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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

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Abstract

This study was designed to evaluate the association between lead, mercury, and arsenic in the soil near maternal residences during pregnancy and mental retardation or developmental disability (MR/DD) in children. The study was conducted using 6,048 mothers who did not move throughout their pregnancies and lived within six strips of land in South Carolina and were insured by Medicaid between January 1, 1997 and December 31, 2002. The mother child pairs were then followed until June 1, 2008, through their Medicaid reimbursement files, to identify children diagnosed with MR/DD. The soil was sampled for mercury (Hg), lead (Pb), and As based on a uniform grid, and the soil concentrations were Kriged to estimate chemical concentration at individual locations. We identified a significant relationship between MR/DD and As, and the form of the relationship was nonlinear, after controlling for other known risk factors.

Keywords

Mental retardation/developmental delay; Soil arsenic; Maternal residence; Kriging; Nonlinear

1. Introduction

The most prevalent and permanent disability of childhood is mental retardation which occurs in 1-3 percent of all children. In the US the most widely used definition of MR is “Significant sub-average intellectual functioning existing concurrently with deficits in adaptive behavior, and manifest during the developmental period” (Luckasson et al., 2002). The term developmental delay (DD) includes children with a delay in development such as speech and language disorders, dyslexia, and reading and mathematics disorders (NCHS and CMS, 2007). According to the American Academy of Pediatrics (AAP), pediatricians have identified

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about 9 percent of children under the age of 36 months have a possible developmental problem, such as difficulty learning, communicating, playing, or performing physical activities or practical skills. In the US 16 to 18 percent of children (birth to age 18 years) have disabilities such as speech and language impairments, mental retardation, learning disabilities, and emotional and behavioral problems and some of the disabilities will disappear by the time the child is school age. Less than 3 percent of these children have persistent severe disabilities, such as mental retardation, autism, cerebral palsy, or serious vision or hearing problems (AAP, 2001). Many of the etiologic factors and pathologic mechanisms associated with MR and DD are not well understood and the actual causes remain unknown for approximately 50 percent of individuals with MR. A toxic exposure, such as chemical compounds containing lead, mercury, polychlorinated biphenyls (PCBs) and maternal EtOH use, is identified in 4-5 percent of cases with known cause, although it is possible that toxic exposures account for a substantial portion of the idiopathic cases (McDermott et al., 2007).

Developmental toxicants are agents that cause a host of maternal and fetal outcomes ranging from pre-implantation loss to mental retardation (MR) (Scorecard Pollution Information, www.scorecard.org/health-effects/). There is growing evidence of the association of environmental contamination and neurodevelopmental outcomes (Ming et al 2008; DeSoto 2009; Lianos and Ronco 2009; Vahter 2009; Palmer et al 2009). The Environmental Protection Agency (EPA) uses a categorization of overall weight of evidence to assess human reproductive hazards, the integrated risk information system, http://cfpub.epa.gov/ncea/iris/index.cfm.

Dose and timing of the chemical exposure are critical variables in predicting neurotoxic outcomes and in many cases human data are insufficient to make accurate assessments of chemical risk (Sullivan and Krieger, 2001).

Lead (Pb) has been the most widely studied neurotoxic substance with respect to neurodevelopmental disorders. Lead can cross the placenta beginning at 12 weeks of gestation, and it accumulates in fetal tissues (Baghurst et al., 1992; Tong et al., 1998; Wasserman et al., 1994; Wasserman et al., 1997). Pregnant women and children can absorb more ingested Pb (up to 70% is absorbed) than the general adult population (20% absorbed) (Sullivan and Krieger, 2001). A recent study explored the association between soil and blood concentrations of Pb in children, and the relationship was both curvilinear and significant (Mielke et al., 2007). Studies of pediatric Pb exposure and IQ suggest that the association between measured blood concentrations and IQ is also nonlinear, with the decline in IQ at even the lowest levels of exposure (Canfield et al., 2003; Bellinger and Needleman, 2003; Lanphear et al., 2005). Although the relationship between soil Pb and blood Pb concentrations and the relationship between blood Pb concentrations and IQ are shown to be nonlinear, the relationship between soil Pb concentrations and MR/DD has not been described.

The study of associations between inorganic chemical exposures during pregnancy and adverse child neuro-developmental outcomes has focused on inorganic lead (Pb) and organic mercury (Hg), although childhood exposure to arsenic (As) has also been shown to negatively impact neurological development of children (Filley and Kelly, 2001; Canfield et at., 2003; Goldman and Koduru, 2000; Wasserman et al., 2004; Factor-Litvak et al., 1999; Murata et al, 2007; Rosado et al, 2007).

There have been some studies describing levels of Hg and As in pregnant women and child health effects, although most studies have been in emerging and developing countries (Counter et al 2002; Zakharova et al 2002; Patel et al, 2005). Methylmercury can rapidly be transported to the fetal blood and all forms of Hg cross the placenta, however there are no published reports of maternal exposure to Hg in soil and neurodevelopmental outcomes in the child. The studies

of Hg and IQ have been primarily conducted in coastal communities where fish are consumed (Davidson et al., 2006; Axelrad et al., 2007).

There is substantial evidence that As crosses the placenta and studies have shown an increased risk of fetal death and impaired growth (Vahter 2009; Llanos and Ronco 2009). As in water has been associated with reduced intellectual functioning in children (Calderón et al., 2001; Wasserman et al., 2004), and recent studies have found that As levels in children's blood were associated with lower scores on tests of cognitive function (Wang et al., 2007; Rosado et al., 2007).

It is often assumed that urban areas are more contaminated than rural areas due to more sources of pollution (Aelion et al, 2008; Li et al 2004). However, rural soils also contain high concentrations of metals from natural geologic sources, pesticides, and industrial facilities. Principal component analyses (PCA) has been used by our group to analyze the commonalities of distribution, concentration and potential sources of metals in the soil. We found both Pb and Hg were derived primarily from anthropogenic sources corroborating results of Mooler et al (2005) and Rodriquez Martin et al (2006). Arsenic was associated with naturally occurring metals in two strips, it was grouped with Pb and Hg in one strip, with Pb in one strip, and with copper and chromium in one strip. This suggests that there is greater complexity associated with the distribution of As in soil and there are multiple sources (Davis et al, 2009).

The purpose of this study was to describe the relationship between soil levels of As, Hg, and Pb and the outcome of MR/DD for children whose mothers remained in one residential location during pregnancy. We first identified six strips of land which included both a cluster of MR/DD and a gradient of MR/DD risk from low to high, using a well documented Bayesian clustering algorithm. Then we sampled soil within the strips for the inorganic metals using a grid. The soil sample data were used to estimate the soil chemical concentration at each residential location using a Kriging method. We explored the associations of the Kriged values of soil concentrations of As, Hg and Pb with child MR/DD, controlling for confounders.

2. Materials and methods

2.1 Study population

The analysis of the relationship between soil concentrations of As, Pb, and Hg and the outcomes of child MR/DD relies on soil sampling information at the location where mother lived during pregnancy, controlling for maternal and child characteristics. The project was reviewed and approved by the state Medicaid agency, which provides insurance coverage for the poor mothers and children included in this study. 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 data.

The Medicaid inpatient and outpatient reimbursement files for women who were pregnant from January 1, 1996 though December 31, 2002, birth certificate data, and hospital and outpatient care for the child through May 2008 were merged. The identification of cases of MR and DD in this study included two important steps. The strategy was designed to identify all cases of MR and then exclude those that had a known genetic, infectious, injury, or alcohol-related cause of MR/DD. This allowed us to have a study group of maternal-child pairs for whom an inorganic chemical exposure could be a risk factor. The first step involved identifying infants and children with ICD9 code 317 (mild MR), 318 (moderate and severe MR), 319 (MR severity unspecified), 315.3-315.5 (language, coordination, mixed delay), or 315.8-315.9 (other specific delay and unspecified delay) in the Medicaid data file. Second, we identified a list of known causes of MR and DD and their ICD9 codes (McDermott et al., 2007). We excluded 245 babies with the following known causes of MR/DD: 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.

After the exclusion step, a dataset of mother-child pairs was created including 277 cases of unknown cause MR and 1,213 cases of unknown cause DD, totaling 1,490 cases of MR/DD (24.64%) within the six study strips. Addresses were obtained from a Medicaid eligibility file for each month of pregnancy, and these were geo-coded. We only included the mothers who had one residential address throughout pregnancy.

As a result, we had 6-12 years following birth to identify codes for MR/DD in the Medicaid record for 6,048 mother-child pairs within the six study strips which are described in the next section.

2.2 Strips of land for soil sampling

Six areas of residential land (strips) within South Carolina were selected for soil sampling based on a balance between having sufficient sample size to find differences in occurrence of the outcome and the ability to do the soil sample collection. These strips all contained a cluster of MR/DD. We computed the relative risk of MR/DD and the corresponding P-value for each geo-coded location, and the P-value was contoured as a heat image to identify the clusters. The procedure for cluster analysis is described by Zhen, Lawson, McDermott, Pande –Lamichhane and Aelion (Zhen et al., 2008). Each strip included a risk gradient (from low to high MR/DD risk) so that a range of outcomes would be included in the soil sampling mesh. This sampling area was defined as a strip, and latitude and longitude of the four corners of the rectangular strip area were identified. As is characteristic of South Carolina the strips included four small towns (1,550-15,000 residents) and two neighborhoods in small cities (40,000-56,000 residents).

The soil sampling procedure was previously described, and involved a process where the coordinates for each strip area were mapped and a uniform grid with 120 nodes was overlaid (Aelion et al., 2008; Aelion et al., 2009). Sampling at the grid nodes were approximately 1.0 to 3.0 km apart and some node points were inaccessible, for example, on building locations or water bodies, thus soil samples were collected as close to the grid node as possible. Samples were collected over a two week period in each strip and the six strips were sampled over an eighteen month period. 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; Aelion et al., 2009). Soil was collected for metals from 60 sites in Strip 1, 119 sites in Strip 2 and Strip 4, 114 sites in Strip 3 and Strip 6, and 120 sites in Strip 5. A total of 646 sample sites were used in the Kriging stage of the analysis.

At each sample site, a 30-g grab sample of topsoil was collected from 0 to 5-cm depth. The samples were stored on ice and refrigerated in the lab upon return. Duplicate samples were collected at 10% of the sampling locations for quality assurance and quality control purposes. After sampling, the soil was analyzed for As, Pb (EPA method 6010B), and Hg (EPA method 7471A) by an independent analytical laboratory (Pace Analytical, Huntersville, NC). Table 1 shows the As, Pb and Hg findings for the soil samples. Most notably, the distribution of As, Pb, and Hg in six strips is skewed to the lower values. The detection limit for each analyte varied but was approximately 0.5 mg/kg for As and Pb and 0.0055 mg/kg for Hg (Aelion et al, 2008). We substituted non-detectable values with half of the minimum detectable limit according to the EPA Guidance for Data Quality Assessment (EPA, 2000).

2.3 Statistical analysis

2.3.1 Kriging and cross validation—Due to issues of confidentiality of the South Carolina Medicaid data, neither the identity of the individuals nor the location of the residences was known for purposes of soil sampling. No soil was measured at a specific residence; instead a uniform grid was used to select where soil samples were collected. To connect the information between soil sampling and the Medicaid data base, we interpolated the grid sample measurements and predicted As, Pb and Hg concentration at mother's residence during pregnancy by Bayesian Kriging (Diggle et al., 1998; Diggle and Ribeiro, 2002, 2007) based on de-identified x-y coordinates. Let (Y_i,x_i), for $i = 1,\ldots,n$, denote the measurement of chemical concentration Y_i at the sampling location x_i. Following the Bayesian Kriging model defined by Diggle and Ribeiro (2002), we assumed Y_i given the underlying spatial process $S(x)$ are independent and follow normal distribution, which is expressed as $Y_i \mid S \sim N(\mu(x_i) + S(x_i), \tau^2)$, where $S(x)$ is a stationary Gaussian process with mean zero, variance σ^2 and exponential correlation through parameter φ; $\mu(x_i)$ is the expectation of the conditional distribution which is further modeled as a linear function along spatial coordinates with expression $\mu(x_i) = \beta_0 + \beta_1 x_{i\_latitude} + \beta_2 x_{i\_longitude}$; τ^2 is the classical nugget effect whose value was fixed in the setting. Non-informative prior distributions were set to parameters $(\beta_0,\beta_1,\beta_2,\varphi)$ and a reciprocal prior was set to σ^2. Based on an appropriate Box-Cox transformation of data, the posterior distribution for each parameter given data was estimated, and the estimated chemical concentration at mother's pregnancy residence was calculated from the predictive distribution. The estimated chemical concentration value was then transformed back to its original scale and merged with Medicaid data base. We conducted this process by *Krige.bayes* function of geoR library in R (Ribeiro and Diggle, 2001).

We used the leave-one-out cross validation (LOOCV) method to evaluate the quality of the prediction by Bayesian kriging. This method involved removing each datum in turn and then kriging at the location of the removed point using the remaining data. Two summary statistics were calculated: Mean error $(\mathrm{ME}=1/n \sum[\widehat{Y}_i - Y_i])$ and mean square deviation ratio $(\mathrm{MSDR}=1/n \sum\{[\widehat{Y}_i - Y_i]^2/\sigma_i^2\})$, where $\hat{Y}_i$ and σ_i^2 are the predicted value and the Kriging variance at location x_i. The ME should ideally be zero for unbiased estimation, and the MSDR is the mean squared deviation ratio of residuals with Kriging variance, whose value should be close to 1 if the model is correctly specified. These quantities are frequently used as a yardstick in cross-validation (Webster and Oliver, 2007; Aelion et al., 2009). We examined each chemical individually in each strip, and based on an appropriate transformation, the MSDR and ME were all close to reference. Overall, the results suggest that a high degree of accuracy was achieved.

2.3.2 Statistical Model—The contingency table is calculated between MR/DD and each of the mother and child covariates by using PROC FREQ in SAS (version 9.1). The covariates are mother's age at delivery, maternal race, alcohol use during pregnancy, gestational age, parity, child gender, and small-for-gestational-age (SGA) which is defined as < the 10th percentile birth weight for gestational age. The frequency and p-value of the association are reported.

To uncover the potential structure of the relationship between risk of MR/DD and concentrations of As, Pb, and Hg in the soil proximal to the maternal residence during pregnancy, we relaxed the usual parametric assumption and fitted a semi-parametric additive model by using the generalized additive model (GAM) (Hastie and Tibshirani, 1990; Wood, 2006). GAM is a general form of the generalized linear model (GLM), in which part of the linear predictor is specified in terms of a sum of smooth functions of predictor variables, and used in other related studies (Kim et al, 2007). In this paper, *gam* function with automatic

smoothness selection inside *mgcv* package of statistical software *R* was mainly used, and a complete guide about *gam* function is provided by Wood (2006).

The response variable MR/DD in these data is coded as 0 and 1, and it is assumed to be a random variable and follow a Bernoulli distribution with probability (MR/DD=1) = p. A set of covariates is available ($\{X_i\}_{i=1,\ldots,n}$) including both mother and child covariates and the Kriged concentration for soil chemicals. A semi-parametric model, of the following form, is considered:

$$\text{logit}(p_i)=\alpha_0 + \sum_{i=1}^{m}\alpha_i X_i + \sum_{i=m+1}^{n} f_i(X_i)$$

where n is the total number of predictors, and the first m predictors are assumed to be linearly associated with logit(p) by parameter α, which are also called *parametric terms*, and the remaining predictors are nonlinearly associated with responses, which are called *smooth terms*. The thin plate regression splines basis is set for each of the smooth terms. For continuous variable As, Hg, Pb, and child age at last follow-up, unadjusted smooth for each of them is estimated and plotted.

The generalized additive model we fitted under the binomial distribution is also a general form of logistic regression. We followed the variable selection strategy by Hosmer and Lemeshow (2000), performing variable selection through backward elimination by starting a full model with all categorical variables in the parametric terms and all continuous variables in the smooth terms. If the estimated degrees-of-freedom for a smooth term is close to 1, which essentially means the relationship is linear, we put it into the parametric terms. The backward elimination stops when the largest p-value in the model is less than or equal to 0.2, otherwise, the associated variable is considered as the candidate for elimination in the next step. Based on the likelihood ratio test from the models with and without the candidate, we further ensured the candidate could be removed safely. The likelihood ratio test is calculated as $LRT = -2(lnL_0 - lnL_1)$ where L_1 and L_0 are the likelihood from the model with and without the candidate. LRT approximately follows a Chi-square distribution. We made the decision by comparing LRT to the 95% quantile of the Chi-square distribution with k degrees-of-freedom, where k is the degrees-of-freedom associated with the candidate. If the LRT is smaller, we removed the candidate from the model one at a time. The main effects model was determined by backwards elimination first, and then two-way interaction terms among selected variables were investigated one by one, also based on LRT. The interaction between a smooth term and a parametric term was specified using a "by" variable in the *gam* function. For comparison, the final variable list was refitted by a logistic regression by assuming all the variables were parametric in *gam* function.

3. Results

The overall prevalence of the outcome MR/DD in the six strip area was 24.6% (4.6% MR and 20.0% DD) with 1,490 cases and 4,558 normal comparison children. The characteristics of the 6,048 mothers-child pairs are shown in Table 2. Those mother-child pairs with MR/DD were more likely to be African-American, advanced parity, male infants, gestational age ≤ 36 weeks, and infants who were SGA.

The continuous variables include the Kriged soil chemicals As, Pb, and Hg and child age at last follow-up (based on birth year children were 6-12 years old). The estimated unadjusted smooth function for each continuous variable was plotted in Figure 1. Significant non-linear relationships with the logit of MR/DD = 1 were found in As, Pb and child age with p-value < 0.001 and estimated degrees-of-freedom for smoothness are 7.7, 2.3 and 5.7 respectively. The estimated degrees-of-freedom is calculated based on the trace of the estimated smoother matrix, and it needs not to be an integer (Hastie and Tibshirani, 1990). The smooth function for Hg has the estimated degrees-of-freedom near 1, which indicates a linear relationship with the outcome. In Figure 1 the non-linear relationships are plotted. The y-axis is labeled as partial logit of MR/DD = 1, setting the estimated logit of MR/DD = 1 for one variable given all other parameters are zero. The spline of As has an irregular shape, but the increasing trend with estimated partial logit of MR/DD =1 over As can be found when As < 8 mg/kg and As >13 mg/kg. Spline of Pb has a quadratic shape, and the probability increases when Pb < 400 mg/kg, and then it starts to decrease with a wide confidence band. With estimated degrees-of-freedom near 1, the spline of Hg tends to be linear and there is a slight downwards trend. We put the spline functions with the parametric terms in the full model before the variable selection. The wider confidence band in the larger value of chemicals in As, Pb and Hg can be explained by the sparseness of data at larger values and the skewness of data. The estimated partial logit of MR/DD = 1 increases with child age, which indicates MR/DD is more likely to be diagnosed as children grow older.

Using the backwards elimination procedure, neither Hg nor Pb was retained in the model due to non-significant LRT, and we found no significant interactions among variables. Table 3 shows the parameter estimates for the variables that remain in the final model. For the parametric terms in Table 3, the interpretation of parameters is the same as the logistic regression, and we see that higher risk of MR/DD is observed in male infants, African-American mothers, infants born with < 36 weeks gestation, non-first-born, and SGA. There is also a significant difference in the strips, with Strip 3 and 6 having a significantly higher risk of MR/DD compared to Strip 1. There were differences in the characteristics of the six strips, such as land use, organic chemicals in the soil, quantity of residential and commercial structures, which were not included in the modeling. Therefore we added a strip variable (named Strip 1-6) in the GAM analysis to account for this variation. After controlling for all other variables, the spline of child age ($p < 0.001$) and As ($p = 0.006$) are significantly nonlinear with estimated degrees of freedom > 1.

In Figure 2, the two estimated splines were plotted with a 95% confidence band, with the y-axis being partial logit. The y-axis can be transformed to the probability of MR/DD by predicting the probability over a sequence of one variable given the values for all other covariates, but the pattern of the spline As and child age will be retained as in Figure 2. The spline of As has a very similar shape as the unadjusted one in Figure 1. For As < 8 mg/kg the logit increases steadily, for 8 mg/kg < As < 13 mg/kg there is a declining trend in logit, and for As > 13 mg/kg logit starts to climb rapidly. The spline of child age indicates that the older the age of a child in Medicaid, the more likely he/she is to be diagnosed with MR/DD, and the diagnosis of MR/DD stabilizes after 7 years old.

For comparison, in Table 4 we refitted the final variable list into a logistic regression model, in which As and child age are put into the parametric terms in the GAM model and hence their relationships with outcome are forced to be linear. When compared with Table 3, only slight change in the estimation of all other variables occurs, and overall As has a significant positive effect on MR/DD, that is, for every unit increase in As, the risk of MR/DD is $e^{0.06} = 1.06$ times higher and 95% CI for odds ratio is $(e^{0.02}, e^{0.1}) = (1.020, 1.105)$, and for every year older a child, it is $e^{0.247} = 1.280$ times more likely to be diagnosed with MR/DD. Although the logistic

regression model is easier to interpret, with the smaller AIC, the GAM model fitted the data better and captured the real pattern in the relationship.

4. Discussion

The most notable finding of this investigation is that we detected a statistically significant nonlinear relationship between soil concentrations of As and MR/DD. This association has not been previously reported in the literature. Another important finding was the null results for soil concentrations of Hg and Pb and MR/DD after controlling for other confounders. Although Mielke et al. (2007) found that soil and blood levels of Pb were associated, no significant association was found between Pb and the outcome of MR/DD in this study. This is probably due to the fact that the median soil Pb concentrations measured by Mielke et al. (2007) were more than 10 times greater than those measured in the current study.

It is important to note that the mean concentrations for As in all six strips were higher than the most conservative EPA Region 9 Preliminary Remediation Goals (PRG) residential soil limit (RSL) for carcinogenic risk of 0.39 mg/kg, and >70% of sample concentrations were greater than the RSL. However none of the samples were higher than the other health risk level of 22 mg/kg. For Strips 1, 2, 3, 4, 5, and 6 respectively, 25%, 45%, 11%, 92%, 92% and 48% of sample concentrations were greater than the As industrial soil limit (ISL) of 1.6 mg/kg. Principal component analysis (PCA) indicated that As has both natural and anthropogenic sources in the six strips, but it does not identify a specific source (Aelion et al, 2009). The PRG RSL for carcinogenic risk was 400 mg/kg for Pb and 23 mg/kg for Hg. And no sample had a concentration above this level from Strip 1, 2, 3, 4 and 6. Strip 5 had 11% of samples above a Pb level of 400 mg/kg.

These findings need to be interpreted in light of previous research that has shown in utero exposure to As has been associated with some teratogenic effects and neonatal death in laboratory animals and humans (Willhite and Ferm, 1984; Vahter 2009; Llanos and Ronco 2009). At higher soil concentrations of As there has been evidence of cognitive impairments in a large group of children ages 6-8 years (Rosado et al. 2007). However, concentrations of environmental chemicals in blood or urine reflect exposure from numerous sources, including air, water, food, soil, and dust, and the dose that has entered the body through ingestion, inhalation, or dermal absorption. We did not have measures of these other sources nor did we have blood or urine levels of the chemicals. It is known that the organic form of chemicals, such as methylmercury and methylarsonic, cross the placenta and are bioavailable (Davidson et al., 2006; Axelrad et al 2007; Vahter 2009; Llanos and Ronco 2009). This study was not able to address the speciation of the metals and whether the chemical was in an organic or inorganic form, since this requires costly laboratory testing. Instead we focused only on the association of soil Pb, Hg, and As soil concentrations and child outcomes.

Studies of the association between environmental chemical exposures during pregnancy and child outcomes require a large sample size and the ability to find and test children years after the exposure. While our study used 6,048 mother-child pairs, it did not involve individual contact with the study subjects and instead relied on merged secondary data. We did not have individual assessment of the outcome and the home environment of the family, nor did we have data on parent occupations and exposures, household exposures including lead paint, gardening practices and exposure to chemicals in other venues. Despite the reliance on secondary data, we had access to some confounders which are known risk factors for idiopathic MR/DD including male child gender, SGA, higher parity, younger gestational age, and older child age at last follow-up. We had 12 years of follow-up time for a diagnosis of MR/DD to be made for the children born in 1996 (n = 496), and 6 years of follow-up time for those born in 1996 -2001 (n = 308). Previous literature suggests the diagnosis of MR/DD peaks around age 9-11 years,

or at 5th grade (Pless, 1994). In our study, child age had a nonlinear association with MR/DD, and this relationship started to flatten at approximately age 7 years. In addition, it was reported that As in drinking water could lead to preterm birth (Ahmad et al., 2001) which could be in the causal pathway from As to MR/DD. We tested this by removing gestational age from our final model and refitting the data, and found no change of the pattern of As spline, which means gestational age is not a mediator in the model. By using the plug-in Kriged chemical concentration, we ignore the variation in the Kriged value itself, which could cause a potential bias. Such variation may be taken into account by a Bayesian approach through additional random effects.

We did not identify an association between Pb and Hg with the outcome of MR/DD in our study, although this relationship is well established. This is probably due to the low concentrations of these metals in the soil. Finally, we conducted our investigation in areas of high prevalence of MR/DD, (24.01%) and we used data only for mothers and children insured by Medicaid. Medicaid insures pregnant women in South Carolina if their income is under 185% of poverty level, and Medicaid covers children in families living below 150% of poverty level. Because of the income limits for Medicaid eligibility this study focused on the children with the highest risk for the outcome, so the results might not be generalizable to the entire population of pregnant women and their children (South Carolina Department of Health and Human Services website http://www.dhhs.state.sc.us). However, these limitations of our approach are balanced by its efficiency. In the future, it will be important to use other approaches so the pathway between exposure and outcome can be identified.

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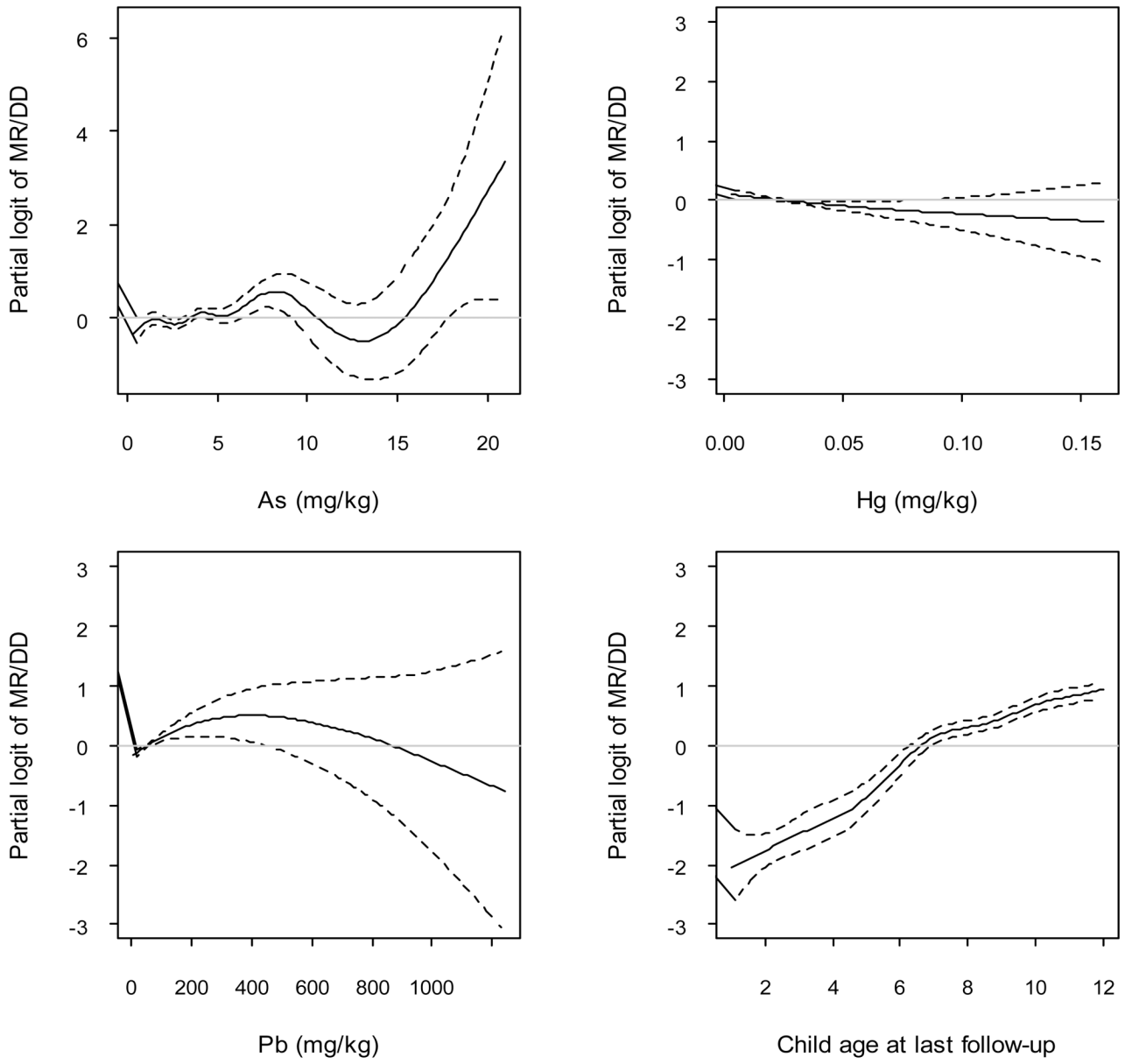
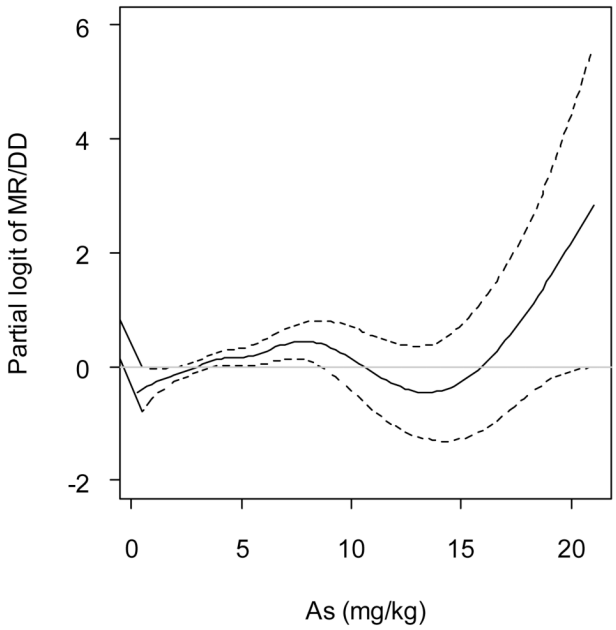
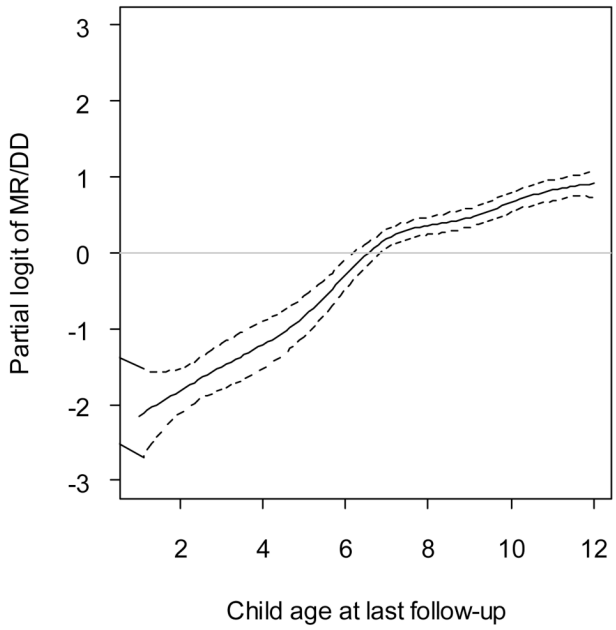


* MR/DD = mental retardation or developmental delay

Figure 1. Unadjusted smooth function (solid line) for As, Pb, Hg, and child age at last follow-up with 95% confidence interval (dashed lines)





* MR/DD = mental retardation or developmental delay

Figure 2. The estimated smooth function (solid line) for As and child age at last follow-up with 95% confidence interval (dashed lines) after controlling for other covariates

Table 1

Minimum, maximum, mean and median concentrations for As, Pb and Hg, and percent of samples below detection limit in six strips

Metal	Strip	# of sample	Minimum	Maximum	Mean	Median	% Samples below DL[2]
As (mg/kg)	1	60	ND[1]	6.4	1.30	1.10	17
	2	119	ND	20	2.00	1.50	7
	3	114	ND	7.4	0.97	0.95	27
	4	119	0.66	42.1	4.07	2.9	0
	5	114	ND	36.9	4.48	3.25	0.83
	6	120	ND	10.1	1.8	1.5	3.5
Hg (mg/kg)	1	60	ND	0.12	0.03	0.026	12
	2	119	ND	0.19	0.04	0.034	5
	3	114	ND	0.06	0.022	0.021	3
	4	119	ND	0.22	0.023	0.018	26.9
	5	114	ND	0.22	0.022	0.017	0.83
	6	120	0.0048	0.056	0.016	0.015	0
Pb (mg/kg)	1	60	2.1	53	12.14	8	0
	2	119	6.5	200	30.15	19	0
	3	114	1.6	140	17.14	11	0
	4	119	2.4	288	44.8	28.8	0
	5	114	0.9	1800	69.4	38.3	0
	6	120	1.7	314	25.6	14.8	0

[1] ND = not detected, and a value of half the detectable limit (DL) was used in Kriging.

[2] DL = detection limit.

Table 2
Characteristics of the mother child pairs (n=6048)

Variable	Level	Controls (n=4,558)	Cases [1] (n=1,490)	P-value[2]
		N (%)	N (%)	
Mother's age at delivery	18-34 years	3880 (85.1)	1250 (83.9)	0.456
	>34 years	137 (3.0)	45 (3.0)	
	<18 years	541 (11.9)	195 (13.1)	
Mother's race	White	2191 (48.1)	591 (39.7)	<0.001
	African-American	2235 (49.0)	771 (59.2)	
	Other	131 (2.9)	17 (1.1)	
Alcohol use during pregnancy	Yes	39 (0.9)	12 (0.8)	0.855
	No	4515 (99.1)	1476 (99.2)	
Gestational age (weeks)	> 36	3750 (86.6)	1156 (82.9)	0.001
	28-36	546 (12.6)	220 (15.8)	
	< 28	34 (0.8)	19 (1.3)	
SGA	Yes	628 (14.5)	227 (16.3)	0.109
	No	3699 (85.6)	1168 (83.7)	
Parity	0	2111 (46.3)	575 (38.6)	<.0001
	≥1	2447 (53.7)	915 (61.4)	
Child gender	Male	2123 (46.6)	948 (63.6)	<.0001
	Female	2435 (53.4)	542 (36.4)	

[1] Cases = MR/DD: mental retardation or developmental delay.

[2] P-value is based on Chi-square for two way table.

Table 3

Variables selected to be associated with MR/DD[1] by backward elimination[2] and parameter estimates by the GAM

Parametric terms	Level[3]	Estimate[4]	95% Confidence Interval	P-value[5]
Intercept		-1.408	(-1.738, -1.077)	<0.001
Child gender	Female	-0.783	(-0.916, -0.651)	<0.001
Mother's race	African-American	0.101	(-0.037, 0.238)	0.151
	Other	-0.750	(-1.314, -0.187)	0.009
SGA	Yes	0.232	(0.052, 0.412)	0.011
Parity	>= 1	0.288	(0.156, 0.421)	<0.001
Gestational age (weeks)	28-36	0.271	(0.088, 0.453)	0.004
	< 28	1.432	(0.749, 2.116)	<0.001
Strip	2	-0.085	(-0.441, 0.270)	0.638
	3	1.538	(1.142, 1.934)	<0.001
	4	0.122	(-0.238, 0.482)	0.506
	5	0.043	(-0.336, 0.423)	0.822
	6	0.663	(0.227, 1.098)	0.003
Smooth terms		**Est. d.f.**	**Chi-Square**	**P-value[6]**
Child age at last follow-up		5.4	311.2	<.001
As		5.9	19.0	0.006

*AIC = 5597.5 (Akaike Information Criterion)

[1]MR/DD: mental retardation or developmental delay.

[2]The eliminated variables include alcohol use during pregnancy, mother's age at delivery, Hg and Pb.

[3]The missing level of each categorical variable is the statistical reference group.

[4]The exponential of the parameter estimate is interpreted as odd ratio.

[5]P-value is based on t test.

[6]P-value is based on Chi-square test.

Table 4

Variables selected to be associated with MR/DD[1] by backward elimination[2] and parameter estimates by the logistic regression model

Variables	Level[3]	Estimate[4]	95% Confidence Interval	P-value[5]
Intercept		-3.568	(-3.890, -3.246)	<0.001
Child gender	Female	-0.780	(-0.912, -0.647)	<0.001
Mother's race	African-American	0.113	(-0.023, 0.250)	0.103
	Other	-0.716	(-1.277, -0.155)	0.012
SGA	Yes	0.244	(0.064, 0.423)	0.008
Parity	>= 1	0.297	(0.165, 0.429)	<0.001
Gestational age (weeks)	28-36	0.282	(0.099, 0.464)	0.002
	< 28	1.349	(0.699, 1.999)	<0.001
Strip	2	0.052	(-0.229, 0.334)	0.715
	3	1.538	(1.147, 1.928)	<0.001
	4	0.299	(0.049, 0.550)	0.019
	5	0.232	(-0.045, 0.51)	0.101
	6	0.740	(0.346, 1.135)	<0.001
Child age at last follow-up		0.247	(0.221, 0.272)	<0.001
As		0.060	(0.020, 0.100)	0.003

*AIC = 5637.6 (Akaike Information Criterion).

[1]MR/DD: mental retardation or developmental delay.

[2]The eliminated variables include alcohol use during pregnancy, mother's age at delivery, Hg and Pb.

[3]The missing level of each categorical variable is the statistical reference group.

[4]The exponential of the parameter estimate is interpreted as odd ratio.

[5]P-value is based on t test.