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Are different soil metals near the homes of pregnant women associated with mild and severe intellectual disability in children?

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Abstract

AIM—We explored the association of relatively low concentrations of metals in the soil proximal to maternal residence during pregnancy, with intellectual disability. We hypothesized different metals would be associated with mild versus severe intellectual disability.

METHOD—We used a mixed methods design, starting with a retrospective cohort from 1996–2002, of 10 051 pregnant mothers, soil sampling in the areas where these mothers resided during pregnancy, and follow-up of their children to determine if there was an intellectual disability outcome. We tested the soil and then predicted the soil concentration at the maternal homes, and modeled the association with the severity of the child's intellectual disability.

RESULTS—We found a significant positive association between mild intellectual disability and soil mercury ($p=0.007$). For severe intellectual disability, there was a significant positive association with the soil arsenic and lead ($p=0.025$).

INTERPRETATION—This is the first report of the differential impact of metals in soil and severity of intellectual disability in children. Soil mercury concentration in the area the mother lived during pregnancy is associated with significantly increased odds of mild intellectual disability; a combination of arsenic and lead is associated with significantly increased odds of

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Supporting information

The following additional material may be found online.

Appendix S1: Comparisons of percentage difference between ID group and no ID group

severe intellectual disability. These associations are present when controlling for maternal, child, and neighborhood characteristics.

Intellectual disability (previously classified as ‘mental retardation’) is a lifelong disability that affects performance in cognition and usually has its onset before birth. The most widely used definition of intellectual disability in the USA is: “Significant sub-average intellectual functioning existing concurrently with deficits in adaptive behavior, and manifesting during the developmental period.”¹ Significant sub-average intellectual functioning is operationally defined as two standard deviations (SD) below the mean on standardized IQ tests. IQ test scores are normally distributed with a mean of 100 (15 SD), so approximately 2.5% of the population has intellectual disability, defined as an IQ of less than 70 (with a standard error of 3 points). Within the category of intellectual disability, approximately 85% of individuals score in the mild range (IQ 50–70. Moderate intellectual disability is defined as an IQ of 35–49, severe intellectual disability, IQ 20–34, and profound intellectual disability an IQ of less than 20 (henceforth those with moderate to profound intellectual disability are referred to as having severe intellectual disability).²

The causes of intellectual disability are multifactorial and a single specific insult is only identified in a minority of cases. The risk factors for intellectual disability include biomedical, social, behavioral, and educational events that occur prenatally, perinatally, and postnatally.¹ Lead, mercury, and arsenic are developmental toxicants that are associated with lower intelligence test scores in children, even at low levels of exposure.^{3–9} There is substantial evidence that mercury and lead cross the placenta and accumulate in fetal tissues;^{10–15} however, though prenatal exposure to arsenic has been correlated with some adverse effects in fetuses, the mechanism for this has not been clearly elucidated.^{12,15} The reported exposure routes for pregnant women are oral (consumption of fish with mercury, hand to mouth consumption of lead), and dermatological (handling lead and arsenic).^{10,16–19} There is also evidence of a statistically significant association between soil and blood concentrations of lead and arsenic in children that is posited to occur through hand to mouth transfer of dust and metal residue on both indoor and outdoor surfaces that contain these metals.^{20–24} Elevated soil metal concentrations in urban areas have been associated with industrial and transportation sources and elevated rural soil concentrations of metals have been associated with natural geological sources, pesticides, and industrial facilities.^{24–27} However, there are no published reports that describe associations of different metals by severity of intellectual disability.

The US Environmental Protection Agency (EPA) sets two acceptable levels for human exposures to soils containing metals. The more stringent human health residential soil screening level is to protect against the risk of cancer.²⁸

The EPA also sets a higher soil screening level to protect against non-cancerous effects. These levels of risk are benchmarks for safe exposure.²⁸ Our group and others have posited that low-income pregnant women reside in sites where metal concentrations in the soil are within residential norms, but there are variations, and at these concentrations higher levels could contribute to higher risk for intellectual disability in their children. Longitudinal studies of low-income pregnant women living in areas where metal concentrations are

within acceptable EPA levels are needed to identify the adverse effects of metals at low concentrations on the intellectual disability.

This study adds an important element to the research on soil metal concentrations during pregnancy and child outcomes. Our research team has already identified an association between elevated arsenic levels in soil and the combined outcome of intellectual disability and developmental delay, and we have found the combination of higher levels of both arsenic and lead is associated with an enhanced risk for intellectual disability.^{29–34} At the onset of these analyses we did not know if arsenic and lead were equally associated with mild and severe intellectual disability and we did not know if another metal would emerge as significant after we stratified the outcome by mild and severe intellectual disability. Thus, we started our analyses by entering all the metal concentrations and other variables into the models, to explore independent effects, effect modification, and interactions. The approach used in the current study elaborates our previous work that utilized geocoding of maternal residences during pregnancy, measurement of soil for eight metals at regularly placed sampling locations, and Bayesian kriging to estimate soil metal concentrations at residential addresses, followed by analytical methods to identify associations between intellectual disability and the metals and other independent variables. 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 disproportionately affected by environmental pollution and the outcome of mild intellectual disability.³¹ The purpose of this study was to answer the question, Are different soil metals proximal to maternal residence during pregnancy associated with mild and severe intellectual disability in children?

METHOD

Study population

This was a retrospective cohort study of pregnant women who were insured by South Carolina Medicaid from 1996 through 2002 and resided in one of 10 residential study areas during the sixth month of pregnancy. The study received exempt status from the institutional review board of the University of South Carolina on the basis of de-identified data.

Study area 1 was the control area, without a cluster of high prevalence of intellectual disability, however, even in the control area there were cases of intellectual disability and variation in the measured concentrations of the metals. Each of the other nine study areas contained a cluster of a higher than expected prevalence of intellectual disability, based on a statewide average. We combined the data from the control area along with the data from the other study areas and there was a gradient of risk for intellectual disability from highest prevalence to lowest prevalence and variation in the soil metal concentrations in each of the ten areas. We merged the Medicaid reimbursement files for the mothers and children, birth certificates, and the school and disability agency records for children's services from January 1996 through March 2011. We used computerized records of administrative data to follow the women through pregnancy and delivery and then we followed the children until they were at least 9 years of age to see if they received a diagnosis of intellectual disability. In South Carolina pregnant women living below 185% of poverty (in 2000, 185% of poverty for a family of 4 was \$31, 542) during the study period were eligible for Medicaid insurance

until their child was 1 year of age and then the eligibility for continued insurance for mothers and children became 125% of poverty (in 2000, 125% of poverty for a family of 4 was \$21,312). South Carolina is a poor state; thus approximately 50% of the births during the study period, were insured by Medicaid.

Identification of cases of intellectual disability

We started with a statewide data set that included all births to Medicaid-insured mothers during the period January 1 1996 through December 31 2002. We eliminated twins and higher order multiples in our dataset and the subsequent births of mothers who had more than one birth during the study period. In our primary analysis we included all singleton births, in a final analysis however we used only the first birth. Throughout the study period the Medicaid data included International Classification of Disease, 9th revision (ICD9),² codes so there were no changes in the coding taxonomy. Since the study was designed to identify risk factors for unknown causes of intellectual disability we excluded 245 infants with the following known causes of intellectual disability using ICD9 codes: Trisomy 13, 16–18, other chromosomal aberrations, Prader-Willi syndrome, Rett syndrome, phenylketonuria, fragile X syndrome, postnatal injury, prenatal rubella, meningitis, encephalitis, and fetal alcohol syndrome,.

The data we used to identify cases of intellectual disability was based on having at least two ICD9 diagnoses of intellectual disability in the Medicaid file or a public school special education assignment to educable or mild intellectual disability (EMH), trainable or moderate intellectual disability (TMH), or profound and severe intellectual disability (PMH), or a diagnosis of mild, moderate, or severe intellectual disability in the state disability agency. The Medicaid file contains ICD9 codes for 317, 318, and 319 and this includes codes from physician, psychologist, occupational and physical therapists, and speech and language therapists. We also had codes from public school special education placement for EMH, TMH, and PMH. Finally we had a code from the disability service provider. The public school intellectual disability code was based on actual IQ and adaptive test scores from a licensed psychologist and the categories were mild (IQ 50–70), moderate (IQ 35–49), severe (IQ 20–34), and profound (IQ<20).

In cases when multiple diagnoses were made our decision rule was: (1) If there were at least two diagnoses of the ICD9 codes 317 to 319 and a public school placement code, we used the school placement code to assign severity: EMH placement is considered mild; TMH and PMH placement is considered severe; (2) If there were at least two diagnoses of 317–319 and a state disability agency code, we used the state disability placement code to assign severity; (3) If there were no school placement codes and no state agency codes, we used the ICD9 codes for 317 or 318 to override a 319 code; (4) If there were no school placement codes and no state agency codes, and there were multiple 317 and 318 codes we assigned the code most often used.

The case group included 104 children with an ICD9 code of 317 or EMH (mild intellectual disability), 258 children with ICD9 code of 318 or TMH or PMH placement (moderate, severe, and profound ID).² We also included 152 children with the ICD9 code of 319 in the unknown severity group; these cases were only included in the ‘any intellectual disability

group.’ The final dataset had 8 229 comparison children without intellectual disability, resulting in 8 743 mother-child pairs who resided in the nine case areas and one control area during the sixth month of pregnancy.

Study areas and geocoding of maternal residences

We identified nine geographical areas that contained a cluster of intellectual disability using cluster analysis and one control area as described by Zhen et al.³² The study areas were in both rural and urban areas of the state. Addresses were obtained from a Medicaid eligibility file for the sixth month of pregnancy and these were geocoded using ArcGIS version 9.3.

Soil sampling and metal analysis

The soil sampling was carried out using a grid overlaid in each of the 10 residential areas, instead of close to the maternal residences, in order to maintain confidentiality for the families. The soils were sampled from June 2006 to June 2011 when the children were 4 to 10 years of age. The latitude and longitude of the four corners of each of the 10 rectangular residential areas were identified. Each area was approximately 105km² in size and a uniform grid was overlaid at locations 1.0–3.0km apart. Global Positioning System (GPS) latitudes and longitudes were taken at each sampling location with a handheld GPS device (Garmin Etrex, Olathe, KS, USA) and soil was collected at 5cm depths.^{25–26} The metals from a total of 1092 sample sites were analyzed by an independent analytical laboratory (Pace Analytical, Huntersville, NC, USA) and these data were used in the kriging stage of the analysis.

Kriging to assign chemical concentration at each residence

After we obtained the concentrations of arsenic, barium, chromium, copper, lead, manganese nickel and mercury at each sample site we used Bayesian kriging and the R software to estimate the soil sample concentrations at the geocoded maternal residential sites.^{35–37} Thus, after the kriging we had an estimate for each metal at each maternal residential area. 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.³⁸ The non-detected rate was less than 15% for most of the metals. The detection limit for each metal varied but it was approximately 0.5mgkg⁻¹ for arsenic and lead, and 0.00055 mgkg⁻¹ for mercury.

Covariate definitions

The covariates 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 age, sex, weeks of gestation (>36 weeks, 28–36 weeks, and <28 weeks), birthweight (>2500g, 1500–2500g, and <1500g), and small for gestational age (above 10% and below 10% for the confidence interval for weight for weeks’ gestation).³⁹ The maternal covariates were maternal age (18–34, <18 years, and >34 years); race/ethnicity (non-Hispanic white, others); parity (0, 1, 2, and 3 or more); and tobacco and alcohol use (yes or no on medical record or birth certificate). We added two census block level characteristics 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. Finally, we created a variable for each of the study areas since the characteristics of these areas differed in ways we could not measure.

Statistical analysis

The hypothesis for this study was that soil concentrations of different metals are associated with mild and severe intellectual disability, when each severity group is compared to the non-intellectual disability group. Our previous research used fewer areas of residence and no data about the severity of the intellectual disability; however we found an interaction between soil concentrations of lead and arsenic. Therefore in this study we had an a priori hypothesis that there would be an interaction between lead and arsenic, in association with the intellectual disability outcome. We did not hypothesize which metals would be significantly associated with mild and severe intellectual disability. We used two separate logistical models, the first to model mild intellectual disability versus no intellectual disability, and the second to model severe intellectual disability versus no intellectual disability, using SAS statistical software, version 9.2 (SAS Institute, Cary, NC, USA).

The distribution of all the metals was skewed to the lower values. We used the generalized additive model (GAM) to explore the associations between concentrations of each metal with the risk of intellectual disability. GAM does not involve strong assumptions about the relationship that is implicit in standard parametric regression since such an assumption may force the fitted relationship away from its natural path at critical points. The spline (or smooth) functions were used for the metals. The other variables were modeled to have linear effects. We chose to investigate the nonlinear interaction of the metals using a smoother product since it is invariant to linear rescaling of covariates and computationally efficient. The 'mgcv' package in R 2.13.1 software with automatic nonlinear (smoothness) selection was used for GAM model fitting.⁴⁰ We explored the association between the concentration of each metal with the risk of mild and severe intellectual disability using two GAMs. We explored 18 variables in the study: the spline function of the concentration of arsenic, lead, mercury, chromium, copper, nickel, manganese, and barium, gestational age at birth, sex of the child, child age at last follow-up, parity, race of the mother, mother's smoking status, mother's alcohol drinking status, population density of residential area, the average residential building age in the census block, and the area in which they resided.

The binary response variable (mild intellectual disability versus no intellectual disability, or severe intellectual disability versus no intellectual disability) is assumed to follow a Bernoulli distribution with $\Pr(\text{intellectual disability}=1) = p$. The covariates ($\{X_j\}_{j=1, \dots, m}$) include both mother and child demographical information and the kriged concentration for soil chemicals. A semi-parametric model, $\text{logit}(p_i) = \alpha_0 + \sum_{j=1}^s \alpha_j x_{ij} + \sum_{j=s+1}^m s_j(x_{ij})$, $i = 1, \dots, n$, $j = 1, \dots, m$, was used, where $s(\cdot)$ is a smooth and possibly nonlinear function, n ($n=10051$) is the sample size and m ($m=18$) is the total number of predictors. The first s ($s=10$) predictors are assumed to be linearly associated with $\text{logit}(p)$ by a parameter vector α (parametric terms) and the remaining predictors (including all eight metals) are nonlinearly associated with the logit of the response (smooth terms). The backward elimination

procedure was used to identify the final parsimonious model. All the candidate models were assessed via $AIC > 2$ entry and $p < 0.10$ criteria.

RESULTS

The overall prevalence of intellectual disability for children insured by Medicaid in the state was 4.7% during the study period. In the nine case areas where we conducted this research the intellectual disability prevalence for Medicaid children was 5.9%. In the control area the prevalence was 3.2%. The control area data were combined into the dataset with the nine case areas since there was variation in the concentrations of the metals within the sample sites. The characteristics of the study group are shown in Table 1. The total sample size, including cases and comparison children was 8743. When we compared the children with mild intellectual disability and children with severe intellectual disability, to those with no intellectual disability, those with intellectual disability were significantly more likely to be male, less than 28 weeks' gestation at birth, less than 1500g at birth, and small for gestational age. Maternal risk factors associated with a child with intellectual disability included being less than 18 years old, races other than non-Hispanic white, and parity greater than one. It is noteworthy that there was variability in the rate of both mild intellectual disability and severe intellectual disability between the areas in which the mothers resided during pregnancy. Finally, the soil concentration for elevated mercury was significantly associated with mild intellectual disability and the soil concentrations for elevated arsenic and barium were significantly associated with severe intellectual disability. The comparisons of percentage difference with the confidence interval between intellectual disability group and no intellectual disability group under different categories of covariates are shown in the Appendix SI (online supporting information).

Table I shows the parameter estimates for the variables in the final GAM model. The variables in the final model are birth weeks, parity, age or residential building, the sex of the infant, mother's race, mercury, lead, and the interaction of arsenic and lead. Overall, the higher risk of intellectual disability is observed in the infants with earlier gestational age, parity, male sex, black mother, and older residential building age. We then modeled the relationship between intellectual disability and the metals, the mother, child, and neighborhood covariates to find the best predictors of the two levels of intellectual disability in children through variable selections. The sample sizes for each regression model were different, as shown in Table II.

Both the nonlinear term mercury ($p=0.006$), and the nonlinear interaction of arsenic and lead ($p=0.006$) were statistically significant in all levels of intellectual disability model after adjusting all other covariates. However, when we modeled the mild level of intellectual disability, the only metal that was statistically significant in the mild intellectual disability model was the nonlinear term mercury ($p=0.007$). Figure 1 shows the plot of the smoothed response of mercury to mild intellectual disability, adjusting for mother's race, weeks 'gestation, infant's sex, parity, age of building, mother's tobacco use, the smoothed lead, and the smoothed interaction of arsenic and lead. The risk of mild intellectual disability increases with increasing levels of mercury when the concentration is less than 2mgkg^{-1} . The slightly decreasing trend at high concentrations of mercury is due to the small number

of observations with higher concentrations in the data, which can be confirmed by the sparse distributions on the x axis and the much wider confidence intervals. Approximately 95% of the predicted variables fall within the gray area. The dashes on the x axis show the distribution of mercury values, which are skewed toward the low concentrations.

For the severe intellectual disability model the statistically significant association was with the interaction term of arsenic and lead ($p=0.037$) and the nonlinear term lead ($p=0.025$). Finally, because the interaction results for arsenic and lead are difficult to interpret we plotted the smoothed response of intellectual disability against both metals, shown in Figure 2. The figure illustrates the increasing probability of severe intellectual disability as the concentration of arsenic and lead increases. In order to show these relationship we had to hold some covariates constant; thus in Figure 2 we demonstrate the results for a female child, with a black mother, normal weeks' gestation, self-reported tobacco use, one other living child, building age of 46 years, and mercury at 0.01mgkg^{-1} . We observed a significant increasing impact of the interaction between increasing lead and arsenic with regard to the probability of severe intellectual disability. For example, with arsenic at 20mgkg^{-1} and lead at 58mgkg^{-1} the risk for severe intellectual disability was 1%; with arsenic at 20mgkg^{-1} and lead at 344mgkg^{-1} , the risk of having severe intellectual disability was 12%; with arsenic at 24mgkg^{-1} and lead at 344mgkg^{-1} the probability of severe intellectual disability was 28%.

DISCUSSION

We believe this is the first study to investigate the association of a specific soil metal proximal to maternal residence during pregnancy and the impact on the severity of intellectual disability in children. The key finding is that elevated soil mercury concentration is associated with significantly increased odds of mild intellectual disability in the children and a combination of elevated lead and arsenic is associated with significantly increased odds of severe intellectual disability in the children. These associations are present when controlling for maternal, child, and neighborhood characteristics. The significance of the interaction of arsenic and lead (Table II) means that the risk of severe intellectual disability is different for the combination of different levels of arsenic and lead.

It has already been established that lead, arsenic, and mercury are neurotoxins and they interfere with central nervous system development including neural proliferation, cell migration, synaptogenesis, development of transmitters and receptors, myelination, and apoptosis.⁵ Lead, arsenic, and mercury neurotoxicity has been shown to have a substantial impact on the developing brain even at low exposures.^{4,8} Because bioavailability can vary depending on the type of soil, and the specific metal and its speciation, the total metal concentrations were used in this analysis. It is also important to recognize the importance of epigenetical effects, including DNA methylation and histone proteins that affect gene expression, have been identified following maternal exposure to metals during pregnancy.^{41–43} These mechanisms need to be considered to understand the biological plausibility of the association we have identified.

This study does have a number of limitations. First, we did not measure the actual exposure of pregnant women to soil metals. Instead we used a less invasive approach that used soil concentrations of metals to explore associations with the outcome. Second, we relied on secondary data for the outcome variable and the covariates. The main exposure variables, the metal concentrations in soil, were directly measured but the other variables were obtained through Medicaid billing files, birth certificates, or school records. We did not measure children's IQ or examine any individuals. We used the ICD9 codes in the Medicaid file, public school records, and receipt of services from the state disability service agency, to ascertain the outcome of intellectual disability. The public school system and the disability service agency require a formal psychological assessment with IQ testing before a child is eligible for special education classes or intellectual disability-related services. In order to increase the specificity of our case definition we limited cases to those identified in the public school or the service agency records or diagnosed with intellectual disability on at least three occasions in the Medicaid file. Third, we did not study the entire state population of pregnant women; instead we only used Medicaid mother-child pairs since they are the most vulnerable to the risks for intellectual disability. Fourth, we did not have access to all the variables associated with lower socioeconomic status, such as maternal education and access to prenatal care, thus there was undoubtedly some residual confounding and our findings may not be generalizable to middle- and upper-income families or to other geographical areas outside of the southern USA. The datasets also contained missing values for almost all of the variables and this could cause bias since there are different proportions of missing values. Finally, there are measurement errors caused by kriging, which could affect the results. In order to determine the standard error of the kriged concentrations, we randomly split the sample into three parts and used two-thirds of the data to predict the third group. For mercury the standard error is 0.378, which was calculated based on the retained one-third of observed values ($n=365$) and the kriged predicted concentrations. We believe the test set error is probably an overestimate of error for a model built on the full dataset ($n=10,051$), and this error is not large enough to have an impact on the interpretation of our findings.

One of the biggest strengths of this study was the availability of data on the severity of intellectual disability. We had codes for mild intellectual disability (either ICD9 317 or public school placement in a class for EMH). For severe intellectual disability we also had codes (ICD9 318 or public school placement in a class for TMH and PMH). Another strong point was our soil testing for metals in areas where pregnant women resided and our use of kriging of the concentrations for each maternal address during pregnancy. This is an innovative way to estimate exposure since surface soils accumulate long-lived contaminants deposited from air and applied to soils over time, and metals are generally long-lived and environmentally stable. Thus, our approach assumes people track soil and dust into their homes, where it accumulates.^{44–46} Third, studies confirm that metals in soils are bioavailable to humans. Metals have been measured in children exposed to metal-contaminated soils^{45,46} including lead in blood of children residing in areas with high soil lead concentrations^{18,45–50} and arsenic in urine of individuals exposed to arsenic from soil.^{51,52}

Our analytical method allowed us to take into account potential non-linearity in the relationships between soil metal concentrations and the outcome intellectual disability. We controlled for a number of potentially important mother, infant, and neighborhood factors, and we also had a variable for the area in which the women resided to account for some uncontrolled confounding. And we excluded children with birth defects, chromosomal conditions, or other diagnoses known to be causes of intellectual disability, so our findings are directly relevant for the approximately 50% of cases of intellectual disability that do not have known causes.

Additional epidemiological study in different geographical and socio-economic groups is needed to test our findings. In addition, basic science and translational research are needed to provide a better understanding of the potential mechanism(s) whereby soil metal concentration may affect fetal brain development. An understanding of the mechanisms underlying the observed association is necessary for the development of effective preventive interventions for women who are, or desire to become, pregnant.

CONCLUSIONS

We found in areas where residential soil metal concentrations did not exceed EPA standards, that higher soil mercury concentrations where the mother lived during pregnancy is associated with significantly increased risk of mild intellectual disability in the child. A combination of higher concentrations of soil arsenic and lead are positively associated with significantly increased risk for severe intellectual disability in the children, when controlling for maternal, child, and neighborhood characteristics. This study did not explore the mechanism of exposure so the only preventive strategy that could reduce risk associated with contaminated soil would be removal of shoes and hand-washing when people go indoors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

EMH	Educable or mild intellectual disability
EPA	Environmental Protection Agency
GAM	Generalized additive model
GPS	Global Positioning System
PMH	Profound and severe intellectual disability

TMH Trainable or moderate intellectual disability

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What this paper adds

- Soil concentrations of arsenic and lead near the homes of pregnant women were positively associated with risk for severe intellectual disabilities in children.
- The association remained after controlling for maternal, child, and neighborhood characteristics.
- Soil concentrations of mercury proximal to maternal residence during pregnancy were positively associated with increased risk for mild child intellectual disability.

Figure 1.

Relationship between levels of mercury in soil samples taken from mothers' residence during pregnancy and mild intellectual disability in children. The plot is adjusted for mother's race, weeks of gestation, infant's sex, parity, building age, mother's tobacco use, smooth lead, and smooth interaction of arsenic and lead. Note: the dashes on the x axis show the distribution of mercury values.

Figure 2.

Three-dimensional plot of interaction of arsenic (As) and lead (Pb) and probability of severe intellectual disability. This plot illustrates the smooth interaction of arsenic and lead by fixing other variables: female children, black mother with normal gestational weeks, reported tobacco use, parity=1, building age=46 years, and Hg=0.01mgkg⁻¹. ID, intellectual disability.

Table 1

Characteristics of the mother child pairs ($n=8743$)

	No intellectual disability ($n=8229$)	Mild intellectual disability ($n=104$)	Severe intellectual disability) ($n=258$)	Odds ratio ^a (mild intellectual disability versus no intellectual disability)	Odds ratio ^a (severe intellectual disability versus no intellectual disability)	Odds ratio ^a (intellectual disability versus no intellectual disability)
Infant sex						
Female	4084	64	188			
Male	4014	40	70	0.64 (0.42, 0.94)	0.38 (0.29, 0.50)	0.51 (0.42, 0.62)
Missing	131	0	0			
Weeks of gestation						
>36	6661	84	202			
28–36	1063	13	38	1.03 (0.59, 1.94)	0.85 (0.60, 1.22)	0.67 (0.53, 0.86)
<28	25	2	8	6.54 (0.99, 25.38)	8.95 (3.58, 20.42)	9.92 (5.31, 18.42)
Missing	480	5	10	0.85 (0.27, 2.27)	0.58 (0.27, 1.13)	0.59 (0.36, 0.92)
Birthweight, g						
>2500	7220	87	206			
1500–2500	787	13	35	1.37 (0.73, 2.38)	1.56 (1.06, 2.22)	1.71 (1.31, 2.20)
<1500	91	4	17	3.65 (1.10, 8.98)	6.55 (3.71, 10.91)	9.92 (6.86, 14.18)
Missing	131	0	0			
Above 10%	6440	75	188			
Below 10%	1309	24	60	1.57 (0.97, 2.46)	1.57 (1.16, 2.10)	1.53 (1.22, 1.89)
Missing	480	5	10	0.89(0.31, 2.00)	0.71(0.35, 1.29)	0.86(0.55, 1.29)
Mother's age						
18–34	5591	66	166			
<18	2266	30	74	1.12 (0.72, 1.71)	1.10 (0.83, 1.45)	1.07 (0.87, 1.31)
>34	241	8	18	2.81 (1.23, 5.58)	2.52 (1.47, 4.05)	2.66 (1.83, 3.76)
Missing	131	0	0			
Mother's race						
Non-Hispanic, White	2566	24	62			
Black	5414	80	193	1.58 (1.02, 2.55)	1.48 (1.11, 1.99)	1.58 (1.29, 1.97)

	No intellectual disability (n=8229)	Mild intellectual disability (n=104)	Severe intellectual disability) (n=258)	Odds ratio ^a (mild intellectual disability versus no intellectual disability)	Odds ratio ^a (severe intellectual disability versus no intellectual disability)	Odds ratio ^a (intellectual disability versus no intellectual disability)
Other	115	0	3	0.00 (0.00, 0.76)	1.08 (0.26, 2.97)	1.14 (0.44, 2.44)
Missing	134					
Parity						
0	3990	42	109			
1	2306	32	68	1.32 (0.82, 2.09)	1.08 (0.79, 1.46)	1.22 (0.98, 1.51)
2	1115	22	50	1.87 (1.10, 3.12)	1.64 (1.16, 2.30)	1.64 (1.27, 2.10)
3 or more	687	8	31	1.11 (0.48, 2.24)	1.65 (1.08, 2.45)	1.72 (1.27, 2.30)
Missing	131	0	0			
Self-reported tobacco use						
No	6887	78	210			
Yes	1342	26	48	1.71 (1.07, 2.64)	1.17 (0.84, 1.60)	1.21 (0.96, 1.51)
Self-reported alcohol use						
No	7987	103	255			
Yes	91	1	3	1.17 (0.26, 20.78)	0.97 (0.36, 3.96)	0.72 (0.37, 1.62)
Missing	151	0	0			
Area	No intellectual disability (%)	Mild intellectual disability n (%)	Severe intellectual disability n (%)			
1	615 (96.7)	8 (1.3)	8 (1.3)			
2	147 (98.0)	1 (0.7)	2 (1.3)			
3	705 (95.9)	9 (1.2)	18 (2.4)			
4	1778 (94.3)	20 (1.1)	73 (3.9)			
5	1179 (94.5)	12 (1.0)	35 (2.8)			
6	529 (93.8)	11 (2.0)	14 (2.5)			
7	2504 (93.7)	22 (0.8)	79 (3.0)			
8	192 (90.6)	3 (1.4)	7 (3.3)			
9	444 (91.2)	14 (2.9)	12 (2.5)			
10	136 (87.7)	4 (2.6)	10 (6.5)			
Density	2752.1	2336.0	2872.2	1.00 (1.00,1.00)	1.00 (1.00,1.00)	1.00 (1.00,1.00)

	No intellectual disability (n=8229)	Mild intellectual disability (n=104)	Severe intellectual disability (n=258)	Odds ratio ^d (mild intellectual disability versus no intellectual disability)	Odds ratio ^d (severe intellectual disability versus no intellectual disability)	Odds ratio ^d (intellectual disability versus no intellectual disability)
45.60	44.58	54.14	1.00 (0.98,1.01)	1.00 (1.00,1.00)	1.00 (1.00,1.00)	
3.3 (1.6, 4.2)	3.0 (1.5, 4.0)	3.6 (2.1, 4.4)	0.53 (0.19, 1.31)	1.72 (1.03, 2.77)	1.36 (0.93, 1.96)	
49.9 (21.9, 72.7)	48.1 (17.1, 74.1)	55.1 (24.2, 82.7)	0.98 (0.93, 1.04)	1.04 (1.01, 1.07)	1.00 (0.98, 1.03)	
18.9 (8.4, 25.03)	18.7 (5.1, 25.1)	19.3 (10.7, 25.3)	0.99 (0.85, 1.12)	1.02 (0.93, 1.10)	0.99 (0.93, 1.06)	
17.0 (7.45, 20.6)	16.9 (5.7, 23.1)	17.7 (9.8, 20.2)	0.99 (0.86, 1.11)	1.03 (0.95, 1.10)	1.02 (0.96, 1.08)	
73.4 (25.0, 85.3)	75.7 (25.4, 88.8)	74.2 (30.8, 96.9)	1.00 (0.98, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	
181.1 (62.1, 256.7)	169.2 (60.2, 256.9)	186.8 (73.0, 276.3)	1.00 (0.98, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)	
4.6 (2.3, 5.9)	4.5 (1.7, 6.4)	4.7 (2.6, 6.3)	0.94 (0.52, 1.57)	1.14 (0.81, 1.57)	0.92 (0.70, 1.18)	
0.1 (0.02, 0.04) ^d	0.2 (0.02, 0.05) ^d	0.1 (0.01, 0.04) ^d	401 (5.72, 1324)	0.36 (0.003, 1.73)	14.0 (1.16, 133)	

^b Use of 10th centile based on Groom et al. 2007.

^a crude odds ratio, when there is only one predictor in the model;

^c odds ratio for 10 unit change

^d The large mean of Hg seems strange but it is correct because the distribution of Hg is heavily skewed to the right.

EPA Regional Screening Levels (RSL) for residential soils (mgkg⁻¹) for Carcinogenic Target Risk (CTR) = 1E-06 and Noncancer Hazard Index (HI) = 1 for As are 6.1E-01 (carcinogenic screening level) and 3.4E+01 (non-carcinogenic screening level). Other metals have only non-carcinogenic RSL. RSL for residential soils (mgkg⁻¹) for HI=1 are: Ba 1.5E+04; Total Cr not reported; Cu 3.1E+03; Pb lead and Compounds 4.0E+02; Mn (Non-diet) 1.8E+03; Total Ni not reported; Hg (elemental) 1.0E+01

Table II

Adjusted generalized additive model for association of metals with mild, severe, and any intellectual disability

Variable	Mild ID versus no ID (mild ID=104; no ID=8229)				Severe ID versus no ID (severe ID=258; no ID=8229)				Any ID versus no ID (any ID=514; no ID=8229)			
	Estimate	Standard error	p		Estimate	Standard error	p		Estimate	Standard error	p	
Weeks	-0.0597	0.0376	0.112		-0.084	0.023	<0.001		-0.124	0.015	<0.001	
Parity	0.043	0.084	0.604		0.133	0.050	0.008		0.124	0.037	<0.001	
Building age	-0.002	0.006	0.779		0.001	0.001	0.077		0.001	0.001	0.10	
Infant sex (F vs M)	-0.426	0.209	0.042		-1.022	0.147	<0.001		-0.680	0.010	<0.001	
Reported tobacco	0.707	0.265	0.008		0.228	0.179	0.205		0.291	0.131	0.027	
Mother race												
(Black vs non- Hispanic white)	0.736	0.275	0.007		0.317	0.165	0.054		0.420	0.121	<0.001	
(other vs non- Hispanic white)	- 1.320e+02	6.313e+06	1.000		0.048	0.604	0.937		0.185	0.435	0.671	
	Est df	χ^2	p		Est df	χ^2	p		Est df	χ^2	p	
te (As, Pb) ^a	0.524	1.005	0.153		7.018	12.996	0.037		1.368	6.073	0.006	
te (Hg) ^b	2.224	11.176	0.007		2.767	3.806	0.286		1.641	9.964	0.006	
te (Pb)	1.001	0.919	0.338		1.790	7.303	0.025		1.008	3.105	0.079	

^aTensor (smooth) function of combined effect of arsenic (As) and lead (Pb);^bSmooth function for mercury (Hg); **Bold type** indicates statistical significance. ID, intellectual disability.