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Probability of intellectual disability is associated with soil concentrations of arsenic and lead

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ABSTRACT

Background: The association between metals in water and soil and adverse child neurologic outcomes has focused on the singular effect of lead (Pb), mercury (Hg), and arsenic (As). This study describes the complex association between soil concentrations of As combined with Pb and the probability of intellectual disability (ID) in children.

Methods: We used a retrospective cohort design with 3988 mother child pairs who were insured by Medicaid and lived during pregnancy and early childhood in South Carolina between 1/1/97 and 12/31/02. The children were followed until 6/1/08, using computerized service files, to identify the diagnosis of ID in medical records and verified by either school placement or disability service records. The soil was sampled using a uniform grid and analyzed for eight metals. The metal concentrations were interpolated using Bayesian Kriging to estimate concentration at individual residences.

Results: The probability of ID increased for increasing concentrations of As and Pb in the soil. The Odds Ratio for ID, for one unit change in As was 1.130 (95% confidence interval 1.048–1.218) for Pb was 1.002 (95% confidence interval 1.000–1.004). We identified effect modification for the infants based on their birth weight for gestational age status and only infants who were normal size for their gestational age had increased probability of ID based on the As and Pb soil concentrations (OR for As at normal weight for gestational age = 1.151 (95% CI: 1.061–1.249) and OR for Pb at normal for gestational age = 1.002 (95% CI: 1.002–1.004)). For normal weight for gestational age children when As = 22 mg kg^{-1} and Pb = 200 mg kg^{-1} the risk for ID was 11% and when As = 22 mg $kg^{-1}$and Pb = 400 mg kg^{-1} the probability of ID was 65%.

Conclusion: The probability of ID is significantly associated with the interaction between Pb and As for normal weight for gestational age infants.

1. Introduction

The most prevalent permanent disability of childhood is ID (previously referred to as mental retardation (MR)) which occurs in approximately 15.5 per 1000 children in the US (Bhasin et al., 2006). The most widely used definition of ID (or MR) in the US is "Significant sub-average intellectual functioning existing concurrently with deficits in adaptive behavior, and manifest during the developmental period" (Luckasson et al., 2002, p. 8). Many of the etiologic factors and pathologic mechanisms associated with ID are not well understood and the actual causes remain unknown for approximately 50% of individuals with ID (McDermott et al., 2007). A toxic exposure is identified in 4–5% of cases with known cause, although it is possible that toxic exposures account for a substantial portion of the idiopathic cases (Filley and Kellym, 2001; Ming et al., 2008; DeSoto, 2009; Llanos and Ronco, 2009; Palmer et al., 2009; Vahter, 2009). Lead (Pb), mercury (Hg), and arsenic (As) are developmental toxicants that have been associated with neurobehavioral dysfunctions and have been found to have adverse effects on intelligence in children. At low levels of exposure the impact seems to be subtle but at high doses these metals can cause ID (Goldman and Koduru, 2000; Sullivan and Krieger, 2001; Bellinger, 2006; Scorecard Pollution Information, 2008).

Lead has been the most widely studied substance with respect to neurodevelopmental disorders and ID. Lead can cross the placenta beginning at 12 weeks of gestation, and it accumulates in fetal tissues (Wasserman et al., 1994, 1997; Tong et al., 1998;

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Mielke et al., 2007). Pregnant women and children can absorb more ingested Pb (up to 70% is absorbed) than the general adult population (20% absorbed) (Baghurst et al., 1992). There is evidence the association between soil and blood concentrations of Pb in children is statistically significant (Bellinger and Needleman, 2003) and the association between measured blood concentrations and IQ is nonlinear, with the decline in IQ greater at lower levels of exposure (Goldman and Koduru, 2000; Lanphear et al., 2005; Axelrad et al., 2007).

There have been studies describing levels of Hg and As and neurobehavioral effects, however most have been in developing countries with high concentrations of Hg and As exposure (Counter et al., 2002; Zakharova et al., 2002; Patel et al., 2005). Although methylmercury can be transported to fetal blood and all forms of Hg cross the placenta, the documented neurodevelopmental outcomes in children have been identified in coastal communities where fish containing Hg are consumed (Davidson et al., 2006; Axelrad et al., 2007). There is no evidence that Hg is present in high concentrations in soil, nor is there evidence of an association between soil and blood concentrations.

There is substantial evidence that As is associated with an increased risk of ID (Vahter, 2009; Llanos and Ronco, 2009; Liu et al., 2010). Arsenic detected in a child's urine and As levels in children's blood were associated with lower scores on tests of cognitive function (Calderón et al., 2001; Wasserman et al., 2004; Wang et al., 2007; Rosado et al., 2007). Our research team has identified an association between As in soil and the combined outcome of ID and developmental delay, however there is no evidence of an association of As combined with other metals in soil and the outcome of ID (Liu et al., 2010).

The study of inorganic chemical exposures during pregnancy has mainly focused on the singular impact of Pb, Hg, and As, and has shown negative impacts on neurological development of children (Factor-Litvak et al., 1999; Counter et al., 2002; Wasserman et al., 2004; Patel et al., 2005; Murata et al., 2007; Vahter, 2009). Some studies have used direct measurement of maternal and child blood levels to estimate exposure, and cognitive and neurologic testing of children to assess the outcome. Other studies have used an indirect epidemiologic approach such as measurement of the distance from maternal residence to contaminated sites to estimate exposure. Parent report of neurodevelopmental disabilities for the child has been used to measure outcomes (Croen et al., 1997; Dummer et al., 2003; Langlois et al., 2009).

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 (Li et al., 2004; Aelion et al., 2008; Davis et al., 2009). 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. These levels of risk are benchmarks for safe exposure (EPA, 2000).

The approach used in our study represents a middle ground between direct measurement in individuals and ecologic associations in aggregate data, to identify associations of soil concentrations of metals and intellectual disability (ID) in children, from urban and rural residential neighborhoods. We utilized an innovative approach that includes spatial statistical methods (geocoding of maternal residences during pregnancy, measurement of soil for eight metals at grid locations, and Bayesian Kriging to estimate residential soil metal concentrations at residential addresses) combined with analysis of an interaction of exposure concentrations. We concentrated on the impact of As combined with the seven other metals, since there is sufficient evidence, in the literature and our previous work, to suggest that As is an important contributor to ID (Rosado et al., 2007; Wang et al., 2007). We used Medicaid data to capture the experience of low-income mothers and children, since it has been reported that children in poor neighborhoods are disproportionally impacted by environmental pollution (Bowen, 2002).

The purpose of this study was to answer the question: Are soil concentrations of metals proximal to maternal residence during pregnancy associated with the probability of ID in children? This question builds on the strong association of lead and ID in the literature, and in our previous work that showed a relationship between As and the combined outcome of ID and developmental delay. In this study we hypothesized the probability of having a child born with the more severe outcome of ID is associated with the soil concentrations of As combined with Pb.

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 one of six residential study strips during the sixth month of pregnancy. These women were followed through pregnancy and delivery and then longitudinally to see if their child received a diagnosis of ID. We merged the Medicaid reimbursement files for the mothers and children, birth certificates and the school and agency records for children's services through May 2008. As a result we had 8–12 years of follow-up time to identify codes for ID.

Medicaid is an insurance plan for people living under the federal poverty level, which combines state and federal funding. 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 the state. The Medicaid billing records of the women were followed throughout pregnancy and the children were followed from birth throughout early childhood, using a linked pregnancy file, birth certificate, Medicaid billing record for children, school, and service record from the state disability agency that identifies children with ID.

2.2. Identification of cases of ID

We started with 5617 mother–child pairs who lived in six strips of land where soil sampling was done, during the sixth month of pregnancy. The identification of cases in this study included four steps designed to identify confirmed cases of ID with an unknown cause. The first step involved identifying infants and children with an ICD9 code of 317 (mild MR), 318 (moderate and severe MR), or 319 (MR severity unspecified) in the Medicaid inpatient or outpatient records. Second, we identified a list of known causes of ID and their ICD9 codes (Center for Disease Control, 2007). 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. The third step excluded 1490 children with a diagnosis of developmental delay (ICD9 code 315) since it was not clear if these children belonged in the case or comparison group. The final step identified confirmed cases of ID with both a Medicaid diagnosis and a school placement for ID (or MR) or a record of eligibility determination by an agency that provides services for children with ID. We found that 44.3%, or 109 of the 246 cases of unknown cause ID identified by Medicaid, were confirmed cases. The final dataset included 3988 mother–child pairs, and 246 cases of ID who resided in the strips during the sixth month of pregnancy.

2.3. Geocoding of maternal residences

The study strips were dispersed throughout South Carolina, in rural and urban areas and each strip contained a low and high prevalence area for the outcome of ID. Addresses were obtained from a Medicaid eligibility file for each month of pregnancy and these 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. The coordinates of the grid nodes were provided to the soil sampler, not the actual residential addresses. The address of each residence was known by the investigators who did the statistical analyses.

2.4. Soil sampling and metal analysis

We selected strips of land, for soil sampling, that contained a cluster of ID. The procedure for cluster analysis is described by Zhen et al. (2008). Each strip included a risk gradient (from low to high ID risk) so that a range of outcomes would be included in the soil sampling mesh. The sampling area was defined as a strip, and latitude and longitude of the four corners of the rectangular strip area were identified for six strips. Each strip was approximately 105 km^2 in size and included an area that had a statistically significantly higher rate of ID than the state average for ID (Zhen et al., 2008). The six strips contained residential areas where pregnant women resided and included four small towns (1550–15 000 residents) and two small cities (40,000–56 000 residents).

We sampled soil within the strips using a grid and measured metal concentrations, and then explored the associations of the Kriged values of soil concentration of metals with the ID outcome. The coordinates for each strip area were mapped and a uniform grid was overlaid at locations 1.0–3.0 km apart. Some node points were inaccessible (e.g., on building locations or water bodies), so soil samples were collected as close to the grid node as possible. 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 60 nodes in Strip 1, 119 nodes from Strip 2 and Strip 4, 114 nodes from Strip 3 and Strip 6, and 120 nodes from Strip 5 (Aelion et al., 2009a,b). Duplicate samples were collected at 10% of the sampling locations for quality assurance and quality control purposes. After sampling, soil was analyzed for each metal by an independent analytical laboratory (Pace Analytical, Huntersville, NC). Data from a total of 646 sample sites were used in the Kriging stage of the analysis. The EPA soil screening level to protect against non-cancer effects for As is 22 mg kg^{-1} and for Pb it is 400 mg kg^{-1} (US EPA, 2009). The EPA soil screening level to protect against cancer is 0.39 mg kg^{-1} for As and 400 mg kg^{-1} for Pb (US EPA, 2009).

2.5. Kriging to assign chemical concentration at each residence

Although we sampled soil at nodes within six strips and had concentrations of As, barium (Ba), chromium (Cr), copper (Cu), Pb, manganese (Mn), Nickel (Ni) and Hg at each node, there is a misalignment between concentrations at soil sample sites and ID at 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, 2007) to get unbiased estimates of missing data, and used the measured chemical concentrations at the nodes to predict the unobserved values. Since the metal concentrations were highly asymmetric we used the Box–Cox transformation of these variables. By quantifying spatial variability through the covariance function, Kriging can produce maps of optimal predictions from incomplete and noisy spatial data (Banerjee et al., 2004). The model parameters were sampled from their posterior distributions with proper priors. This process was implemented by using the Krige.bayes function of "geoR" library in R (Ribeiro and Diggle, 2001). 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, 2007). The MSDR and ME were close to reference levels after transformation, indicating that Box–Cox transformation yielded a good approximation.

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 (EPA, US, 2000), since the non-detected rate was less than 15% for most of the metals. The detection limit for each analyte varied but was approximately 0.5 mg kg^{-1} for As and Pb, and 0.00055 mg kg^{-1} for Hg.

2.6. Covariate definitions

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), weeks of gestation (greater than 36 weeks, 28–36 weeks and less than 28 weeks), birth weight (greater than 2500 g, 1500–2500 g, and less than 1500 g), and small for gestational age (above 10% and below 10% for weight for weeks gestation). The standard for small for gestational age used the cut-points identified by Groom et al. (2007). The maternal covariates were maternal age (18–34, less than 18 years, and greater than 34 years). Maternal race was non-Hispanic white, non-Hispanic black and all 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 where the mother resided during the sixth month of pregnancy.

2.7. Statistical analysis

The hypothesis for this study was the probability of having a child born with ID is associated with soil concentrations of As and Pb for pregnant women. We started our analysis by exploring the Spearman rank correlation between each of the eight metal concentrations. The distribution of all the metals was skewed to the lower values and the highest correlation was 0.603 for As and Pb. Then we explored the association between the concentration of As and each metal with the risk of ID using the generalized additive model (GAM). GAM represents a method of fitting a smooth relationship between the response variable and an additive predictor through a scatter plot of data points. GAM does not involve strong assumptions about the relationship that is implicit in standard parametric regression since such assumptions may force the fitted relationship away from its natural path at critical points (Hastie and Tibshirani, 1990; Wood, 2006). We started with a full model that included the metals, and the infant and maternal variables. The categorical variables were considered linear terms

Table 1
Characteristics of the mother child Pairs (n = 3988).

		No ID (n = 3879)	Confirmed ID (n = 109)	Percent (confirmed ID)	Odds ratio[*] (confirmed ID)
Infant characteristics					
Infant sex	Girl	2095	32	1.50	
	Boy	1784	77	4.14	2.83(1.86–4.23)
Weeks of gestation	>36	3356	85	2.47	
	28–36	509	21	3.96	1.63(1.00–2.65)
	<28	14	3	17.65	8.46(2.39–29.99)
Birth weight (in grams)	>2500	3528	92	2.54	
	1500–2500	317	12	3.65	1.45(0.79–2.68)
	<1500	34	5	12.82	5.64(2.16–14.75)
Small for gestational age[a]					
	Above 10%	3312	89	2.62	
	Below 10%	567	20	3.41	1.31(0.80–2.15)
Maternal characteristics					
Mother's age	18–34	3302	93	2.74	
	<18	463	11	2.32	0.84(0.45–1.59)
	>34	114	5	4.20	1.56(0.62–3.90)
Mother's race	Non-Hispanic White	1761	34	1.89	
	Non-Hispanic Black .	2026	74	3.52	1.89(1.25–2.85)
	Other	91	1	1.09	0.57(0.08–4.21)
Parity	0	1775	40	2.20	
	1	1222	33	2.63	1.20(0.75–1.91)
	2	613	27	4.22	1.96(1.19–3.21)
	3+	269	9	3.24	1.49(0.71–3.09)
Tobacco use	No	3080	91	2.87	
	Yes	799	18	2.20	0.76 (0.46–1.27)
Alcohol use	No	3845	108	2.73	
	Yes	31	1	3.13	1.15(0.16–8.49)
Neighborhood characteristics		No ID (n = 3879)	Confirmed ID (n = 109)	P-value	Odds ratio
Density	Popn/sq. mile	1937.20	2115.35	0.23	1.01(1.00–1.02)[**]
Median age of residence	Years	40.45	42.83	0.03	1.02 (1.00–1.04)[***]
Metal concentrations in soil in mg kg^{-1}[***]					
Arsenic (As)		2.83	3.24	0.02	1.13(1.05–1.22)
Barium (Ba)		73.64	65.54	0.02	1.01(1.00–1.01)
Chromium (Cr)		21.77	19.71	0.07	1.02(0.99–1.03)
Copper (Cu)		16.53	14.02	0.02	1.03(1.01–1.05)
Lead (Pb)		67.94	55.99	0.05	1.00(1.00–1.00)
Manganese (Mn)		265.18	262.49	0.89	1.00(0.99–1.00)
Mercury (Hg)		0.03	0.03	0.59	0.04(0.00–99.0)
Nickel (Ni)		6.14	5.67	0.22	1.03(0.98–1.07)

[a] 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 100 unit change.
[***] Odds ratio for 10 unit change, odds ratio for one unit change.

and the continuous variables were considered smooth terms. We chose to investigate the smooth interaction of multiple predictors using the tensor product smoother since it is invariant to linear rescaling of covariates and computationally efficient. The "mgcv" package in R with automatic smoothness selection was used for GAM model fitting (Wood, 2006).

The binary response variable ID is assumed to follow a Bernoulli distribution with probability (ID = 1) = p. The covariates ($\{X_j\}_{j=1,\ldots,m}$) include both mother and child covariates and the Kriged concentration for soil chemicals. A semi-parametric model, $\text{logit}(p_i) = \alpha_0 + \sum_{j=1}^{s}\alpha_j x_{ij} + \sum_{j=s+1}^{m} f_j(x_{ij}) i = 1,\ldots,n, j = 1,\ldots,m$, was considered, where n is the sample size, m is the total number of predictors, and the first s predictors are assumed to be linearly associated with logit(p) by parameter α (parametric terms). The remaining predictors are spline terms which are nonlinearly associated with the ID outcome.

We explored interactions for the mother and child variables and identified effect modification for the relationship between infants who were in the lowest 10% of birth weight for gestational age category (Small for Gestational Age or SGA) and infants who were normal size for gestational age. Then we stratified our analysis by SGA level and put the interaction between As and Pb into tensor product smooth terms and used the backwards elimination procedure to find the final model for the two levels of SGA. We confirmed our results by using forward selection and found the interaction term of As and Pb remained significant. All candidate models (including main effect and interaction terms) were assessed via a ΔAIC > 2 entry criterion (Burnham and Anderson, 2002). Based on the final model, we created a 3D plot for male children, with mean values for gestational age, parity, and child age at last follow-up. The plot shows the concentrations of As and Pb against risk of ID, using wireframe function in the R lattice package.

3. Results

Table 2 shows the metal concentrations for the soil samples. All of the soil samples were below the EPA Regional Soil Screening Level (RSSL) for non-cancer hazard index for the metals. The mean concentration for As in all strips was higher than the EPA Preliminary Remediation Goals (PRG) residential soil sample limit (RSSL) for carcinogenic target risk of 0.39 mg kg^{-1}, and >70% of sample concentrations were greater than this level. 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 screening level

Table 2
Metal concentrations from soil samples at nodes within strips.

Metal ($n = 646$)	Range (mg kg^{-1} dw)	Mean (mg kg^{-1} dw)	Median (mg kg^{-1} dw)	EPA PRG-RSSL[a] (mg kg^{-1} dw)	% Samples exceeding EPA PRG-RSSL
As	0[b]–42.1	**2.6**	**1.8**	**0.4**	**94.3**
Ba	2.1–474.0	48.5	30.5	5400	0
Cr	1.0–590.0	15.8	9.6	210	0.2
Cu	0. 5–204.0	9.8	5.7	3100	0
Pb	0.9–1800.0	35.4	19.0	400	0.3
Mn	0–5100.0	209.4	110.0	1800	0.5
Ni	0–51.0	3.9	2.1	1600	0
Hg	0[b]–0.2	0.3	0.0	23	0

[a] EPA Region 9 Preliminary Remediation Goals (PRG), residential soil screening level (RSSL) for cancer risk.

[b] =Below reportable concentrations. A value of half the minimum detectable limit was used in statistical analyses.

(ISSL; 1.6 mg kg^{-1}). No other metal concentrations from Strip 1, 3, 4, and 6 were above the PRG RSSLs. For Strip 2, 3% of soils were above the Mn RSSL (1800 mg kg^{-1}), and 1% of Strip 5 soils were above both the RSSL and ISSL for Pb (RSSL 400 mg kg^{-1}/ISSL 800 mg kg^{-1}).

For the analysis of the impact of soil metal concentrations on _infants we deleted all cases where data were incomplete and this resulted in 3988 mother child pairs. The characteristics of these pairs are shown in Table 1. The overall prevalence of confirmed ID in the six strip areas was 2.73% with 109 cases and 3879 comparison children. Male infants were more than twice as likely to be diagnosed with ID, premature infants less than 28 weeks of gestation were at 8.5-fold risk, and very low birth weight babies (<1500 g at birth) were at 5.6-fold risk of ID. Mothers who were African–American were 90% more likely to have a child with ID, and those with two or more children were at twofold risk for having a child with ID. There was also a significant association with the outcome of ID with both older homes (possibly with Pb based paint) and density in the census block in which the mother lived. We explored the univariate association of the eight metals with ID, as shown at the bottom on Table 2. Four metals had a statistically significant relationship with ID-As, Pb, copper and barium. The odds ratio for As was the highest (O.R. 1.130 (95% Confidence Interval 1.048–1.218).

We mapped the concentration of As in each strip. Strip 5 is shown, as an example of one of the six strips, in Fig. 1. The concentration of As is overlaid with the location of ID cases (marked as X) and comparisons births (marked as 0). Strip 5 is 15.8 km (9.9 miles) long and 4 km (2.5 miles) wide. The irregular lines and oval areas display contours of concentrations of As, with a number showing the interpolated concentration of As.

We tested seven models that included an interaction between As and one metal as well as the main effects of the six remaining metals. The model with the lowest AIC value was the one with an interaction term for As and Pb. We then started with a full model that included infant, maternal, and neighborhood characteristics, Ba, Cr, Cu, Hg, Mn, Ni, and the interaction of As and Pb in a tensor product smooth term. Infants who were normal weight for gestational age had a statistically significant association for As (OR 1.151, 95% CI 1.061–1.249) and Pb (OR 1.002, 95% CI 1.000–1.004), whereas infants who were small for gestational age did not have a significant association for As and Pb with ID.

We modeled the relationship between the metals and the mother and child covariates to find the best fit with prediction of ID in children. Table 3 shows the parameter estimates for the variables that remain in the final model at the two levels of SGA. For the parametric terms in Table 3, the interpretation of parameters is the same as the logistic regression, and a higher risk of ID is observed in infants with younger gestational ages, male infants, women with more live born children, and for older children at last time for follow-up. These variables are well documented in the literature as predictors for ID. For SGA infants, after controlling for the covariates, the nonlinear tensor term for the interaction of As and Pb was not statistically significant ($p = 0.602$). However, when infants were normal weight for gestational age the nonlinear tensor term for the interaction of As and Pb was statistically significant ($p = 0.019$). When we included As and Pb as independent

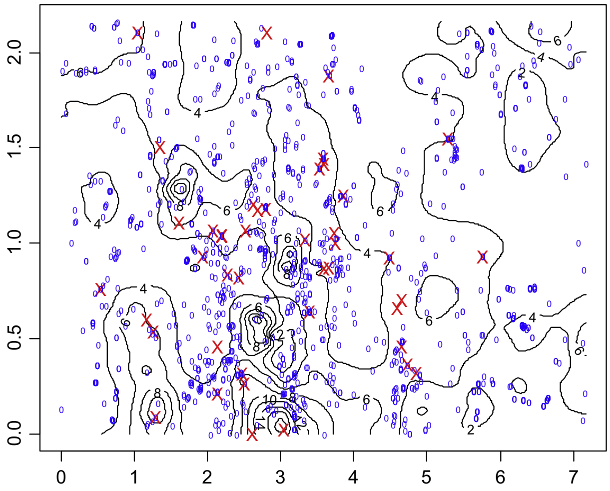

Fig. 1. Map of Strip 5* Contours of Arsenic Concentration and Location of ID and Comparison Children's Maternal Residence during Pregnancy. * Strip 5 is 15.8 km (9.9 miles) long and 4 km (2.5 miles) wide. One unit (1.0) on X axis = 1.15 miles; One unit on Y axis = 1.38 miles. Numbers imbedded in map are concentration levels of arsenic.

Table 3
The parameter estimates in the final model for month 6 of pregnancy, by gestational age status.

Variable	OR Est.	95% confidence limits		P-value
Small for gestational age infants				
Gestational age	0.749	0.624	0.899	0.002
Male infant	2.897	1.101	7.621	0.031
Parity	1.516	1.024	2.244	0.037
Child age at last follow-up	1.593	1.253	2.025	0.0001
	Est df	Chi sq		P-value
te(As, Pb)	4.038	3.304		0.602
Normal for gestational age infants				
Gestational age	0.902	0.834	0.974	0.009
Male infant	3.483	2.126	5.706	<.0001
Parity	1.186	1.000	1.406	0.049
Child age at last follow-up	1.366	1.241	1.505	<.0001
	Est df	Chi sq		P-value
te(As, Pb)	5.284	13.42		0.019

tensor terms, with the same covariates, neither one was statistically significant associated with ID.

Figs. 2a and 2b provides the smooth interaction of As and Pb, and is the 3D plot for male children who were normal weight for gestational age at birth (Fig. 2a) or were small for gestational age (SGA, Fig. 2b) at birth. Both figures show that as the concentration of As increases, the risk of ID also increases. For normal weight for gestational age children when As = 22 mg kg^{-1} and Pb = 200 mg kg^{-1} the risk for ID was 11% and when As = 22 mg kg^{-1} and Pb = 400 mg kg^{-1} the probability of ID was 65%. For small for gestational age infants there is not a statistically significant interaction between As and Pb.

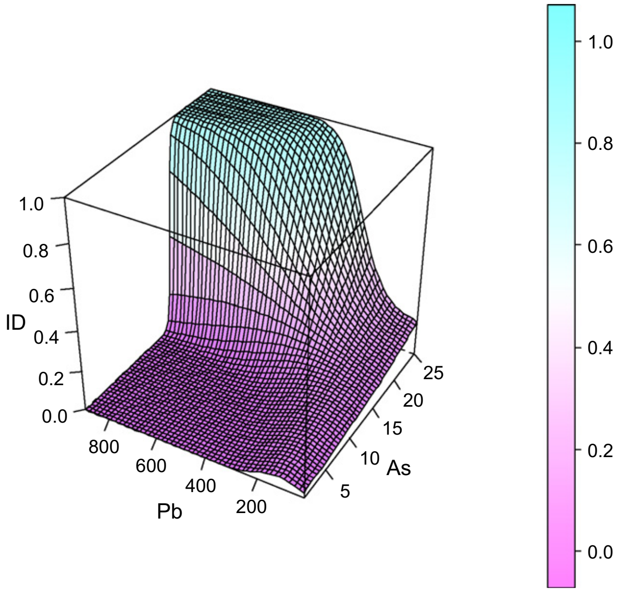

Fig. 2a. Three-dimensional plot of arsenic (As) and lead (Pb) and probability of ID, for male children, who were normal weight for gestational age at birth.

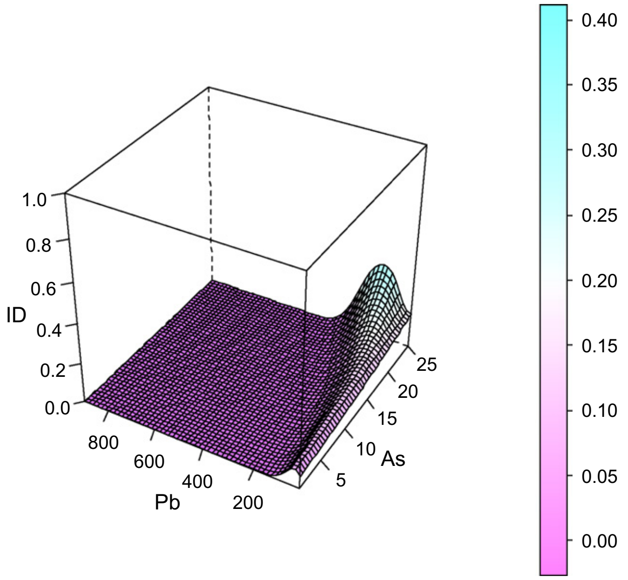

Fig. 2b. Three-dimensional plot of As and Pb and probability of ID, for male children, who were small for gestational age at birth.

4. Discussion

We detected a statistically significantly association between soil concentrations of As and Pb with validated ID in children who were normal weight for gestational age at birth. We used a novel approach that combined epidemiology with spatial statistics and environmental health sciences.

Arsenic is the only one of the eight metals sampled that was above the recommended residential soil screening level for carcinogenic risk in the majority of soil samples; therefore we focused on both the main effect of As and two-way interactions between As and other metals. The Kriging estimation of the soil concentrations of each of the chemicals is known as the best linear unbiased estimator of the true covariates. One of the properties of the Kriging estimation is that it assumes no measurement error is incurred. Since there are no covariates other than chemicals at the soil sample sites, it is reasonable to use the Kriging as an unbiased linear estimator for interpolating the chemical at the residential sites (Cressie, 1993). One way to deal with such a problem is to incorporate an additive measurement error or Berkson measurement error (Carroll et al., 2006) in the interpolated value. In the final model selected by AIC criterion, the effects of As and Pb on ID were estimated with adjustment of the other potential confounders, which provides interpretable associations between ID and As and Pb.

One of the limitations of our study was we could not distinguish between exposures that occurred in utero and those that occurred during early childhood, since we were not able to determine what proportion of mothers remained in the same residence during their child's early life. Although ID is usually a result of perinatal events, the time of diagnosis depends on the presentation of signs and symptoms of known syndromes and the observation of developmental delay in the developing child. Identification of ID contributes to its prevalence estimate, since the onset (incidence) usually occurs in utero. Previous literature suggests the diagnosis of ID peaks around age 9–11 years, or at 5th grade (Pless, 1994; McDermott et al., 2007). In this study the children were 6–11 years of age when our case identification for the ID diagnosis was carried out. We observed that child age had a nonlinear association with ID, and it started to level out at approximately age 7 years.

We did not have individual assessments 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 confounders for idiopathic ID including infant male gender, higher parity, younger gestational age at birth, and age of homes. This study does not suggest a mechanism of exposure, nor a critical time during pregnancy. Nor does this study address the specific source of exposure but instead focuses on the association of soil metal concentrations during pregnancy with child ID. Finally, we conducted our investigation in areas that include a high prevalence of ID (2.85%) and we used data only for mothers and children insured by Medicaid in South Carolina. Because this study focused on poor children with the highest risk for ID it is not possible to generalize the results to the entire population of pregnant women and their children.

Our findings can be interpreted in light of previous research that has shown in utero exposure to As is associated with some teratogenic effects in laboratory animals and humans (Willhite and Ferm, 1984; Unis et al., 2009). Our previous work found that As was associated with ID and DD in this study population (Liu et al., 2010). It is noteworthy that we did not find mediation in which an infant's birth weight for gestational age at birth (the variable: SGA) was an intermediate between As and Pb exposure and ID. Instead we identified effect modification, with only the normal weight for gestational age infants impacted. The fact that the association between the interaction of As and Pb and ID was not observed in SGA infants suggests that masking, or a collider effect, was occurring. SGA is thought to be the result of placental insufficiency, resulting in malnutrition of the developing fetus. The known risk factors for SGA include poor nutrition, tobacco smoking, alcoholism, severe maternal anemia and thrombophilia, pre-eclampsia, chromosomal abnormalities, maternal infections, and multiple births (Gardosi, 2006; Creasy et al., 2008). The factors associated with SGA are also risk factors for ID and it is likely that these factors took precedence over the As and Pb exposures.

For the normal weight for gestational age children, an interaction effect between soil As levels over 17 mg kg^{-1} and Pb levels over 400 mg kg^{-1} was identified. In fact, when we extended our modeling results to levels of residential soil Pb $\geqslant$ 600 mg kg^{-1} the probability of ID in the child, was over 99% when As concentrations in the soil were 21 mg kg^{-1} (Figs. 2a and 2b). Another study demonstrated a similar interaction between As and Pb on the central monoaminergic systems of the adult mouse (Mejía et al., 1997).

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. Our study used 3988 mother–child pairs but it did not involve individual contact with any of the study subjects and instead relied on merged secondary data. The results are compelling since we have shown a significant association between Kriged concentrations of soil metals (concentrations of As combined with Pb) proximal to maternal residences with ID in the normal weight for gestational age infants. Future studies are needed to focus on the biologic pathways between exposure and outcome and dose response relationships between As and Pb with ID.

Conflict of interest

None of the authors have a conflict of interest in terms of a personal or financial relationship that would bias their work. Funding for this research was provided by the NIH, NIEHS Grant No. R01 ES012895-01A1.

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