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Adverse neurodevelopmental effects and hearing loss in children associated with manganese in well water, North Carolina, USA

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Abstract

Aim—Heavy metals such as manganese, arsenic and lead can act as neurotoxins. There have been few human studies of neurobehavioral/neurodevelopmental effects of arsenic and manganese on children in the United States. Since 1998, North Carolina has tested all new private wells for manganese, arsenic and lead. This study was conducted to evaluate adverse neurodevelopmental effects (delayed milestones, speech/language disorders and hearing loss) in children and metal concentrations in well water.

Methods—A quasi-regression model of the number of children (0–35 months of age) with adverse neurodevelopmental effects as outcome measures and aggregate mean metal concentration (arsenic, lead, and manganese) in private well water in each county as exposures.

Results—Over 70,000 private well water samples from 1998 to 2011 were analyzed for metal content. From 2008 to 2011, an average of 17,000 children was enrolled in the Infant Toddler Program. On average, 1.7% of children in this age range in each county had a speech/language disorder, 0.24% had a diagnosis of delayed milestones, and 0.026% had a diagnosis of hearing loss. The county mean manganese concentration was significantly and positively associated with the prevalence of delayed milestones and hearing loss in the children. No association was found for metal concentrations and speech/language disorders.

Conclusion—This ecological study indicates that further investigation of manganese in well water and associated neurodevelopmental health outcomes in children is needed.

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Keywords

Delayed milestones; hearing loss; manganese; neurodevelopment; well-water

INTRODUCTION

The brains of fetuses, infants, and children are susceptible to the accumulation of excess metals, leading to the development of adverse neurological disorders characterized by both central nervous system (CNS) and neurobehavioral disturbances [1–4]. Many studies have found that exposure to lead (Pb) or arsenic (As) may cause adverse cognitive and behavioral effects in children [5–8]. In addition, exposures to various chemicals including Pb, mercury, organic solvents and pesticides have been associated with hearing loss [9–12].

Manganese (Mn) is a natural element found in rocks, soil, water, and food. Manganese is considered an essential nutrient in all living organisms, involved in the formation of bone and in amino acid, lipid, and carbohydrate metabolism. However, intake of high levels of Mn may cause adverse health effects. The epidemiological evidence of toxic effects for occupational inhalation and food-related overexposure to Mn are well documented [13–15]. Studies of adverse effects from Mn in drinking water have been limited because it was assumed that homeostatic regulation of essential nutrients was protective and prevented their accumulation to toxic levels [13,16]. In addition, water intakes of Mn are generally considered minor compared with intakes from food [17]. However, it is now thought there are differences in the uptake of Mn from water ingestion relative to food.

A number of studies have found associations between elevated Mn in drinking water and detrimental effects on academic achievement, cognitive function, including short-term memory, attention, manual dexterity, non-verbal memory, and visuoperceptive speed in children [18–27]. Ingestion of Mn in water, at concentrations previously thought to be safe, may lead to neurotoxic effects in fetuses, infants, and children [18,28–30].

Approximately 42% (4 million) of the North Carolina (NC) population relies on groundwater as a source of drinking water [31]. The U.S. Environmental Protection Agency (EPA) health reference value for Mn in water is 300 μg/L [17] while the current health-based standard for Mn in NC drinking waters is ≤ 200 μg/L. These health advisories, both federal and state, are not enforceable standards for action but instead describe nonregulatory concentrations of the contaminant in water that are expected to be without adverse effects on health. The World Health Organization (WHO) recently discontinued the drinking-water guidelines for manganese [32]. The U.S. EPA maximum contaminant level (MCL, an enforceable federal standard) for arsenic in drinking water is 10 μg/L and for lead is 15 μg/L [33].

To explore possible impacts of the ingestion exposure to Mn, As and Pb in groundwater on young children (0–35 months of age) in NC, a county-level ecologic study was conducted to determine if there is an association between groundwater Mn, As and Pb levels and adverse neurodevelopment (speech and language disorders, hearing loss, and delayed milestones).

METHODS

Outcome Measures

The study population was children referred to and enrolled in the NC Infant-Toddler Program (ITP) during 2008–2011. The ITP serves approximately 5% of NC children aged 0–35 months. To enter the ITP, children are referred to their local Child Development Services Agency (CDSA). There are 18 CDSAs serving the 100 counties in NC. Children are eligible for the program based on having a diagnosis of an established condition known to be associated with a high probability of delayed milestones, or through testing that determines that delayed milestones currently exists for the child in one or more of the following five areas: cognitive, physical (including gross and fine motor), communication, social/emotional, and adaptive.

Specific conditions through which a child may be deemed eligible in the established conditions category are as follows: Congenital anomaly/genetic disorders/inborn errors of metabolism; congenital infections; autism; attachment disorder; hearing loss; visual impairment; neurologic disease/central nervous system disorders; neonatal conditions and associated complications.

The evaluation of the child is multidisciplinary and includes: Administration of agency approved, standardized, norm-referenced testing instruments which evaluate multiple developmental domains; interview with parents/family to take the child's history; identification of the child's level of functioning in each of the developmental areas; gathering of information from other sources such as family members and other caregivers, medical providers, social workers, and educators, if necessary, to understand the full scope of the child's unique strengths and needs; and review of medical, educational, or other records. A child is eligible if he or she demonstrates a delay in one or more of the five developmental areas, as measured by appropriate diagnostic instruments and procedures administered by qualified personnel. Informed clinical opinion given by qualified personnel may also be used as an independent basis to establish a child's eligibility even when instruments do not establish eligibility.

Once a child is determined eligible, parental consent is needed to provide services. For the time period under review, about 45% of referred children were found eligible and enrolled in the program, with an additional 3% eligible but declining enrollment. Once the parents have consented to services, an Individualized Family Service Plan is developed, and at this point the child is considered "enrolled" in the ITP.

Children with a "developmental speech or language disorder," "delayed milestones," or "sensorineural hearing loss" were included in this analysis. Classifications were made using the International Classification of Disease, 9th edition codes 315.31, 315.32, 315.34, 315.35 and 315.39 for developmental speech or language disorder, 783.42 for delayed milestones, and 389.1–389.3 for hearing loss. These codes were abstracted from the ITP's database, the health information system (HIS). The HIS is used by the ITP to bill for services provided to enrolled children. The HIS was queried for any child who had at least one relevant code for any of their billed services during 2008–2011.

Each child was associated with the county in which they first enrolled in the ITP. Counts were aggregated by county. Due to the very low percentage of the population using well water (2.3%) and the unavailability of billing data for the Mecklenburg County CDSA, as it does not bill through HIS, it was excluded, leaving 17 CDSAs (which included the remaining 99 NC counties) for our analysis.

Additional aggregate variables abstracted from the ITP database included the total number of children aged 0–35 months in each county. The percentage of children who are black or Hispanic was obtained from the U.S. Census Bureau [http://quickfacts.census.gov/qfd/states/37000.html]. The ratio of the number of children enrolled in the ITP in each county per year and the number of total children in the county was obtained from HIS. The percentage of extremely low birth weight (<1,000 g) births by county in 2010 was obtained from the NC State Center for Health Statistics [http://www.schs.state.nc.us/]. Information on the number of doctors by county was obtained from the North Carolina Health Professions Data System [http://www.shepscenter.unc.edu/hp/prof2011.htm]. The percentage of persons below the poverty level was obtained from the U.S. Census Bureau [http://quickfacts.census.gov/qfd/states/37000.htm].

Exposure Assessment

Mn, As, and Pb levels in private wells were measured using well water samples collected by environmental health officials in each county and analyzed by the NC State Public Health Laboratory [Table 1]. The geographic distribution of detectable metals in private wells follows a pattern similar to the geologic deposits found in the Carolina Slate Belt for As and Mn more so than for Pb. Lead is not believed to be associated with geological deposits in this area, but may be related to local anthropogenic influences such as well construction materials. The concentration of each metal was calculated as the average of county private well samples from the period 1998–2011 [Figure 1].

As recommended by the U.S. EPA [http://www.epa.gov/reg3hwmd/risk/human/info/guide3.html], non-detected results were set at one-half the sample detection limit (detection limit was 30 μg/L for Mn, 1 μg/L for As, and 5 μg/L for Pb). The percentage of county residents on well water was calculated using the 2010 census for total county population and the USGS Estimated Use of Water in the U.S County-Level Data for 2005 for “Domestic, self-supplied population” [http://water.usgs.gov/watuse/data/2005/].

Statistical Methods

A quasi-Poisson regression model was used to compare three outcomes (the number of children with delayed milestones, speech/language disorder, or hearing loss) with aggregate mean metal concentrations in private well water by county. The quasi-Poisson regression was used rather than a Poisson regression to account for “over-dispersion.”

Y_i was denoted as the number of cases in county i, and Ni as the number of children in county i. Y_i was assumed to have mean $N_i\lambda_i$, where λ_i is the relative risk for county i. The log relative risk includes the county’s mean concentration of Mn, As, or Pb and six county covariates: percentage Hispanic (“Hisp”) and black populations; the percentage of households that use well water (“PctWell”); the percentage of extremely low weight births

("PctELWB"); the number of doctors in the county ("NumMD"); and the percentage of poverty in the county. Table 2 shows the numerical summaries of the values for the 99 counties used in the study. These covariates were included because they have previously been shown to be associated with the responses of interest [34]. The sources for these variables are given above, in the outcome measures and exposure assessment sections.

$$\log(\lambda i) = \beta 0 + \beta 1 \mathrm{Hispi} + \beta 2 \mathrm{Blacki} + \beta 3 \mathrm{PctWelli} + \beta 4 \mathrm{PctELWBi} + \beta 5 \mathrm{NumMDi} + \beta 6 \mathrm{Pct\ Pov} + \beta 7 \mathrm{Metali}$$

All covariates were centered and scaled to have mean zero and variance of one, so that $\exp(\beta_j)$ is interpreted as the relative risk corresponding to an increase of one standard deviation unit for covariate j. Three models were calculated that included a single metal [Tables 3 and 4], three metals simultaneously [Tables 3 and 4], and three metals with pairwise interactions between the three metals [Tables 3 and 4]. The level of significance was set at 0.05. Statistical analysis was performed using the glm function in the software package R (R Foundation for Statistical Computing, Vienna, Austria. 2012).

RESULTS

From 2008 to 2011, the annual average number of children aged 0–35 months living in NC was 376,163. The annual average number of children enrolled in ITP (children with active service plans at any point in the year) was 17,000. The average age of children enrolled in ITP services at the 17 CDSAs was 1.6 years: 13% were <12 months old, 27% were 12–<24 months of age, and 60% were 24–35 months old. By race, 21% were black and 79% were non-black. By ethnicity, 16% were listed as Hispanic. Of the children enrolled in ITP, 21% of the population lived in poverty. The average percentage of NC households using private wells as a source of drinking water was 24%. The percentage of the population using private wells by county ranged from 1.2% to 88.2% of households [Figure-1].

Laboratory samples collected from 1998 to 2011 [Table-1] included 73,220 wells for Mn, 72,290 wells for As, and 82,195 wells for Pb. The majority (69.5%) of the tested wells had non-detectable levels of the metals. The number and percentage of wells with detectable levels of Mn was 22,400 (31%), the number and percentage of wells with detectable levels of As was 8,362 (12%), and the number and percentage of wells with detectable levels of Pb was 11,309 (14%). For As, 2.6% of wells were greater or equal to 10 μg/L and for Pb, 6.4% of wells were ≥15 μg/L (U.S. EPA MCLs). For Mn, 7.9% of wells were ≥200 μg/L (NC health advisory level) and 5.2% of wells were ≥300 μg/L (U.S. EPA health advisory level).

Table 1 summarizes the concentrations of all wells in the state and is included to give information about the nature of the data before aggregation, such as range of values and the percent above the detection limit. All regression analyses used the county-level summaries of concentrations presented in Table 2.

Prevalence rates for delayed milestones, speech/language disorder, and hearing loss are shown in Figure 2. The average statewide prevalence of speech/language disorders was 1.7% of children 0–35 months of age (range of 0.2–6% by county). The average statewide

prevalence of delayed milestones was 0.24% (range of 0–2% by county). The average statewide prevalence of hearing loss was 0.026% (range 0–0.289% by county).

The mean county concentration of Mn in private wells was significantly and positively associated with the prevalence of delayed milestones (log relative risk 0.39; 95% confidence interval: 0.18, 0.61). This is equivalent to a 48% increase in the risk of delayed milestones [exp(0.39)=1.48] corresponding to a one standard deviation unit increase in the county's average private well Mn concentration. The mean county As and Pb concentrations were not associated with the prevalence of delayed milestones [Table 3].

No interaction was observed between the mean county metal concentrations and delayed milestones, and delayed milestones was not associated with any of the other variables included in the model.

No associations were observed between the prevalence of speech/language disorders and the mean county Mn, As or Pb concentrations in private wells individually or in combination [Table 4]. The only variable consistently associated with speech/language disorder was negative associations with the percentage of the population living in poverty [Table 4].

No associations were observed between hearing loss and mean county As or Pb concentrations. However, an increase in the mean county Mn well water concentration was associated with an increase in the prevalence of hearing loss (log relative risk 0.14, 95% confidence interval: 0.03, 0.026) [Table 5]. This is equivalent to a 15% increase in the risk of hearing loss (exp(0.14)=1.15) corresponding to a one standard deviation unit increase in the county's average private well Mn concentration.

DISCUSSION

Manganese (Mn) is a common contaminant found in drinking water wells. In the U.S., a recent national survey found that 12% of wells tested had levels of Mn above the U.S. EPA recommended human health advisory level of 300 μg/L [35]. The frequency of detection and concentration of Mn in well water varied across state aquifers [http://pubs.usgs.gov/sir/2011/5059/pdf/sir2011-5059_report-covers_508.pdf]. This study found that 5.2% of wells in NC had levels above 300 μg/L.

Research indicates that ingestion of Mn may cause adverse cognitive and neurobehavioral effects in infants and children [23,26,27,36–38]. A recent study found that exposure to even low levels of Mn in water (arithmetic mean of 99 μg/L, geometric mean of 20 μg/L), commonly encountered in North America, to be associated with poorer neurobehavioral performance in children [30].

The current study encompasses a younger age group than other studies. This study found that as the average concentration of Mn in private well water in a county increased, the rate of delayed milestones in that county also increased in children 0–35 months of age enrolled in the NC ITP. This is consistent with other studies evaluating associations of well water manganese concentrations with adverse neurodevelopmental effects [18,22,26,36,37].

Other studies have found that exposure to Pb or As may cause adverse cognitive and behavioral effects in children [6–8]. However, Hamadani et al [38] did not find an adverse effect of pre or postnatal As exposure on child development at 18 months, and Tofrail et al [39] did not find an effect on infant development of As exposure at 7 months. A significant effect of average Pb or As concentration on the prevalence of delayed milestones was not observed in this current study.

The synergistic effect of metals on cognitive and behavioral function has been evaluated in other studies. Many studies have found a positive interaction between Mn and Pb [40–42] or Mn and As [43], although this interaction was not found in one study of adolescents [44]. In contrast, Wasserman et al [27] studied children 8–10 years of age consuming well water which was stratified by As and Mn concentrations. They found that As and Mn levels in the childrens' blood were each negatively and significantly related to most Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV) subscale scores, but Mn-by-As interactions were not significant. The current study did not find any interaction between average county levels of Mn and As, Mn and Pb, or Pb and As and prevalence of delayed milestones. The lack of interaction noted in this study may be due to water quality characteristic differences in aquifers. The pH, redox potential, prevalence of other divalent cations and organic matter in the well water may affect the bioavailablity and thus toxicity of these other metals, and aquifer systems differ across the country. In addition, this study did not account for other potential exposure sources such as ingestion of lead found in dust from paint or blinds in older homes, or lead or arsenic from food intake such as rice, juices, candies, or in toys or metal jewelry which infants may put in their mouth [45,46].

Solvents and heavy metals are often considered to have ototoxic effects [47–51]. Recent literature suggests an adverse effect of Mn exposure on the auditory system. Mn exposure, alone or in combination with excessive noise exposure, has been associated with effects on the vestibular-auditory system [52–55]. Mn caused significant damage to the sensory hair cells, peripheral auditory nerve fibers and spiral ganglion neurons (SGN) in cochlear organotypic cultures isolated from postnatal day three rats and caused significant loss and shrinkage of SGN soma [56]. The present study found an increase in the frequency of sensorineural hearing loss in counties that had an increased mean Mn concentration in the well water. Possible reasons why this study did not find an association with sensorineural loss and arsenic or lead in well water may include different thresholds at which adverse effects are manifested by each metal, different mechanisms of action, potentially different dose-response curves, different exposure concentrations relative to levels of potential effects, and different absorption characteristics based on the matrix where the metal is present (e.g. lead in water versus lead in paint chips or dust).

This study has certain limitations. It is important to note that not all children with delayed milestones or established health conditions are referred to the Infant-Toddler Program. Additionally, parents have a choice regarding services for their children, and not all families with a child found eligible choose to participate in the program; thus, not all cases are in the dataset, which could lead to selection bias. Also, definitions of delayed milestones vary by states and thus make it difficult to compare rates in NC to other states.

An important consideration for interpreting this analysis is the ecologic context; it cannot be used to infer causality between metal exposure in well water and health effects. The exposure variables are the mean metal concentrations in the county, and we do not have specific information about the wells of the children with the disorders of interest, or even information on the proportion of these children that use well water as the primary source of water. Our associations are based solely on the mean metal concentrations for all private wells tested in each county and the county-level early childhood program data. The mean metal concentration is assumed to be representative of all well-water-exposed children 0–35 months in the county in the ITP database. The wells tested in each county are primarily newly dug wells and were assumed to provide representative data for all well water supplies in the county. A well is constructed by a certified driller using prescribed drilling/casing methods that result in the well providing a consistent water sample representative of the groundwater source at the time it is collected. Since repeated private well water testing is often not performed, any remediation measures (e.g. filtration systems) implemented by the owner are not accounted for. Therefore, initial test results may not represent continued exposure levels. There is also the possibility of laboratory measurement errors for extreme or censored values.

CONCLUSION

This ecologic analysis is consistent with recent research finding adverse neurobehavioral/neurodevelopmental and neurocognitive effects in children. There are plausible mechanisms to explain neurotoxic and ototoxic effects of Mn, and there is coherence between epidemiological findings and experimental research in non-human primates. The results of this study add to the growing literature that adverse effects may occur in children at levels below the current U.S. EPA primary standard for manganese in drinking water. WHO and U.S. EPA should revisit current standards or recommended levels in drinking water.

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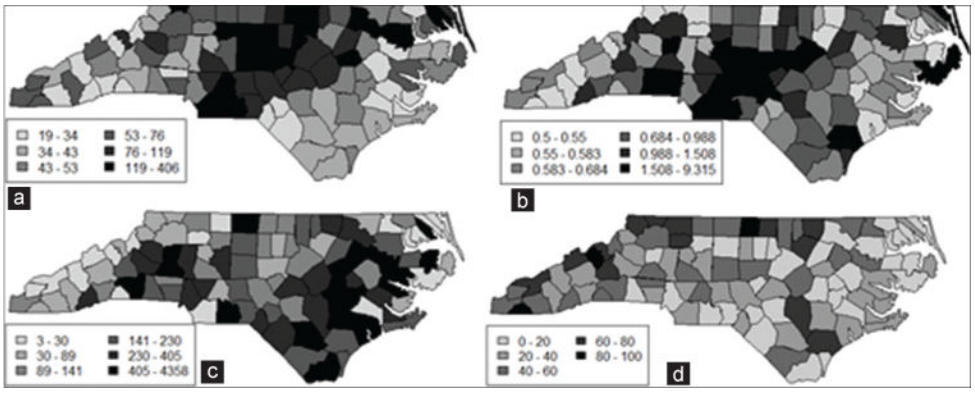

Figure 1.

Maps of the county mean concentration of manganese, arsenic, and lead, and the percentage of households in each county that use well water, (a) Manganese (μg/L), (b) Arsenic (μg/L), (c) Lead (μg/L), (d) Percent that use well water (%)

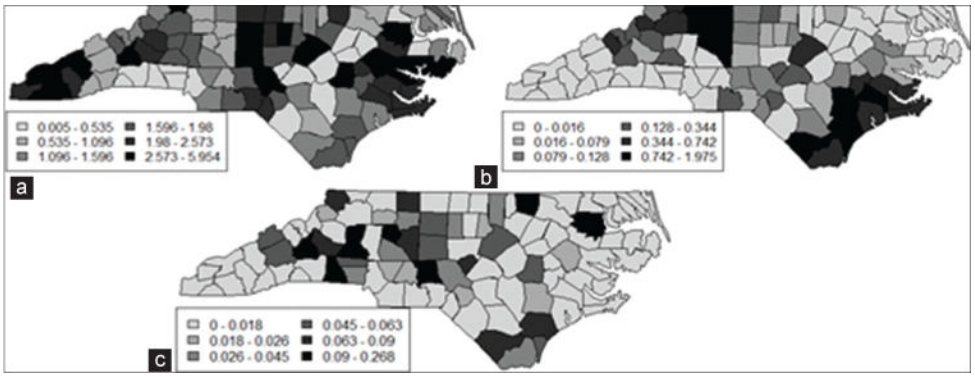

Figure 2.

Maps of disorder rates by county, (a) Speech/language disorder (%), (b) Delayed milestones (%), (c) Hearing loss (%)

Table 1

Number of observations and mean, standard deviation, and maximum (μg/L) for manganese, arsenic, and lead in well water in all counties combined in North Carolina from 1998 to 2011

	Arsenic	Lead	Manganese
Number of wells (excluding missing values)	72,290	82,195	73,220
Number above detection limit	8,362	11,309	22,400
Percent above detection limit	12	14	31
Mean concentration	1.55	162.91	82.02
Standard deviation	8.11	2,491.88	469.34
Maximum	806	300,000	46,300

* Metal concentrations represent the means of all wells and are not separated by county

Table 2

Numerical summaries of values for the variables used in the analysis, per county

	Mean	Median	IQR	Min	Max
Population size	4,544	2,558	3,636	181	52,056
Percent black	20.50	17.80	27.50	0.20	62.50
Percent Hispanic	6.40	5.50	4.80	1.30	20.60
Percent extremely low birth weight	9.40	9.50	2.60	4.30	19.60
Percent using well water	34.30	28.90	33.30	1.20	88.10
Percentage in poverty	19.20	18.50	6.20	9.20	31.50
Number of doctors	303	243	259	0	2,274
Percent with speech/language disorder	1.69	1.61	1.44	0.16	5.95
Percent with delayed milestones	0.24	0.03	0.25	0.00	1.97
Percent with hearing loss	0.026	0	0.056	0.00	0.289
*Manganese (μg/L)	71.50	54.44	52.94	18.70	406.35
*Arsenic (μg/L)	1.15	0.68	0.59	0.50	9.32
*Lead (μg/L)	284.03	139.23	261.66	2.77	4,357.94

*Metal concentrations represent the mean and median of the 99 county means, and medians, IQR: Interquartile range

Table 3

Results of quasi-Poisson regressions for delayed milestones

	Model 1	Model 2	Model 3	Model 4	Model 5
# Doctors	−0.18 (−0.97,0.61)	−0.16 (−0.96,0.64)	−0.42 (−1.59,0.75)	−0.46 (−1.58,0.67)	−0.42 (−1.67,0.83)
% Poverty	−0.03 (−0.49,0.43)	0.09 (−0.36,0.54)	0.30 (−0.33,0.93)	0.14 (−0.53,0.81)	0.10 (−0.64,0.84)
% Hispanic	0.24 (−0.20,0.68)	0.22 (−0.22,0.66)	−0.15 (−0.87,0.57)	−0.16 (−0.86,0.54)	−0.17 (−0.95,0.61)
% Black	−0.56 (−1.33,0.22)	−0.48 (−1.24,0.27)	−0.76 (−1.79,0.28)	−0.82 (−1.83,0.18)	−0.69 (−1.86,0.48)
% Well water	−0.36 (−0.97,0.24)	−0.37 (−0.98,0.24)	−0.43 (−1.26,0.40)	−0.39 (−1.16,0.38)	−0.33 (−1.15,0.50)
% ELWB	−0.17 (−0.88,0.55)	−0.28 (−1.03,0.47)	−0.75 (−1.85,0.35)	−0.60 (−1.64,0.43)	−0.68 (−1.84,0.47)
Arsenic	−0.28 (−0.81,0.25)			−0.32 (−0.96,0.33)	0.05 (−1.01,1.10)
Lead		−0.10 (−0.03,0.83)		0.08 (−0.90,1.06)	−0.59 (−3.07,1.90)
Manganese			0.39 (0.18,0.61)	0.39 (0.19,0.60)	−0.18 (−1.43,1.08)
Arsenic*lead					0.61 (−2.27,3.49)
Arsenic*manganese					−0.27 (−1.61,1.06)
Lead*manganese					−1.95 (−6.15,2.25)

The five models differ by their treatment of the exposure variable. Model 1 includes only arsenic, Model 2 includes only lead, Model 3 includes only manganese, Model 4 includes all three metals; and Model 5 includes all three metals and their interactions. The table reports the estimated log relative risks (beta) and associated 95% confidence intervals. Significant associations are bolded

Table 4

Results of quasi-Poisson regressions for speech/language disorder

	Model 1	Model 2	Model 3	Model 4	Model 5
# Doctors	0.08 (−0.01, 0.17)	0.08 (−0.01, 0.17)	**0.10 (0.02, 0.19)**	0.09 (−0.01, 0.18)	0.09 (−0.01, 0.18)
% Poverty	**−0.24 (−0.40, −0.07)**	**−0.18 (−0.34, −0.03)**	**−0.22 (−0.37, −0.06)**	**−0.23 (−0.40, −0.06)**	**−0.23 (−0.40, −0.06)**
% Hispanic	−0.11 (−0.26, 0.04)	−0.12 (−0.27, 0.03)	−0.09 (−0.24, 0.07)	−0.09 (−0.25, 0.06)	−0.10 (−0.26, 0.06)
% Black	0.14 (−0.06, 0.34)	0.15 (−0.05, 0.35)	0.17 (−0.03, 0.37)	0.17 (−0.04, 0.37)	0.18 (−0.03,0.39)
% Well water	−0.07 (−0.24, 0.11)	−0.07 (−0.25, 0.10)	−0.05 (−0.23, 0.12)	−0.06 (−0.23, 0.11)	−0.06 (−0.23, 0.12)
% ELBW	−0.14 (−0.36, 0.08)	−0.17 (−0.40, 0.06)	−0.13 (−0.35, 0.09)	−0.14 (−0.37, 0.09)	−0.15 (−0.38, 0.09)
Arsenic	−0.08 (−0.20, 0.04)			−0.07 (−0.20, 0.05)	−0.02 (−0.31, 0.28)
Lead		−0.08 (−0.34, 0.19)		−0.10 (−0.37, 0.18)	−0.07 (−0.41, 0.27)
Manganese			−0.06 (−0.15, 0.03)	−0.05 (−0.14, 0.05)	−0.07 (−0.18, 0.05)
Arsenic*lead					0.07 (−0.53, 0.68)
Arsenic*manganese					−0.02 (−0.24, 0.20)
Lead*manganese					−0.08 (−0.37, 0.21)

ELWB: Extremely low weight births, The five models differ by their treatment of the exposure variable. Model 1 includes only arsenic, Model 2 includes only lead, Model 3 includes only manganese, Model 4 includes all three metals, and Model 5 includes all three metals and their interactions. The table reports the estimated log relative risks (beta) and associated 95% confidence intervals. Significant associations are bolded

Table 5

Results of the quasi-Poisson regressions for hearing loss

	Model 1	Model 2	Model 3	Model 4	Model 5
# Doctors	−1.82 (−3.98, 0.35)	−1.85 (−3.93, 0.23)	−1.86 (−4.00, 0.28)	−1.96 (−4.13, 0.21)	−1.61 (−3.56, 0.34)
% Poverty	−0.07 (−0.34, 0.19)	0.01 (−0.24, 0.27)	0.01 (−0.24, 0.27)	0.00 (−0.28, 0.29)	0.04 (−0.25, 0.32)
% Hispanic	−0.09 (−0.37, 0.19)	−0.10 (−0.37, 0.17)	−0.19 (−0.49, 0.11)	−0.21 (−0.52, 0.10)	−0.18 (−0.48, 0.12)
% Black	−0.22 (−0.61, 0.17)	−0.21 (−0.58, 0.17)	−0.27 (−0.65, 0.11)	−0.29 (−0.68, 0.11)	−0.21 (−0.61, 0.19)
% Well water	−0.02 (−0.34, 0.31)	−0.02 (−0.34, 0.29)	−0.03 (−0.36, 0.30)	−0.02 (−0.36, 0.31)	−0.03 (−0.35, 0.29)
% ELWB	0.18 (−0.22, 0.58)	0.13 (−0.28, 0.53)	0.10 (−0.32, 0.51)	0.09 (−0.34, 0.52)	−0.01 (−0.45, 0.43)
Arsenic	−0.08 (−0.29, 0.14)			−0.11 (−0.33, 0.10)	**0.42 (0.04, 0.80)**
Lead		−0.34 (−0.94, 0.26)		−0.29 (−0.91, 0.32)	−0.25 (−0.86, 0.36)
Manganese			**0.14 (0.03, 0.26)**	**0.14 (0.02, 0.26)**	0.13 (−0.06, 0.33)
Arsenic*lead					0.18 (−0.76, 1.13)
Arsenic*manganese					**−0.46 (−0.88, −0.05)**
Lead*manganese					0.00 (−0.60, 0.60)

ELWB: Extremely low weight births, The five models differ by their treatment of the exposure variable. Model 1 Includes only arsenic, Model 2 Includes only lead, Model 3 includes only manganese, Model 4 includes all three metals, and Model 5 includes all three metals and their interactions. The table reports the estimated log relative risk (beta) and associated 95% confidence interval. Significant associations are bolded