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doi: 10.1289/ehp.1002321 (available at http://dx.doi.org/)
Online 20 September 2010

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National Institute of Environmental Health Sciences

National Institutes of Health
U.S. Department of Health and Human Services

Intellectual Impairment in School-Age Children Exposed to Manganese from Drinking Water

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Acknowledgments: The Canadian Institutes for Health Research provided the funding (NRF-82899), as well as a fellowship to Maryse Bouchard. We wish to acknowledge the participants who kindly gave their time to help us carry out the study. We have no financial interests to declare.

Running head: Water manganese and children's intellectual quotient

Key words: children, manganese, water, neurotoxicity, intellectual quotient

Abbreviations:

Arsenic: As

Confidence interval: CI

Copper: Cu

Environmental Protection Agency: EPA

Generalized estimating estimations: GEE

Hair manganese concentration: MnH

Inductively coupled plasma mass spectrometry: ICP-MS

Intellectual quotient: IQ

Iron: Fe

Lead: Pb

Manganese: Mn

Water manganese concentration: MnW

Wechsler Abbreviated Scale of Intelligence: WASI

World Health Organization: WHO

Zinc: Zn

ABSTRACT

Background: Manganese is an essential nutrient, but in excess, can be a potent neurotoxicant. Despite the common occurrence of manganese in groundwater, the risks associated with this source of exposure are largely unknown.

Objectives: Our first aim was to assess the relations between exposure to manganese from drinking water and children's intellectual quotient (IQ). Secondly, we examined the relations between manganese exposures from water consumption and from the diet with children's hair manganese concentration.

Methods: This cross-sectional study included 362 children ages 6 to 13 years living in communities supplied by groundwater. Manganese concentration was measured in home tap water (MnW) and children's hair (MnH). We estimated manganese intake from water ingestion and the diet using a food frequency questionnaire, and assessed IQ with the Wechsler Abbreviated Scale of Intelligence.

Results: The median MnW in children's home tap water was 34 µg/L (range: 1–2700 µg/L). MnH increased with manganese intake from water consumption, but not with dietary manganese intake. Higher MnW and MnH were significantly associated with lower IQ scores. A 10-fold increase in MnW was associated with a decrease of 2.4 IQ points (95% confidence intervals: -3.9, -0.9; $P < 0.01$), adjusting for maternal intelligence, family income, and other potential confounders. There was a 6.2-IQ point difference between children in the lowest and highest MnW quintiles. MnW was more strongly associated with Performance IQ than Verbal IQ.

Conclusions: The findings of this cross-sectional study suggest that exposure to manganese at levels common in groundwater is associated with intellectual impairment in children.

INTRODUCTION

Manganese (Mn) is an essential nutrient, involved in the metabolism of amino acids, proteins, and lipids, but in excess, can be a potent neurotoxicant. Occupational and environmental exposure to airborne manganese has been associated with neurobehavioral deficits in adults and children (Zoni et al. 2007; Riojas-Rodríguez et al. 2010). In exposed workers, neurobehavioraldeficits have been shown to correlate with manganese deposition in the brain observed by magnetic resonance imaging (Chang et al. 2009).

Manganese is commonly found in groundwater due to the weathering and leaching of manganese-bearing minerals and rocks into the aquifers; concentrations can vary by several orders of magnitude (Groschen et al. 2009). Because homeostatic mechanisms regulate manganese concentration in the organism, notably low absorption levels and a high rate of presystemic elimination by the liver (Roth 2006), it is generally believed that the oral route poses no significant toxic risk (Boyes 2010). Moreover, exposure to manganese from water consumption has been of little concern because the intake of manganese from ingestion of water is small compared to that from foods, except for infants (Deveau 2010).

Little data are available on the risks from exposure to manganese from drinking water. One study on adults (Kondakis et al. 1989) and three studies in children (Bouchard et al. 2007; He et al. 1994; Wasserman et al. 2006) suggest that high manganese levels in water can be neurotoxic. In the Chinese province of Shanxi, 92 children 11–13 years, exposed to 240–350 µg manganese/L in water had elevated hair manganese concentration (MnH), impaired manual dexterity and speed, short-term memory, and visual identification, when compared with children from a control area (He et al. 1994). In Bangladesh, higher manganese concentration in water (MnW) was significantly

associated with lower intellectual quotient (IQ) in 142 children aged 10 years; the mean MnW was 800 µg/L (Wasserman et al. 2006). In Quebec (Canada), our pilot study on 46 children 6–15 years showed that those exposed to higher MnW had significantly higher MnH, and the latter was associated with teacher-reported hyperactive and oppositional behaviours (Bouchard et al. 2007). Finally, there are two case reports of child manganese intoxication from water containing more than 1000 µg manganese/L, one presenting with attention and memory impairments (Woolf et al. 2002), and the other with neurologic symptoms including a repetitive stuttered speech, poor balance, coordination, and fine motor skills (Sahni et al. 2007).

Manganese concentration in drinking water is not regulated in the U.S. or Canada. Health-based guidelines for the maximum level of manganese in drinking water are set at 300 µg/L by the U.S. Environmental Protection Agency (EPA 2004), and at 400 µg/L by the World Health Organization (WHO 2008).

To date, no epidemiologic study has examined possible neurotoxic effects at manganese concentrations common in North American aquifers. In the present study, we assessed the relationship between exposure to manganese from drinking water and IQ of school-age children living in communities relying on groundwater. In addition, we examined the relations between MnH and estimated manganese intakes from water consumption and from the diet.

METHODS

Study design and recruitment

We conducted this cross-sectional study in southern Quebec (Canada) between June 2007 and June 2009. Municipalities were considered as potential study sites if their aqueduct was supplied by groundwater. We selected 8 municipalities to achieve a gradient of MnW. We explained the study to the elementary schools' principal and teachers who accepted to distribute recruitment letters children's to families. The families' response rate was 60% and the participation rate was 52%. Recruitment was restricted to children who had lived in the same house for more than 3 months to ensure continuous exposure to the same source of water for this minimum period of time. Three hundred and sixty two children participated in the study (age 6-13 years). The Human Research Ethics Board of the Université du Québec à Montréal approved the study protocol. We obtained parents' signed informed consent and child's verbal assent to participate in the study.

Measurements of manganese hair concentration

We collected a hair sample from the occiput of children, cutting as close as possible to the root with surgical stainless steel scissors. We used the 2 cm closest to the scalp and washed samples to minimize external contamination with the method described in Wright et al. (2006). In a test phase, we photographed hair strands with an electronic microscope, and observed that the washing procedure effectively removed all particulates from the surface of the hair strand without compromising its structural integrity. We measured metals (Mn, Pb, Fe, As, Zn, and Cu) by ICP-MS. Details of the analyses are in Supplemental Material.

When manganese concentrations for certified hair material were outside of the designated concentrations, we excluded the measures from the analyses. Nine children who reported using hair

dye in the last 5 months were also excluded, because hair dye could influence manganese hair content (Sky-Peck 1990). Children who reported use of hair dye had higher MnH compared with the others (GM, 1.1 µg/g, and 0.7 µg/g, respectively). A total of 302 children were included in the analyses of MnH.

Measurements of manganese and other elements in residential tap water

During the home visit, a parent responded to an interview-administered questionnaire about the source of the domestic tap water (private well/public well), residential history, and changes to domestic water treatments. We collected a water sample from the kitchen tap, and a second sample was also collected when there was a point-of-use filter (filter attached to the tap). We used the following procedure to standardize tap water sampling (van den Hoven and Slaats 2006) : 1) open the tap for 5 min, 2) close and leave untouched for 30 min, and 3) collect first draw. We added 0.15 mL nitric acid (50%) to the 50 mL water sample and stored them at 4ºC. We measured metals (Mn, Pb, Fe, As, Zn, and Cu) by ICP-MS. Calibration curves were run every 30 samples, along with field and laboratory blanks, and quality controls (Environment Canada-Proficiency Testing Program) every 15 samples.

For a subsample of participating families (n=20), we sampled tap water on three occasions over a 1-year period in order to examine time-dependent variability.

Estimation of manganese intake from the diet and water consumption

During the home visit, we orally administered a semi-quantitative food frequency questionnaire to the parent and the child to assess manganese intake from the diet and water consumption. We used 3-D models of portion size to obtain more precise estimates for all sites except the first site, thus data for these participants (n=16) were not included in the analyses on dietary intake. We estimated

manganese intake from water consumption for direct water ingestion, and water incorporated in food preparations. We estimated water consumption from different sources, i.e. bottled, tap, tap filtered with a pitcher, and tap with an attached filter. For each water source , the amount consumed was multiplied by the measured or estimated concentration of manganese, yielding a total intake in ug/month. Further methodological details can be found in Supplemental Material.

Assessment of intellectual quotient and covariates

We used the Wechsler Abbreviated Scale of Intelligence (WASI) to assess general cognitive abilities (Wechsler 1999). This standardized test yields a Verbal IQ score (based on the subtests Vocabulary and Similarities), a Performance IQ score (Block Design and Matrix Reasoning), and a Full Scale IQ score. Throughout the study, 3 psychometricians administered the WASI, but all scoring was performed by the same person. We administered the WASI within 1 week of tap water sampling.

We collected information from the mother on factors that might confound the association between manganese exposure and children's cognitive abilities, such as socio-economic status indicators (i.e., maternal education, family income and structure), parity, and alcohol and tobacco consumption during pregnancy. We assessed maternal non-verbal intelligence with the Raven's Progressive Matrices Test (Raven et al. 2003), home cognitive stimulation with a modified version of the Short-Form HOME interview (Bradley et al. 2001), and maternal symptoms of depression with the Beck Depression Inventory-II (Beck et al. 1996). Data on family income was missing for 4 families, and the Raven score was missing for 1 mother; for missing data, we assigned the mean value of individuals with data.

Statistical analysis

The distributions of manganese concentrations in hair and water, as well as manganese intakes, were considerably skewed. We thus employed $\log_{10}$-transformation in order to normalize residuals. Likewise, we log-transformed the concentrations of other elements measured in water. Manganese intakes from consumption of water and from the diet were divided by the child's weight for use in the analyses (µg/kg/month). We used generalized estimating estimations (GEE), to examine relationships between exposure to manganese and children's IQ scores. GEE is an extension of generalized linear models for non-independent data (Zeger and Liang 1986). These analyses were used to account for the community- and family-clustered data in our study. Some of the advantages of using GEE instead of the more common approach of mixed models with random intercepts, are more efficient estimators of regression parameters, and reasonably accurate standard errors (i.e. confidence intervals with the correct coverage rates). With GEE, the computational complexity is a function of the size of the largest cluster rather than of the number of clusters—an advantage and a source of reliable estimates, when there are many small clusters (Hanley et al. 2003), such as in the present study (i.e. the 251 families). Confidence intervals were calculated with Wald statistics. An exchangeable working covariance matrix was used, with a robust estimator providing a consistent estimate of the covariance even when the working correlation matrix is misspecified.

Changes in IQ were examined in relation to 4 manganese exposure metrics reflecting different assumptions for exposures pathways and toxicokinetics, i.e. MnW, MnH, manganese intake from water consumption, and dietary manganese intake. The change in IQ (ß) associated with a 10-fold increase in manganese exposure indicators was examined with adjustments for two sets of covariates. The first set of covariates (model A) was chosen based on the examination of directed acyclic graphs (Greenland and Brumback 2002), and included several socio-economic indicators.

Because manganese causes esthetical problems, families who have the means might treat water domestically to remove it. The second set of covariates (model B) included the same variables as model A as well as variables significantly associated with IQ or MnW, in order to reduce the unexplained variance thus diminishing type II error (Bellinger 2007). We conducted sensitivity analyses on inclusion of additional covariates in the models. We used 0.05 as the threshold for statistical significance (2-sided tests). We examined residuals for normality and homoscedasticity, and detected no problem.

RESULTS

Descriptive statistics

This study included 362 children from 251 families. Most children (85%) had resided for more than 12 months in their present home. The children's mean age was 9.3 years (standard deviation [SD]: 1.8 years; range: 6.2–13.4 years), and 99% of children were white. Seventy eight percent of mothers had at least some college education (Table 1). Tap MnW ranged from 1 to 2700 µg/L (Table 2), with an arithmetic mean of 98 µg/L and a geometric mean (GM) of 20 µg/L. MnW from repeated sampling in the same residence over a period of 1 year had an intra class correlation coefficient of 0.91.

MnW was not associated with socio-economic or other family characteristics, such as family income, family structure, home stimulation score, and non-verbal maternal intelligence, and maternal education (Table 1). MnW was lower in houses with a private well (GM: 8 µg/L) than in those on a public well (GM: 55 µg/L). The concentration distribution for elements other than manganese in residential tap water is in Supplemental Material. The Pearson correlation of MnW with other elements was 0.68 (Fe), 0.26 (Zn), 0.11 (Cu), 0.06 (As), and -0.02 (Pb).

Estimated manganese intakes and in children's hair manganese

The median of estimated manganese intakes from direct consumption of water (1.6 µg/kg/month) was similar to the median of intakes from water incorporated into food preparations (1.9 µg/kg/month) (Table 2). The estimated dietary manganese intakes were much higher than the intakes from water consumption, with a median of 2335 µg/kg/month (Table 2).

Children's MnH increased with MnW and estimated manganese intake from water consumption (Figure 1a), but not from the estimated dietary manganese intake (Figure 1b). In a multivariate model, MnH was significantly associated with manganese intake from water consumption ($P < 0.001$), and not with dietary intake ($P = 0.76$). In this multivariate model, there was no difference in MnH between boys and girls ($P = 0.46$, GM for both: 0.7 µg/g), and age was not associated with MnH ($P = 0.88$).

Manganese exposure and children's IQ

Estimated dietary manganese intake was not significantly associated with IQ scores in unadjusted or adjusted analyses (results not shown). Table 3 presents unadjusted and adjusted changes in IQ scores for a 10-fold increase in exposure level for 3 exposure indicators: MnW, estimated manganese intake from water consumption, and MnH. In unadjusted analyses, the 3 indicators were significantly associated with lower Full Scale IQ scores. Adjustment for covariates, with either model A or B, did not considerably change the point estimates. Higher MnW was significantly associated with lower Full Scale IQ scores in model A (change in scores for a 10-fold increase in concentration [ß]: -1.9 [95% CI: -3.1, -0.7]) and model B (ß: -2.4 [95% CI: -3.9, -0.9]). Higher MnW was also significantly associated with lower Performance IQ scores in model A (ß: -2.3 [95% CI: -3.7, -0.8]) and model B (ß: -3.1 [95% CI: -4.9, -1.3]). Higher MnW was associated with lower Verbal IQ scores, significantly for model A but not for model B (the point estimates were similar for both models but the 95% CI were larger for model B). Higher estimated manganese intake from water consumption was significantly associated with lower Full Scale and Performance IQ, in both model A and B. Sex-stratified analyses on MnW and Full Scale IQ resulted in higher point estimate for girls (using model B, ß: -3.2 [95% CI: -5.0, -1.5]) than for boys (ß: -2.3 [95% CI: -4.8, 0.2]), but the term for interaction with sex was not significant ($P = 0.14$).

When examining MnH as the predictor of IQ in unadjusted analyses, it was significantly associated to lower Full Scale IQ scores but not Performance or Verbal IQ scores. In adjusted analyses, higher MnH was associated with lower Full Scale IQ scores, both in model A (ß: -3.7 [95% CI: -6.5, -0.8]) and model B (ß: -3.3 [95% CI: -6.1, -0.5]). MnH was also associated with lower Performance and Verbal IQ scores, although these relations did not reach statistical significance except for Verbal IQ in model A (ß: -3.1 [95% CI: -5.9, -0.3]). Sex-stratified analyses resulted in higher point estimates for the association between MnH and Full Scale IQ for girls (ß: -4.8 [95% CI: -8.1, -1.6]) than for boys (ß: -3.5 [95% CI: -8.7, 1.6]), but the term for interaction with sex was not significant (P = 0.55).

The shape of dose-response relations are shown in Figure 2. IQ scores decrease steadily with increasing MnW (Figure 2a). Children in the highest MnW quintile (median: 216 µg/L) scored 6.2 points below those in the lowest quintile (median: 1 µg/L). For estimated manganese intake from water ingestion (Figure 2b), children in the lowest quintile had the highest IQ scores and those in the highest quintile had the lowest scores, but point estimates in the middle quintiles did not show a consistent pattern of increasing or decreasing trend. For MnH (Figure 2c), IQ scores decreased only slightly between children in the lowest quintile and the middles quintiles, and there was a steeper decrease for children in the highest quintile. A similar plot for dietary manganese intake showed no association, even in the higher range of intakes (data not shown).

We conducted sensitivity analyses on the inclusion of additional covariates in the models: child's birth weight, child's rank in the family, maternal smoking or alcohol consumption during pregnancy, maternal depressive symptoms, psychometrician, and concentration of Pb, As, Cu, and Zn in tap water. We did not retain these covariates because they did not change point estimates by more than 10%, and were not significantly associated with IQ scores (P > 0.2).

DISCUSSION

The present study shows that children exposed to higher concentration of manganese in tap water had lower IQ scores. This finding was robust to adjustment for socio-economic status indicators and other metals present in water. The association between water manganese concentration and IQ scores was strong, with a 6.2 Full Scale IQ-point difference between the children exposed to water with 1 and 216 µg manganese/L (median of lowest and highest quintiles). Manganese intake from water ingestion, but not from the diet, was significantly associated with elevated manganese concentration in children's hair. These findings suggest that manganese exposure from drinking water is metabolized differently than that from the diet, and can lead to overload and subsequent neurotoxic effects expressed by intellectual impairments in children.

The communities included in the present study were chosen to ensure a gradient of manganese concentrations in drinking water. This selection was not random, and levels are not representative of the distribution of manganese concentration in wells used for human consumption in Canada or the United States. Nonetheless, the concentrations measured are not unusual in North-Eastern America. In New England, 45% of wells for public use have manganese concentrations exceeding 30 µg/L (Groschen et al. 2009). Throughout the United States, approximately 5% of domestic household wells have concentrations above 300 µg/L (U.S. Geological Survey 2009). Elevated manganese in groundwater is common in several countries including Sweden (Ljung and Vahter 2007), Vietnam (Agusa et al. 2006), and Bangladesh (Wasserman et al. 2006).

The present findings are consistent with the two previous studies examining drinking water manganese-related cognitive deficits in children. Albeit, in the present study, the mean manganese concentration was considerably lower than the others, i.e. 100 µg/L versus approximately 300 µg/L

(He et al. 1994) and 800 µg/L (Wasserman et al. 2006). Similar to our findings, Wasserman et al. (2006) observed a stronger association of water manganese level with Performance IQ than Verbal IQ.

The different manganese exposure indicators showed consistent associations with lower IQ scores, although the shape of the dose-response curve differed by exposure indicators. Full scale IQ scores decreased steadily with increasing water manganese, but a discernable diminution in IQ was only present at higher concentrations of hair manganese. Interestingly, tap water manganese concentration was a better predictor of children's IQ scores than the estimated intake from water ingestion, possibly because of error measurement in intakes. However, there may be pathways of exposure that are not captured by assessment of the ingested dose, such as inhalation of aerosols containing manganese ions in the shower (Elsner and Spangler 2005), although this hypothesis is debated (Aschner 2006). More studies are needed on manganese toxicokinetic and neurotoxicity to better understand these findings.

The present study does not address the mechanisms involved in manganese-related cognitive impairments, but an extensive body of literature shows perturbation of neurotransmitter activities (Olanow 2004), notably, disruption of the striatal dopaminergic system. Studies also reported data suggestive of perturbations of gamma-aminobutyric acid and serotonin (Dobson et al. 2004; Eriksson et al. 1987). Manganese effects can be persistent; adult mice exposed by gavage as juveniles had decreased striatal dopamine activity (Moreno et al. 2009). In nonhuman primates, chronic manganese exposure causes accumulation of the metal in the basal ganglia, white matter, and cortical structures, with signs of neuronal degeneration (Guilarte et al. 2006, 2008). Perturbations in the regulation of other metals in the brain could also be implicated in the cognitive impairment associated with manganese exposure (Fitsanakis et al. 2009).

In the present study, dietary manganese intake was similar to the recommended dietary allowance of 1.5–1.9 mg/day for children ages 6 to 13 years (Food and Nutrition Board 2004). Manganese intake from ingestion of water was very small compared to the amount ingested from foods (by more than 2 orders of magnitude) and yet only intake from water was significantly associated to hair manganese content. Previous studies have likewise reported a relation between the concentration of manganese in drinking water and hair (Agusa et al. 2006; Bouchard et al. 2007; He et al. 1994; Kondakis et al. 1989). This suggests that there might be differences in the regulation of manganese present in food and water. The chemical form of manganese, notably the valence state and solubility, might modify its toxicity, perhaps because of changes in toxicokinetic properties (Michalke et al. 2007). Moreover, manganese absorption is decreased in the digestive system with concurrent intake of dietary fiber, oxalic acids, tannins, and phytic acids (Gibson 1994).

Currently, no consensus has emerged as to the optimal biomarker of exposure to manganese (Smith et al. 2007). Even at very high water manganese concentrations, no relation was observed between water manganese and blood manganese in children (Wasserman et al. 2006) or adults (Kondakis et al. 1989). Blood manganese can vary widely on the short-term, and thus might not reflect long-term exposure. For instance, in a case report of suspected manganese intoxication, three consecutive blood samples for plasma manganese on a single day showed large variability: 0.6, 2.2, and 2.4 μg/L (Sahni et al. 2007). In contrast, the manganese content in hair will reflect the metal uptake averaged over the duration of the follicle formation. The mechanism of manganese uptake into hair is not well understood, but its affinity for melanin, a protein present in hair, skin, as well as the central nervous system, could be involved (Lyden et al. 1984).

The strengths of our study include a larger sample size than previous studies, and thorough assessment of manganese exposure by ingestion, including from dietary sources. Repeated water sampling in the same house showed little variations in manganese concentration over the year, suggesting that one measure is representative of long-term exposure. The other metals present in tap water did not affect the association between manganese and IQ. We did not measure non-metal water constituents, but our findings are not likely to be explained by anthropogenic contaminants because the observed manganese concentrations represent natural background levels associated with the bedrock geology, and not human activities. It should be noted that there are no industrial sources of manganese emission in the study area, and since 2004 the gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT) is no longer used in Canada (Finkelstein and Jerrett 2007).

The present study has limitations. As in any epidemiological study, associations could be due to unmeasured confounders, but manganese concentration in tap water was completely dissociated from socio-economic status which diminishes the potential for confounding. Some level of exposure misclassification is expected because we only considered manganese exposure from water consumed at home. However, non-differential misclassification would most likely bias estimates of manganese associations with IQ towards the null. Despite measures taken to wash hair samples, residual external contamination cannot be ruled out completely. For instance, arsenic present in water as been shown to bind to the hair surface and was not removed by sample washing (Concha et al, 2006); it is not known whether this could also apply to manganese.

The inferences that can be drawn from the present findings are limited by its cross-sectional design. It is not known whether exposure during a critical developmental period is responsible for our observations. Most children in the present study had been exposed to the current water manganese

concentration for over one year, but we did not attempt to assess exposure for more remote periods because retrospective data are often unreliable, and this was not our initial objective. Studies employing a prospective design would provide a stronger basis for examining the influence of exposure duration and timing (i.e. critical developmental periods) on manganese neurotoxic effects. Notably, infants and young children could be at risk because of not fully developed homeostatic mechanisms limiting absorption of ingested manganese (Ljung and Vahter 2007; Winder 2010).

CONCLUSIONS

Manganese intake from water ingestion, but not from the diet, was significantly associated with elevated manganese concentration in hair, suggesting that homeostatic regulation of manganese does not prevent overload upon exposure from water. The findings from the present study support the hypothesis that low level, chronic exposure to manganese from drinking water is associated with significant intellectual impairments in children. These findings should be replicated in another population. Because of the common occurrence of this metal in drinking water and the observed effects at low manganese concentration in water, we believe that national and international guidelines for safe manganese in water should be revisited.

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Table 1: Manganese concentrations in domestic tap water (µg/L) by participant's characteristics

Participant's characteristics	Frequency	%	MnW (GM)	P Value [b]
Child's sex [a]				0.71
Boys	168	46%	19	
Girls	194	54%	21	
Child drink tap water [a]				0.41
No	121	33%	23	
Yes	241	67%	19	
Smoking during pregnancy [a]				0.13
No	265	73%	18	
Yes	97	27%	27	
Alcohol consumption during pregnancy [a]				0.10
No	310	86%	22	
Yes	52	14%	13	
Home tap water source [c]				<0.001
Private well	117	47%	8	
Public well	134	53%	55	
Family income [c]				0.28
$50,000 and less	106	42%	27	
More than $50,000	145	58%	20	
Family structure [c]				0.87
2 biological parents	189	75%	22	
1 biological and 1 non-biological parent	37	15%	21	
Single-parent	25	10%	28	
Maternal education [c]				0.86
Less than high school	11	4%	13	
High school diploma	44	18%	24	
Some college	116	46%	24	
Some university	80	32%	21	
Non-verbal maternal intelligence (Raven) [c]				0.71
Less than 23	94	38%	110	
23–25	94	38%	84	
More than 25	63	25%	123	
Maternal depressive symptoms (Beck-II score) [c]				0.08
Normal range	206	82%	24	
Mild symptoms	34	14%	11	
Moderate or severe symptoms	11	4%	40	

[a] One measure per child (n=362)
[b] Difference in MnW, from univariate general linear models
[c] One measure per family (n=251)

Table 2: Distribution of concentrations for manganese in drinking water and children's hair, as well as manganese intakes from water consumption and dietary sources

			Percentiles					
Manganese exposure indicators	N	Min	5	25	50	75	95	Max
Manganese concentrations								
Tap water manganese (ug/L)	362	0.1	0.5	2.5	30.8	128	255	2 700
Hair manganese (ug/g)	302	0.1	0.2	0.3	0.7	1.6	4.7	21
Manganese intakes (µg/kg/month)								
From drinking water	362	0.0	0.0	0.0	1.6	22.9	160	566
From water used in food preparations	362	0.0	0.0	0.2	1.9	14.5	149	480
Total intake from water consumption	362	0.0	0.0	1.0	8.0	59.6	286	945
From dietary sources	346	311	840	1 632	2 335	3 487	6 418	13 159

Table 3: Unadjusted and adjusted changes in children's IQ for a 10-fold increase in indicators of manganese exposure (ß [95% confidence intervals])

Models	Water Mn concentration (n=362)	Mn intake from water consumption (n=362)	Hair Mn (n=302)
Unadjusted model			
Full Scale IQ	-2.1 (-3.5, -0.8)**	-1.3 (-2.5, -0.2)*	-3.2 (-6.2, -0.2)*
Performance IQ	-2.4 (-4.0, -0.7)**	-1.6 (-3.0, -0.3)*	-2.5 (-5.7, 0.8)
Verbal IQ	-1.4 (-2.6, -0.2)*	-0.7 (-1.7, 0.3)	-2.8 (-5.6, 0.5)
Adjusted model A [a]			
Full Scale IQ	-1.9 (-3.1, -0.7)**	-1.2 (-2.3, -0.1)*	-3.7 (-6.5, -0.8)*
Performance IQ	-2.3 (-3.7, -0.8)**	-1.6 (-2.9, -0.3)*	-3.0 (-6.1, 0.1)
Verbal IQ	-1.5 (-2.6, -0.3)*	-0.6 (-1.6, 0.3)	-3.1 (-5.9, -0.3)*
Adjusted model B [b]			
Full Scale IQ	-2.4 (-3.9, -0.9)**	-1.2 (-2.3, -0.1)*	-3.3 (-6.1, -0.5)*
Performance IQ	-3.1 (-4.9, -1.3)**	-1.9 (-3.3, -0.4)*	-2.8 (-5.9, 0.4)
Verbal IQ	-1.2 (-2.7, 0.3)	-0.3 (-1.4, 0.7)	-2.7 (-5.4, 0.1)

[a] Adjusted for maternal education (less than high school/high school diploma/some college/some university) and non-verbal intelligence, family income, home stimulation score, and family structure (2 biological parents/1 biological and 1 non-biological parent/single-parent)

[b] Adjusted for same variables as above, and child's sex and age, IQ testing session (started at 0900/1300/1500), source of water (private well/public well) and Fe concentration in tap water.

* $P < 0.05$, ** $P < 0.01$

FIGURE LEGENDS

Figure 1: Distribution of hair manganese concentration by quintiles of: a) estimated manganese intake from water consumption (n=302), and b) estimated manganese intake from the diet (n=288). (Central bar: 50th percentile, lower and upper bounds of the rectangle: 25th and 75th percentiles, lower and upper tails: 5th and 95th percentiles. The observations outside the 95% CIs are not shown.)

Figure 2: Mean Full Scale IQ (standard error), with respect to manganese exposure indicators, adjusted for covariates in model B.

a) IQ is plotted by median of tap water manganese concentration (µg/L) quintiles. The medians and ranges of water manganese concentration are, for 1st quintile (lowest): 1 (0–2), 2nd: 6 (3–19), 3rd: 34 (20–66), 4th: 112 (67–153), and 5th (highest): 216 (154–2700).

b) IQ is plotted by median of manganese intake from water consumption (µg/kg/month) quintiles. The medians and ranges of manganese intakes are, for 1st quintile (lowest): 0.1 (0–0.7), 2nd: 1.6 (0.71–3.8), 3rd: 7.6 (4.0–14.6), 4th: 39.4 (15.6–82.9), and 5th (highest): 172 (83.3–945).

c) IQ is plotted by median of hair manganese concentration (µg/g) quintiles. The medians and ranges of hair manganese concentrations are, for 1st quintile (lowest): 0.2 (0.1–0.3), 2nd: 0.4 (0.31–0.5), 3rd: 0.7 (0.51–0.9), 4th: 1.2 (0.91–1.9), and 5th (highest): 3.2 (1.91–20.7).

Figure 1a

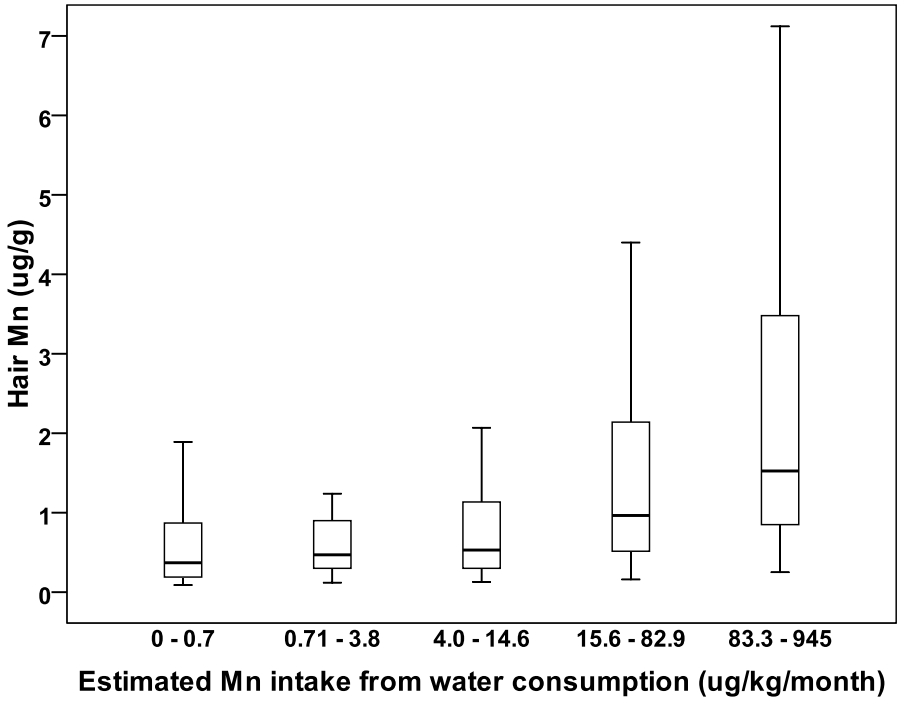

Figure 1b

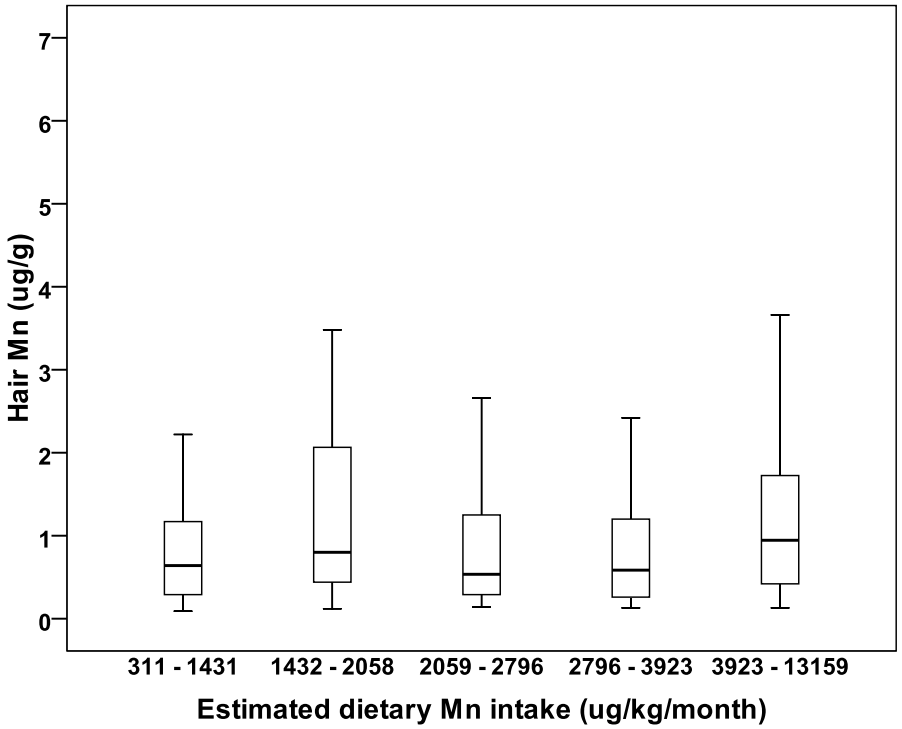

Figure 2a

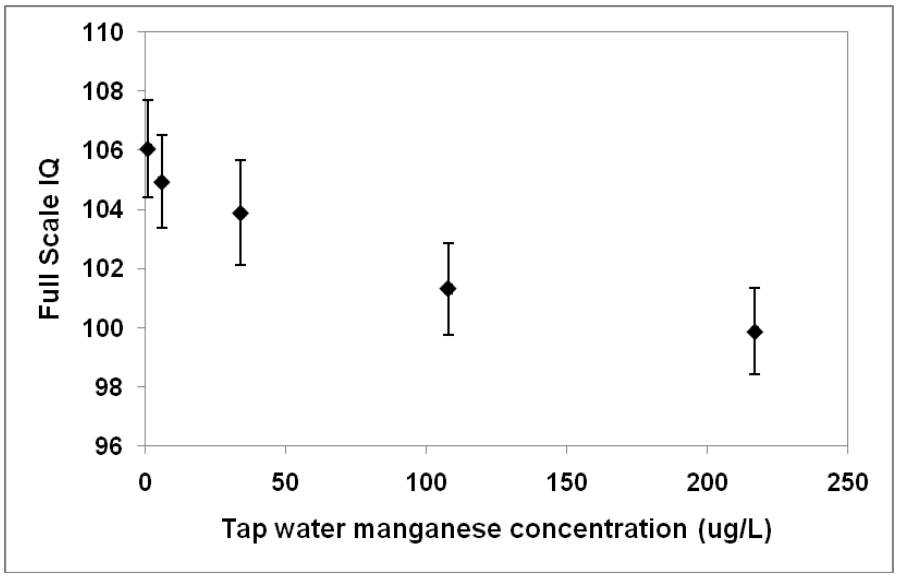

Figure 2b

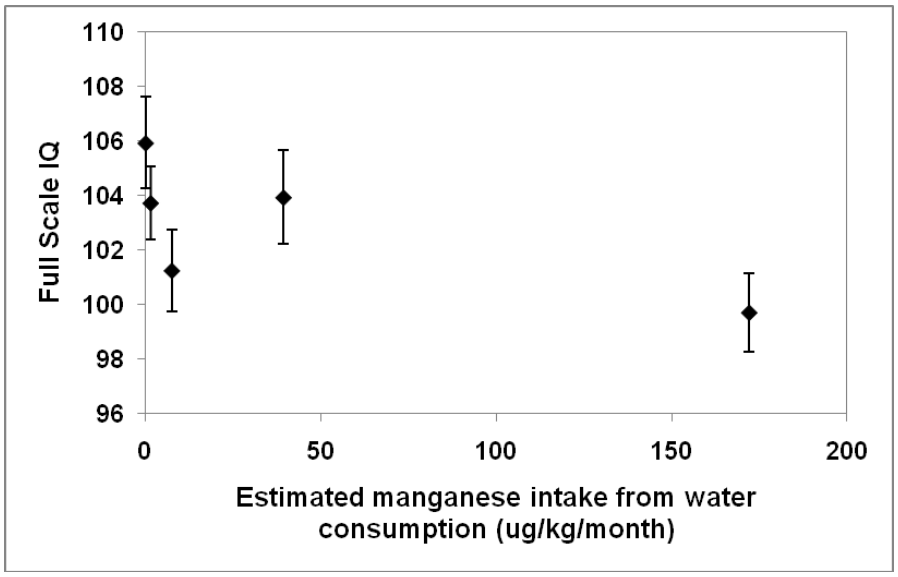

Figure 2c