ASSOCIATION BETWEEN MATERNAL FLUORIDE EXPOSURE DURING PREGNANCY AND IQ SCORES IN OFFSPRING IN CANADA

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IMPORTANCE The potential neurotoxicity associated with exposure to fluoride, which has generated controversy about community water fluoridation, remains unclear.

OBJECTIVE To examine the association between fluoride exposure during pregnancy and IQ scores in a prospective birth cohort.

DESIGN, SETTING, AND PARTICIPANTS This prospective, multicenter birth cohort study used information from the Maternal-Infant Research on Environmental Chemicals cohort. Children were born between 2008 and 2012; 41% lived in communities supplied with fluoridated municipal water. The study sample included 601 mother-child pairs recruited from 6 major cities in Canada; children were between ages 3 and 4 years at testing. Data were analyzed between March 2017 and January 2019.

EXPOSURES Maternal urinary fluoride (MUFSG), adjusted for specific gravity and averaged across 3 trimesters available for 512 pregnant women, as well as self-reported maternal daily fluoride intake from water and beverage consumption available for 400 pregnant women.

MAIN OUTCOMES AND MEASURES Children’s IQ was assessed at ages 3 to 4 years using the Wechsler Primary and Preschool Scale of Intelligence-III. Multiple linear regression analyses were used to examine covariate-adjusted associations between each fluoride exposure measure and IQ score.

RESULTS Of 512 mother-child pairs, the mean (SD) age for enrollment for mothers was 32.3 (5.1) years, 463 (90%) were white, and 264 children (52%) were female. Data on MUFSG concentrations, IQ scores, and complete covariates were available for 512 mother-child pairs; data on maternal fluoride intake and children’s IQ were available for 400 of 601 mother-child pairs. Women living in areas with fluoridated tap water (n = 141) compared with nonfluoridated water (n = 228) had significantly higher mean (SD) MUFSG concentrations (0.69 [0.42] mg/L vs 0.40 [0.27] mg/L; P = .001; to convert to millimoles per liter, multiply by 0.05263) and fluoride intake levels (0.93 [0.43] vs 0.30 [0.26] mg of fluoride per day; P = .001). Children had mean (SD) Full Scale IQ scores of 107.16 (13.26), range 52-143, with girls showing significantly higher mean (SD) scores than boys: 109.56 (11.96) vs 104.61 (14.09); P = .001. There was a significant interaction (P = .02) between child sex and MUFSG (6.89; 95% CI, 0.96-12.82) indicating a differential association between boys and girls. A 1-mg/L increase in MUFSG was associated with a 4.49-point lower IQ score (95% CI, −8.38 to −0.60) in boys, but there was no statistically significant association with IQ scores in girls (B = 2.40; 95% CI, −2.53 to 7.33). A 1-mg higher daily intake of fluoride among pregnant women was associated with a 3.66 lower IQ score (95% CI, −7.16 to −0.14) in boys and girls.

CONCLUSIONS AND RELEVANCE In this study, maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years. These findings indicate the possible need to reduce fluoride intake during pregnancy.

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For decades, community water fluoridation has been used to prevent tooth decay. Water fluoridation is supplied to about 66% of US residents, 38% of Canadian residents, and 3% of European residents. In fluoridated communities, fluoride from water and beverages made with tap water makes up 60% to 80% of daily fluoride intake in adolescents and adults.2

Fluoride crosses the placenta,3 and laboratory studies show that it accumulates in brain regions involved in learning and memory4 and alters proteins and neurotransmitters in the central nervous system.5 Higher fluoride exposure from drinking water has been associated with lower children's intelligence in a meta-analysis6 of 27 epidemiologic studies and in studies7,8 including biomarkers of fluoride exposure. However, most prior studies were cross-sectional and conducted in regions with higher water fluoride concentrations (0.88-31.6 mg/L; to convert to millimoles per liter, multiply by 0.05263) than levels considered optimal (ie, 0.7 mg/L) in North America.9 Further, most studies did not measure exposure during fetal brain development. In a longitudinal birth cohort study involving 299 mother-child pairs in Mexico City, Mexico, a 1-mg/L increase in maternal urinary fluoride (MUF) concentration was associated with a 6-point (95% CI, −10.84 to −1.74) lower IQ score among school-aged children.10 In this same cohort, MUF was also associated with more attention-deficit/hyperactivity disorder-like symptoms.11 Urinary fluoride concentrations among pregnant women living in fluoridated communities in Canada are similar to concentrations among pregnant women living in Mexico City.12 However, it is unclear whether fluoride exposure during pregnancy is associated with cognitive deficits in a population receiving optimally fluoridated water.

This study examined whether exposure to fluoride during pregnancy was associated with IQ scores in children in a Canadian birth cohort in which 40% of the sample was supplied with fluoridated municipal water.

Key Points

**Question** Is maternal fluoride exposure during pregnancy associated with childhood IQ in a Canadian cohort receiving optimally fluoridated water?

**Findings** In this prospective birth cohort study, fluoride exposure during pregnancy was associated with lower IQ scores in children aged 3 to 4 years.

**Meaning** Fluoride exposure during pregnancy may be associated with adverse effects on child intellectual development, indicating the possible need to reduce fluoride intake during pregnancy.

Methods

**Study Cohort**

Between 2008 and 2011, the Maternal-Infant Research on Environmental Chemicals (MIREC) program recruited 2001 pregnant women from 10 cities across Canada. Women who could communicate in English or French, were older than 18 years, and were within the first 14 weeks of pregnancy were recruited from prenatal clinics. Participants were not recruited if there was a known fetal abnormality, if they had any medical complications, or if there was illicit drug use during pregnancy. Additional details are in the cohort profile description.13

A subset of 610 children in the MIREC Study was evaluated for the developmental phase of the study at ages 3 to 4 years; these children were recruited from 6 of 10 cities included in the original cohort: Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax. Owing to budgetary restraints, recruitment was restricted to the 6 cities with the most participants who fell into the age range required for the testing during the data collection period. Of the 610 children, 601 (98.5%) completed neurodevelopmental testing; 254 (42.3%) of these children lived in nonfluoridated regions and 180 (30%) lived in fluoridated regions; for 167 (27.7%) fluoridation status was unknown owing to missing water data or reported not drinking tap water (Figure 1).

This study was approved by the research ethics boards at Health Canada, York University, and Indiana University. All women signed informed consent forms for both mothers and children.

**Maternal Urinary Fluoride Concentration**

We used the mean concentrations of MUF measured in urine spot samples collected across each trimester of pregnancy at a mean (SD) of 11.57 (1.57), 19.11 (2.39), and 33.11 (1.50) weeks of gestation. Owing to the variability of urinary fluoride measurement and fluoride absorption during pregnancy,14 we only included women who had all 3 urine samples. In our previous work, these samples were moderately correlated; intraclass correlation coefficient (ICC) ranged from 0.37 to 0.40.12

Urinary fluoride concentration was analyzed at the Indiana University School of Dentistry using a modification of the hexamethyldisiloxane (Sigma Chemical Co) microdiffusion procedure15 and described in our previous work.12 Fluoride concentration could be measured to 0.02 mg/L. We excluded 2 samples (0.002%) because the readings exceeded the highest concentration standard (5 mg/L) and there was less certainty of these being representative exposure values.

To account for variations in urine dilution at the time of measurement, we adjusted MUF concentrations for specific gravity (SG) using the following equation: $MUF_{SG} = MUF_i \times (SG_{ref} - 1) / (SG_i - 1)$, where $MUF_{SG}$ is the SG-adjusted fluoride concentration (in milligrams of fluoride per liter), $MUF_i$ is the observed fluoride concentration, $SG_i$ is the SG of the individual urine sample, and $SG_{ref}$ is the median SG for the cohort.16 For comparison, we also adjusted MUF using the same creatinine adjustment method that was used in the 2017 Mexican cohort.10

**Water Fluoride Concentration**

Water treatment plants measured fluoride levels daily if fluoride was added to municipal drinking water and weekly or monthly if fluoride was not added to water.12 We matched...
participants’ postal codes with water treatment plant zones, allowing an estimation of water fluoride concentration for each woman by averaging water fluoride concentrations (in milligrams per liter) during the duration of pregnancy. We only included women who reported drinking tap water during pregnancy.

**Daily Fluoride Intake in Mothers**

We obtained information on consumption of tap water and other water-based beverages (tea and coffee) from a self-report questionnaire completed by mothers during the first and third trimesters. This questionnaire was used in the original MREC cohort and has not been validated. Also, for this study, we developed methods to estimate and calculate fluoride intake that have not yet been validated. To estimate fluoride intake from tap water consumed per day (milligrams per day), we multiplied each woman’s consumption of water and beverages by her water fluoride concentration (averaged across pregnancy) and multiplied by 0.2 (fluoride content for a 200-mL cup). Because black tea contains a high fluoride content (2.6 mg/L), we also estimated the amount of fluoride consumed from black tea by multiplying each cup of black tea by 0.52 mg (mean fluoride content in a 200-mL cup of black tea made with deionized water) and added this to the fluoride intake variable. Green tea also contains varying levels of fluoride; therefore, we used the mean for the green teas listed by the US Department of Agriculture (1.935 mg/L). We multiplied each cup of green tea by 0.387 mg (fluoride content in a 200-mL cup of green tea made with deionized water) and added this to the fluoride intake variable.

**Primary Outcomes**

We assessed children’s intellectual abilities with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition. Full Scale IQ (FSIQ), a measure of global intellectual functioning, was the primary outcome. We also assessed verbal IQ (VIQ), representing verbal reasoning and comprehension, and performance IQ (PIQ), representing nonverbal reasoning, spatial processing, and visual-motor skills.

**Covariates**

We selected covariates from a set of established factors associated with fluoride metabolism (eg, time of void and time since last void) and children’s intellectual abilities (eg, child sex, maternal age, gestational age, and parity) (**Table 1**). Mother’s race/ethnicity was coded as white or other, and maternal education was coded as either bachelor’s degree or higher or trade school diploma or lower. The quality of a child’s home environment was measured by the Home Observation for Measurement of the Environment (HOME)-Revised Edition on a continuous scale. We also controlled for city and, in some models, included self-reported exposure to secondhand smoke (yes/no) as a covariate.

**Statistical Analyses**

In our primary analysis, we used linear regression analyses to estimate the associations between our 2 measures of fluoride exposure (MUF and fluoride intake) and children’s FSIQ scores. In addition to providing the coefficient corresponding to a 1-mg difference in fluoride exposure, we also estimated coefficients corresponding to a fluoride exposure
difference spanning the 25th to 75th percentile range (which corresponds to a 0.33 mg/L and 0.62 mg F/d difference in MUFSG and fluoride intake, respectively) as well as the 10th to 90th percentile range (which corresponds to a 0.70 mg/L and 1.04 mg F/d difference in MUFSG and fluoride intake, respectively).

We retained a covariate in the model if its P value was less than .20 or its inclusion changed the regression coefficient of the variable associated factor by more than 10% in any of the IQ models. Regression diagnostics confirmed that there were no collinearity issues in any of the IQ models with MUFSG or fluoride intake (variance inflation factor <2 for all covariates). Residuals from each model had approximately normal distributions, and their Q-Q plots revealed no extreme outliers. Plots of residuals against fitted values did not suggest any assumption violations and there were no substantial influential observations as measured by Cook distance. Including quadratic or natural-log effects of MUFSG or fluoride intake did not significantly improve the regression models. Thus, we present the more easily interpreted estimates from linear regression models. Additionally, we examined separate models with 2 linear splines to test

Table 1. Demographic Characteristics and Exposure Outcomes for Mother-Child Pairs With MUFSG (n = 512) and Fluoride Intake Data (n = 400) by Fluoridated and Nonfluoridated Statusa

<table>
<thead>
<tr>
<th>Variableb</th>
<th>MUFSG Sample (n = 512)c</th>
<th>Maternal-Child Pairs With Fluoride Intake, IQ, and Complete Covariate Data (n = 400)</th>
<th>Nonfluoridated (n = 238)</th>
<th>Fluoridated (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of mother at enrollment, mean (SD), y</td>
<td>32.33 (5.07)</td>
<td>32.61 (4.90)</td>
<td>32.52 (4.03)</td>
<td></td>
</tr>
<tr>
<td>Prepregnancy BMI, mean (SD)</td>
<td>25.19 (6.02)</td>
<td>25.19 (6.35)</td>
<td>24.33 (5.10)</td>
<td></td>
</tr>
<tr>
<td>Married or common law</td>
<td>497 (97)</td>
<td>225 (95)</td>
<td>159 (98)</td>
<td></td>
</tr>
<tr>
<td>Born in Canada</td>
<td>426 (83)</td>
<td>187 (79)</td>
<td>131 (81)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>463 (90)</td>
<td>209 (88)</td>
<td>146 (90)</td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trade school diploma/high school</td>
<td>162 (32)</td>
<td>80 (34)</td>
<td>38 (24)</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree or higher</td>
<td>350 (68)</td>
<td>158 (66)</td>
<td>124 (76)</td>
<td></td>
</tr>
<tr>
<td>Employed at time of pregnancy</td>
<td>452 (88)</td>
<td>205 (86)</td>
<td>149 (92)</td>
<td></td>
</tr>
<tr>
<td>Net income household &gt;$70,000 CAD</td>
<td>364 (71)</td>
<td>162 (68)</td>
<td>115 (71)</td>
<td></td>
</tr>
<tr>
<td>HOME total score, mean (SD)</td>
<td>47.32 (4.32)</td>
<td>47.28 (4.48)</td>
<td>48.14 (3.90)</td>
<td></td>
</tr>
<tr>
<td>Smoked in trimester 1</td>
<td>12 (2)</td>
<td>7 (3)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Secondhand smoke in the home</td>
<td>18 (4)</td>
<td>9 (4)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption, alcoholic drink/mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>425 (83)</td>
<td>192 (81)</td>
<td>136 (84)</td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>41 (8)</td>
<td>23 (10)</td>
<td>11 (7)</td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>46 (9)</td>
<td>23 (10)</td>
<td>15 (9)</td>
<td></td>
</tr>
<tr>
<td>Parity (first birth)</td>
<td>233 (46)</td>
<td>119 (50)</td>
<td>71 (44)</td>
<td></td>
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<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>264 (52)</td>
<td>118 (50)</td>
<td>83 (51)</td>
<td></td>
</tr>
<tr>
<td>Age at testing, mean (SD), y</td>
<td>3.42 (0.32)</td>
<td>3.36 (0.31)</td>
<td>3.49 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Gestation, mean (SD), wk</td>
<td>39.12 (1.57)</td>
<td>39.19 (1.47)</td>
<td>39.17 (1.81)</td>
<td></td>
</tr>
<tr>
<td>Birth weight, mean (SD), kg</td>
<td>3.47 (0.49)</td>
<td>3.48 (0.48)</td>
<td>3.47 (0.53)</td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>107.16 (13.26)</td>
<td>108.07 (13.31)</td>
<td>108.21 (13.72)</td>
<td></td>
</tr>
<tr>
<td>Boysd</td>
<td>104.61 (14.09)</td>
<td>106.31 (13.60)</td>
<td>104.78 (14.71)</td>
<td></td>
</tr>
<tr>
<td>Girlsd</td>
<td>109.56 (11.96)</td>
<td>109.86 (12.83)</td>
<td>111.47 (11.89)</td>
<td></td>
</tr>
<tr>
<td>Exposure variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUFSG concentration, mg/L*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>512</td>
<td>228</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.51 (0.36)</td>
<td>0.40 (0.27)</td>
<td>0.69 (0.42)</td>
<td></td>
</tr>
<tr>
<td>Fluoride intake level per day, mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>369*</td>
<td>238</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.54 (0.44)</td>
<td>0.30 (0.26)</td>
<td>0.93 (0.43)</td>
<td></td>
</tr>
<tr>
<td>Water fluoride concentration, mg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>369*</td>
<td>238</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.31 (0.23)</td>
<td>0.13 (0.06)</td>
<td>0.59 (0.08)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, Canadian dollars; FSIQ, Full Scale IQ; HOME, Home Observation for Measurement of the Environment; MUFSG, maternal urinary fluoride adjusted for specific gravity.

SI conversion factor: To convert fluoride to millimoles per liter, multiply by 0.05263.

a Owing to missing water treatment plant data and/or MUF data, the samples are distinct with some overlapping participants in both groups (n = 369).

b All of the listed variables were tested as potential covariates, as well as the following: paternal variables (age, education, employment status, smoking status, and race/ethnicity); maternal chronic condition during pregnancy and birth country; breastfeeding duration; and time of void and time since last void.

c Maternal urinary fluoride (averaged across all 3 trimesters) and corrected for specific gravity.

d The FSIQ score has a mean (SD) of 100 (15); US population norms used.

* Owing to missing water treatment plant data, the samples in the fluoridated and nonfluoridated regions do not add up to the MUF sample size.
whether the MUF<sub>SG</sub> association significantly differed between lower and higher levels of MUF<sub>SG</sub> based on 3 knots, which were set at 0.5 mg/L (mean MUF<sub>SG</sub>), 0.8 mg/L (threshold seen in the Mexican birth cohort), and 1 mg/L (optimal concentration in the United States until 2015). For fluoride intake, knots were set at 0.4 mg (mean fluoride intake), 0.8 mg, and 1 mg (in accordance with MUF<sub>SG</sub>). We also examined sex-specific associations in all models by testing the interactions between child sex and each fluoride measure.

In sensitivity analyses, we tested whether the associations between MUF<sub>SG</sub> and IQ were confounded by maternal blood concentrations of lead, mercury, manganese, perfluoro-octanoic acid, or urinary arsenic. We also conducted sensitivity analyses by removing IQ scores that were greater than or less than 2.5 standard deviations from the sample mean. Additionally, we examined whether using MUF adjusted for creatinine instead of SG affected the results.

In additional analyses, we examined the association between our 2 measures of fluoride exposure (MUF<sub>SG</sub> and fluoride intake) with VIQ and PIQ. Additionally, we examined whether water fluoride concentration was associated with FSIQ, VIQ, and PIQ scores.

For all analyses, statistical significance tests with a type I error rate of 5% were used to test sex interactions, while 95% confidence intervals were used to estimate uncertainty. Analyses were conducted using R software (the R Foundation). The <em>P</em> value level of significance was .05, and all tests were 2-sided.

**Results**

For the first measure of fluoride exposure, MUF<sub>SG</sub>, 512 of 601 mother-child pairs (85.2%) who completed the neurodevelopmental visit had urinary fluoride levels measured at each trimester of the mother’s pregnancy and complete covariate data (Figure 1); 89 (14.8%) were excluded for missing MUF<sub>SG</sub> at 1 or more trimesters (n = 75) or missing 1 or more covariates included in the regression (n = 14) (Figure 1). Of the 512 mother-child pairs with MUF<sub>SG</sub> data (and all covariates), 264 children were female (52%).

For the second measure of fluoride exposure, fluoride intake from maternal questionnaire, data were available for 400 of the original 601 mother-child pairs (66.6%): 201 women (33.4%) were excluded for reporting not drinking tap water (n = 59), living outside of the predefined water treatment plant zone (n = 108), missing beverage consumption data (n = 20), or missing covariate data (n = 14) (Figure 1).

Children had mean FSIQ scores in the average range (population normed) (mean [SD], 107.16 [13.26], range = 52-143), with girls (109.56 [11.96]) showing significantly higher scores than boys (104.61 [14.09]; <em>P</em> < .001) (Table 1). The demographic characteristics of the 512 mother-child pairs included in the primary analysis were not substantially different from the original MIREC cohort or subset of mother-child pairs without 3 urine samples (eTable 1 in the Supplement). Of the 400 mother-child pairs with fluoride intake data (and all covariates), 118 of 238 (50%) in the group living in a nonfluoridated region were female and 83 of 162 (51%) in the group living in a fluoridated region were female.

**Fluoride Measurements**

The median MUF<sub>SG</sub> concentration was 0.41 mg/L (range, 0.06-2.44 mg/L). Mean MUF<sub>SG</sub> concentration was significantly higher among women (n = 141) who lived in communities with fluoridated drinking water (0.69 [0.42] mg/L) compared with women (n = 228) who lived in communities without fluoridated drinking water (0.40 [0.27] mg/L; <em>P</em> < .001) (Table 1; Figure 2).

The median estimated fluoride intake was 0.39 mg per day (range, 0.01-2.65 mg). As expected, the mean (SD) fluoride intake was significantly higher for women (162 [40.5%]) who lived in communities with fluoridated drinking water (mean [SD], 0.93 [0.43] mg) than women (238 [59.5%]) who lived in communities without fluoridated drinking water (0.30 [0.26] mg; <em>P</em> < .001) (Table 1; Figure 2). The MUF<sub>SG</sub> was moderately correlated with fluoride intake (r = 0.49; <em>P</em> < .001) and water fluoride concentration (r = 0.37; <em>P</em> < .001).

**Maternal Urinary Fluoride Concentrations and IQ**

Before covariate adjustment, a significant interaction (P for interaction = .03) between MUF<sub>SG</sub> and child sex (B = 7.24; 95% CI, 0.81-13.67) indicated that MUF<sub>SG</sub> was associated with FSIQ in boys; an increase of 1 mg/L MUF<sub>SG</sub> was associated with a 4.49 (95% CI, −8.38 to −0.60; <em>P</em> = .02) lower FSIQ score in boys. In contrast, MUF<sub>SG</sub> was not significantly associated with FSIQ score in girls (B = 2.23; 95% CI, −2.77 to 7.23; <em>P</em> = .38) (Table 2).

Adjusting for covariates, a significant interaction (P for interaction = .02) between child sex and MUF<sub>SG</sub> (B = 6.89; 95% CI, 0.96-12.82) indicated that an increase of 1 mg/L MUF<sub>SG</sub> was associated with a 4.49 (95% CI, −8.38 to −0.60; <em>P</em> = .02) lower FSIQ score for boys. An increase from the 10th to 90th percentile of MUF<sub>SG</sub> was associated with a 3.14 IQ decrement among boys (Table 2; Figure 3). In contrast, MUF<sub>SG</sub> was not significantly associated with FSIQ score in girls (B = 2.43; 95% CI, −2.51 to 7.36; <em>P</em> = .33).
**Estimated Fluoride Intake and IQ**

A 1-mg increase in fluoride intake was associated with a 3.66 (95% CI, −7.16 to −0.15; \(P = .04\)) lower FSIQ score among boys and girls (Table 2; Figure 3). The interaction between child sex and fluoride intake was not statistically significant (\(B = 1.17\); 95% CI, −4.08 to 6.41; \(P = .66\)).

**Sensitivity Analyses**

Adjusting for lead, mercury, manganese, perfluorooctanoic acid, or arsenic concentrations did not substantially change the overall estimates of MUFSG for boys or girls (eTable 2 in the Supplement). Use of MUF adjusted for creatinine did not substantially alter the associations with FSIQ (eTable 2 in the Supplement). Including time of void and time since last void did not substantially change the regression coefficient of MUFSG among boys or girls.

Estimates for determining the association between MUFSG and PIQ showed a similar pattern with a statistically significant interaction between MUFSG and child sex (\(P = .007\)). An increase of 1 mg/L MUFSG was associated with a 4.63 (95% CI, −9.01 to −0.25; \(P = .04\)) lower PIQ score in boys, but the association was not statistically significant in girls (\(B = 4.51\); 95% CI, −1.02 to 10.05; \(P = .11\)). An increase of 1 mg/L MUFSG was not significantly associated with VIQ in boys (\(B = −2.85\); 95% CI, −6.65 to 0.95; \(P = .14\)) or girls (\(B = 0.55\); 95% CI, −4.28 to 5.37; \(P = .82\)); the interaction between MUFSG and child sex was not statistically significant (\(P = .25\)) (eTable 3 in the Supplement).

Consistent with the findings on estimated maternal fluoride intake, increased water fluoride concentration (per 1 mg/L) was associated with a 5.29 (95% CI, −10.39 to −0.19) lower FSIQ score among boys and girls and a 1.37 (95% CI, −1.88 to −7.28) lower PIQ score (eTable 4 in the Supplement).

**Discussion**

Using a prospective Canadian birth cohort, we found that estimated maternal exposure to higher fluoride levels during pregnancy was associated with lower IQ scores in children. This association was supported by converging findings from 2 measures of fluoride exposure during pregnancy. A difference in MUFSG spanning the interquartile range for the entire sample (ie, 0.33 mg/L), which is roughly the difference in...
higher levels of fluoride exposure and lower intellectual logic studies that have shown an association between ment for boys in our study for every 1 mg/L of MUF.10 The in IQ in preschool-aged children compared with a 4.5 decre-
osition in a large birth cohort receiving optimally fluoridated water. These findings are consistent with that of a Mexican birth cohort study that reported a 6.3 decrement in Fluoride exposure predominantly occur at the tooth surface after the teeth have erupted.43 Therefore, there is no benefit of systemic exposure to fluoride during pregnancy for the prevention of caries in offspring.44 The evidence showing an association between fluoride exposure and lower IQ scores raises a possible new concern about cumulative exposures to fluoride during pregnancy, even among pregnant women exposed to optimally fluoridated water.

Strengths and Limitations
Our study has several strengths and limitations. First, urinary fluoride has a short half-life (approximately 5 hours) and depends on behaviors that were not controlled in our study, such as consumption of fluoride-free bottled water or swallowing toothpaste prior to urine sampling. We minimized this limitation by using 3 serial urine samples and tested for time of urine sample collection and time since last void, but these variables did not alter our results. Second, although higher maternal ingestion of fluoride corresponds to higher fetal plasma fluoride levels,45 even serial maternal urinary spot samples may not precisely represent fetal exposure throughout pregnancy. Third, while our analyses controlled for a comprehensive set of covariates, we did not have maternal IQ data. However, there is no evidence suggesting that fluoride exposure differs as a function of maternal IQ; our prior study did not observe a significant association between MUF levels and maternal education level.12 Moreover, a greater proportion of women living in fluoridated communities (124 [76%]) had a university-level degree compared with women living in nonfluoridated communities (158 [66%]). Nonetheless, despite our comprehensive array of covariates included, this observational study design could not address the possibility of other unmeasured residual confounding. Fourth, fluoride intake did not measure actual fluoride concentration in tap water in the participant’s home; Toronto, for example, has overlapping water treatment plants servicing the same household. Similarly, our fluoride intake estimate only considered fluoride from beverages; it did not include fluoride from other sources such as dental products or food. Furthermore, fluoride intake data were limited by self-report of mothers’ recall of beverage consumption per day, which was sampled at 2 points of pregnancy, and we lacked information regarding specific tea brand.17,18 In addition, our methods of estimating maternal fluoride intake have not been validated; however, we show construct validity with MUF. Fifth, this study did not include assessment of postnatal fluoride exposure or consumption. However, our future analyses will assess exposure to fluoride in the MIREC cohort in infancy and early childhood.
Conclusions

In this prospective birth cohort study from 6 cities in Canada, higher levels of fluoride exposure during pregnancy were associated with lower IQ scores in children measured at age 3 to 4 years. These findings were observed at fluoride levels typically found in white North American women. This indicates the possible need to reduce fluoride intake during pregnancy.

References


Association Between Maternal Fluoride Exposure During Fetal Development and IQ Scores in Offspring in Canada

Original Investigation Research


