health A*. 2002; 65(2): 149–163. [PubMed: 11820503]
- Cressie N. Regional mapping of incidence rates using spatial Bayesian models. *Med Care*. 1993; 31(5 Suppl):YS60–YS65. [PubMed: 8492588]
- Davidson PW, Myers GW, Weiss B, Shamlaye CF, Cox C. Prenatal methyl mercury exposure from fish consumption and child development: a review of evidence and perspectives from the Seychelles Child Development Study. *Neurotoxicology*. 2006; (27):1106–1109. [PubMed: 16687174]
- Davis HT, Aelion CM, McDermott S, Lawson AB. Identifying natural and anthropogenic sources of metals in urban and rural soils using GIS-based data, PCA, and spatial interpolation. *Environ Pollut*. 2009; 157(8-9):2378–2385. [PubMed: 19361902]
- Diggle PJ, Tawn JA, Moyeed RA. Model-based geostatistics. *Appl Stat*. 1998; 47(Part 3):299–350.
- Diggle PJ, Ribeiro PJJ. Bayesian inference in Gaussian model-based geostatistics. *Geogr Environ Model*. 2002; 6(2):129–146.
- Diggle, PJ.; Ribeiro, PJJ. Model-based Geostatistics. Springer-Verlag; New York: 2007.
- Environmental Protection Agency. Guidance for data quality assessment: Practical methods for data analysis. EPA/G-9, QA00 update. Office of Environmental Information; Washington, DC: 2000.
- Environmental Protection Agency. Regional Screening Level Table (RSL) Master APRIL. Washington, DC: 2009.

- Factor-Litvak P, Wasserman G, Kline JK, Graziano J. The Yugoslavia prospective study of environmental lead exposure. *Environ Health Perspect.* 1999; 107(1):9–15. [PubMed: 9872712]
- Goldman LR, Koduro S. Chemicals in the environment and developmental toxicity to children: A public health and policy perspective. *Environ Health Perspect.* 2000; 108(Suppl 3):443–448. [PubMed: 10852843]
- Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet.* 2006; 368(9553):2167–2178. [PubMed: 17174709]
- Landrigan, PJ. Commission on Life Sciences, National Research Council. National Academy Press; Washington: 1992. *Environmental Neurotoxicology..* ISBN 0309045312
- Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect.* 2005; 113(7):894–899. [PubMed: 16002379]
- Li X, Lee S, Wong S, Shi W, Thornton I. The study of metal contamination in urban soils of Hong Kong using a GIS-based approach. *Environ Pollut.* 2004; 129(1-2):113–124. [PubMed: 14749075]
- Liu Y, McDermott S, Lawson AB, Aelion CM. The relationship between mental retardation and developmental delays in children and the levels of arsenic, mercury and lead in soil samples taken near their mother's residence during pregnancy. *Int J Hyg Environ Health.* 2010; 2:116–213. [PubMed: 20045663]
- Luckasson, R.; Borthwick-Duffy, S.; Buntinx, WHE.; Coulter, DL.; Craig, EM.; Reeve, A., et al. *Mental Retardation: Definition, Classification, and Systems of Supports.* tenth ed.. American Association on Mental Retardation; Washington, DC: 2002.
- McDermott S, Wu J, Cai B, Lawson A, Aelion CM. Probability of intellectual disability is associated with soil concentrations of arsenic and lead. *Chemosphere.* 2011; 84(1):31–38. [PubMed: 21450328]
- Mielke HW, Gonzales CR, Powell E, Jartun M, Mielke PWJ. Nonlinear association between soil lead and blood lead of children in metropolitan New Orleans, Louisiana: 2000-2005. *Sci Total Environ.* 2007; 388(1-3):45–53.
- Miodovnik A. Environmental neurotoxicants and developing brain. *Mt Sinai J Med.* 2011; 78(1):58–77. [PubMed: 21259263]
- Murata K, Dakeishi M, Shimada M, Satoh H. Assessment of intrauterine methylmercury exposure affecting child development: messages from the newborn. *Tohoku J Exp Med.* 2007; 213(3):187–202. [PubMed: 17984616]
- Neisser U. Rising Scores on Intelligence Tests. *American Scientist.* 1997; 85(5):440–447.
- Patel KS, Shrivastava K, Brandt R, Jakubowski N, Corns W, Hoffmann P. Arsenic contamination in water, soil, sediment and rice of central India. *Environ Geochem Health.* 2005; 27(2):131–145. [PubMed: 16003581]
- Rosado JL, Ronquillo D, Kordas K, Rojas O, Alatorre J, Lopez P, et al. Arsenic exposure and cognitive performance in Mexican schoolchildren. *Environ Health Perspect.* 2007; 115(9):1371–1375. [PubMed: 17805430]
- Schroeder SR. Mental retardation and developmental disabilities influenced by environmental neurotoxic insults. *Environ Health Perspect.* 2000; 108(Suppl 3):395–399. [PubMed: 10852834]
- Sullivan, JB.; Krieger, GR. *Clinical Environmental Health and Toxic Exposures.* Lippincott Williams & Wilkins; Philadelphia: 2001.
- Tong SL, Baghurst PA, Sawyer MG, Burns J, McMichael AJ. Declining blood lead levels and changes in cognitive function during childhood: the Port Pirie Cohort Study. *JAMA.* 1998; 280(22):1915–1919. [PubMed: 9851476]
- US Consumer Product Safety Commission: 16 code of Regulations CFR 1303.
- Vahter M. Effects of arsenic on maternal and fetal health. *Annual Review of Nutrition.* 2009; 29:381–399.
- Wang SX, Wang ZH, Cheng XT, Li J, Sang ZP, Zhang XD, et al. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. *Environ Health Perspect.* 2007; 115(4):643–647. [PubMed: 17450237]

- Wasserman G, Graziano JH, Factor-Litvak P, Popovac D, Morina N, Musabegovic A, et al. Consequences of lead exposure and iron supplementation on childhood development at age 4 years. *Neurotoxicol Teratol.* 1994; 16(3):233–240. [PubMed: 7523846]
- Wasserman GA, Liu X, Lolacono NJ, Factor-Litvak P, Kline JK, Popovac D, et al. Lead exposure and intelligence in 7-year-old children: the Yugoslavia Prospective Study. *Environ Health Perspect.* 1997; 105(9):956–962. [PubMed: 9410739]
- Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, van Geen A, et al. Water arsenic exposure and children's intellectual function in Araihaazar, Bangladesh. *Environ Health Perspect.* 2004; 112(13):1329–1333. [PubMed: 15345348]
- Webster, R.; Oliver, MA. *Geostatistics for Environmental Scientists (Statistics in Practice)*. second ed.. John Wiley & Sons, Ltd.; Chichester, UK: 2001.
- Wood, SN. *Generalized Additive Models: An Introduction with R*. Chapman & Hall/CRC; Boca Raton, FL: 2006.
- Wright RO, Amarasiwardena C, Woolf AD, Jim R, Bellinger DC. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. *Neurotoxicology.* 2006; 27(2):210–216. [PubMed: 16310252]
- Zakharova T, Tatano F, Menshikov V. Health cancer risk assessment for arsenic exposure in potentially contaminated areas by fertilizer plants: a possible regulatory approach applied to a case study in Moscow region-Russia. *Regul Toxicol.* 2002; 36(1):22–23.
- Zhen H, Lawson A, McDermott S, Aelion CM. Spatial analysis of mental retardation and residence during pregnancy. *Geospat Health.* 2008; 2(2):173–182. [PubMed: 18686266]

A. Section of State*

B. Sampling Area**

Figure 1. Identification of a cluster and distribution of ID in a residential sampling area

The red box in A is the same as the sampling area in B.

*A. Section of state: each increment of the X axis represents 20km, each increment of the Y axis represents 92km

**B. Sampling area: each increment of the X axis represents 4km, each increment of the Y axis represents 2km

Table 1

Characteristics of the mother child pairs (n=12798)

		No ID (n=12052)	ID (n=746)	Odds ratio [*] (ID versus no ID)
Infant Characteristics				
Infant sex	Girl	5926	485	
	Boy	5823	261	1.83(1.56,2.13)
	Missing	303	0	
Weeks of gestation	>36	9624	538	
	28-36	1477	129	1.56(1.28,1.91)
	<28	72	36	8.94(5.94,13.47)
	Missing	879	43	
Birth weight (in grams)	>2500	10474	563	
	1500-2500	1118	105	1.74(1.41,2.17)
	<1500	157	78	9.24(6.96,12.28)
	Missing	303	0	
Small for Gestational Age ^I				
	Above 10%	9325	544	
	Below 10%	1843	159	1.48(1.23,1.78)
	Missing	884	43	
Maternal Characteristics				
Mother's age	18-34	8199	498	
	<18	3214	198	1.01(0.86,1.20)
	>34	336	50	2.45(1.80,3.34)
	Missing	303	0	
Mother's race	Other	3971	185	
	Black	7773	561	1.55(1.31,1.84)
	Missing	308		
Parity	0	5043	264	
	1	3623	230	1.21(1.01,1.46)
	2	1880	148	1.50(1.22,1.85)
	3+	1203	104	1.65(1.31,2.09)
	Missing	303	0	
Tobacco use	No	10093	600	
	Yes	1950	146	1.26(1.05,1.52)
	Missing	9		
Alcohol use	No	11594	728	
	Yes	131	16	1.95(1.15,3.29)
	Missing	327	2	
Neighborhood Characteristics				
Density	Population/sq. mile	2706.9	2759.6	1.00(1.00,1.00) **
Mean age of houses in years		45.32	48.63	1.02(1.00,1.03) **

	No ID (n=12052)	ID (n=746)	Odds ratio [*] (ID versus no ID)
Metal Concentrations			
Mean Arsenic(As)	3.25	3.35	1.20(0.88,1.63) ^{**}
Mean Lead (Pb)	71.80	77.93	1.01(1.00,1.01) ^{**}
Mean Mercury (Hg)	0.10	0.14	15.10(2.39,95.55) ^{**}

Bold indicates statistical significance

The metal concentration of As, Pb and Hg is the mean value if the mother ever moved.

^I Use of 10th percentile based on Groom et al. 2007.

^{*} Crude odds ratio, when there is only one predictor in the model

^{**} Odds ratio for 10 unit change

Table 2

Metal concentrations from Kriged value within 10 areas

Metal (n=646)	Range (mg kg-1 dw)	Mean (mg kg-1 dw)	Median (mg kg-1 dw)	EPA PRG-RSSL* (mg kg-1 dw)	% Samples exceeding EPA PRG-RSSL
As	0.2-22.7	3.3	2.9	0.4	99.2
Ba	2.4-348.0	49.9	39.0	5400	0
Cr	0.8-126.1	19.0	16.8	210	0
Cu	0.4-384.4	17.2	14.4	3100	0
Pb	1.7-1460.1	74.2	45.5	400	2.2
Mn	2.8-1553.0	180.4	109.8	1800	0
Ni	0-45.5	4.6	4.0	1600	0
Hg	0-4.9	0.1	0	23	0

* EPA Region 9 Preliminary Remediation Goals (PRG), residential soil screening level (RSSL) for non-cancer risk

Table 3
GAMM models to predict ID during each month of pregnancy and at four follow-up times after birth

Variables	Weeks	Baby sex (F vs M)	Parity	Alcohol (No vs Yes)	Residential Building age	Mom race (Other vs Black)	te(As)	te(Pb)	te(Hg)
Time									
Month1 (n=3806)	-0.049 (<0.001)	-0.344 (<0.001)	0.073 (0.004)	-0.714 (0.015)	0.002 (0.277)	/	1.000 (0.002)	/	1.603 (<0.001)
Month2 (n=6502)	-0.057 (<0.001)	-0.371 (<0.001)	0.067 (0.001)	-0.516 (0.012)	0.001 (0.116)	/	1.000 (0.011)	/	1.000 (0.001)
Month3 (n=8312)	-0.054 (<0.001)	-0.342 (<0.001)	0.064 (0.000)	-0.360 (0.044)	0.001 (0.107)	/	1.000 (0.029)	/	1.000 (0.033)
Month4 (n=9363)	-0.052 (<0.001)	-0.305 (<0.001)	0.065 (<0.001)	-0.299 (0.079)	0.001 (0.067)	/	/	1.000 (0.200)	1.000 (0.038)
Month5 (n=9867)	-0.060 (<0.001)	-0.314 (<0.001)	0.569 (0.001)	-0.211 (0.149)	0.001 (0.062)	/	/	1.000 (0.279)	1.000 (0.535)
Month6 (n=10051)	-0.058 (<0.001)	-0.309 (<0.001)	0.053 (0.001)	/	0.001 (0.069)	-0.140 (0.006)	/	1.000 (0.415)	1.000 (0.148)
Month7 (n=10046)	-0.040 (<0.001)	-0.326 (<0.001)	0.066 (<0.001)	/	/	-0.176 (<0.001)	/	1.000 (0.376)	1.000 (0.293)
Month8 (n=9302)	-0.017 (0.154)	-0.327 (<0.001)	0.071 (<0.001)	/	0.001 (0.078)	-0.219 (<0.001)	/	1.000 (0.810)	1.000 (0.409)
Month9 (n=7385)	-0.024 (0.154)	-0.299 (<0.001)	0.073 (<0.001)	/	/	-0.218 (<0.001)	/	1.000 (0.640)	1.000 (0.012)
Month10 (n=1862)	0.065 (0.082)	-0.431 (<0.001)	/	/	0.011 (0.042)	/	/	1.000 (0.428)	1.000 (0.110)
After birth 6 month (n=11038)	-0.056 (<0.001)	-0.326 (<0.001)	0.052 (0.002)	/	0.005 (0.017)	/	/	/	1.000 (0.057)
After birth 12 month (n=10551)	-0.057 (<0.001)	-0.359 (<0.001)	0.059 (0.001)	/	0.005 (0.014)	/	/	/	0.995 (0.009)
After birth 18 month (n=10535)	-0.062 (<0.001)	-0.358 (<0.001)	0.039 (0.025)	/	0.001 (0.044)	/	/	/	1.000 (0.015)
After birth 24 month (n=10365)	-0.066 (<0.001)	-0.396 (<0.001)	0.043 (0.016)	/	0.004 (0.062)	/	/	/	1.000 (0.031)

Note: Bold signifies statistical significance and / means the variable is not in the final model.