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

Rivka Green, MA; Bruce Lanphear, MD; Richard Hornung, PhD; David Flora, PhD; E. Angeles Martinez-Mier, DDS; Raichel Neufeld, BA; Pierre Ayotte, PhD; Gina Muckle, PhD; Christine Till, PhD

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 (MUF_{SG}), 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 MUF_{SG} 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) MUF_{SG} 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 MUF_{SG} (6.89; 95% CI, 0.96-12.82) indicating a differential association between boys and girls. A 1-mg/L increase in MUF_{SG} 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.

Editorial and Editor's Note

Supplemental content

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Christine Till, PhD, Department of Psychology, York University, 4700 Keele St, Toronto, ON M3J 1P3, Canada (ctill@yorku.ca).

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.[1] 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 memory[4] 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-analysis[6] of 27 epidemiologic studies and in studies[7,8] 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]

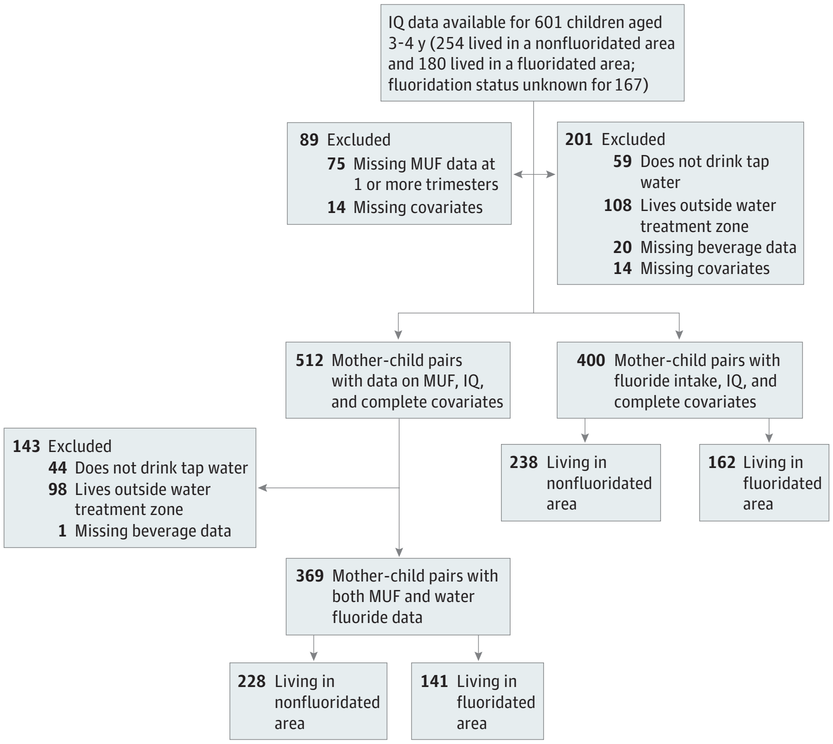
Urinary fluoride concentration was analyzed at the Indiana University School of Dentistry using a modification of the hexamethyldisiloxane (Sigma Chemical Co) microdiffusion procedure[15] and described in our previous work.[12] Fluoride concentration could be measured to 0.02 mg/L. We excluded 2 samples (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: $MUF_{SG} = MUF_i \times (SG_M\text{-}1)/(SG_i\text{-}1)$, 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_M 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

Figure 1. Flowchart of Inclusion Criteria



MUF indicates maternal urinary fluoride.

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),[17,18] 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).[18] 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[19] 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_{SG} 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

Table 1. Demographic Characteristics and Exposure Outcomes for Mother-Child Pairs With MUF_{SG} (n = 512) and Fluoride Intake Data (n = 400) by Fluoridated and Nonfluoridated Status[a]

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

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; MUF_{SG}, 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.

[e] Owing to missing water treatment plant data, the samples in the fluoridated and nonfluoridated regions do not add up to the MUF sample size.

difference spanning the 25th to 75th percentile range (which corresponds to a 0.33 mg/L and 0.62 mg F/d difference in MUF_{SG} 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 MUF_{SG} 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 MUF_{SG} 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 MUF_{SG} 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 whether the MUF_{SG} association significantly differed between lower and higher levels of MUF_{SG} based on 3 knots, which were set at 0.5 mg/L (mean MUF_{SG}), 0.8 mg/L (threshold seen in the Mexican birth cohort),[10] and 1 mg/L (optimal concentration in the United States until 2015).[20] For fluoride intake, knots were set at 0.4 mg (mean fluoride intake), 0.8 mg, and 1 mg (in accordance with MUF_{SG}). 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_{SG} and IQ were confounded by maternal blood concentrations of lead,[21] mercury,[21] manganese,[21,22] perfluoro-octanoic acid,[23] or urinary arsenic.[24] 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_{SG} 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).[25] The *P* value level of significance was .05, and all tests were 2-sided.

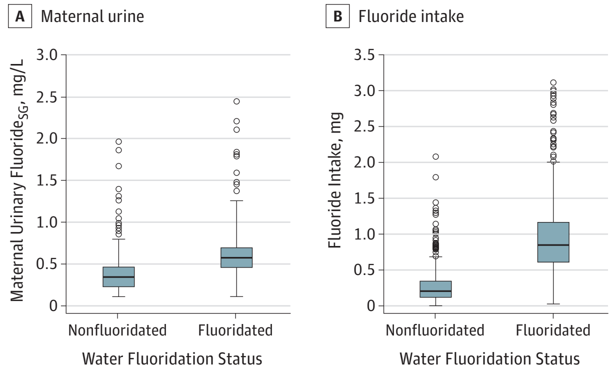
Results

For the first measure of fluoride exposure, MUF_{SG}, 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_{SG} 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_{SG} 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]; *P* < .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.

Figure 2. Distribution of Fluoride Levels in Maternal Urine and for Estimated Fluoride Intake by Fluoridation Status



To convert fluoride to millimoles per liter, multiply by 0.05263.

Fluoride Measurements

The median MUF_{SG} concentration was 0.41 mg/L (range, 0.06-2.44 mg/L). Mean MUF_{SG} 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; *P* < .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; *P* < .001) (Table 1; Figure 2). The MUF_{SG} was moderately correlated with fluoride intake (r = 0.49; *P* < .001) and water fluoride concentration (r = 0.37; *P* < .001).

Maternal Urinary Fluoride Concentrations and IQ

Before covariate adjustment, a significant interaction (*P* for interaction = .03) between MUF_{SG} and child sex (*B* = 7.24; 95% CI, 0.81- 13.67) indicated that MUF_{SG} was associated with FSIQ in boys; an increase of 1 mg/L MUF_{SG} was associated with a 5.01 (95% CI, −9.06 to −0.97; *P* = .02) lower FSIQ score in boys. In contrast, MUF_{SG} was not significantly associated with FSIQ score in girls (*B* = 2.23; 95% CI, −2.77 to 7.23; *P* = .38) (**Table 2**).

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

Table 2. Unadjusted and Adjusted Associations Estimated From Linear Regression Models of Fluoride Exposure Variables and FSIQ Scores

Variable	Difference (95% CI)			
		Adjusted Estimates, Regression Coefficients Indicate Change in Outcome per[a]		
	Unadjusted	1 mg	25th to 75th Percentiles	10th to 90th Percentiles
MUF_{SG}[b,c]	−2.60 (−5.80 to 0.60)	−1.95 (−5.19 to 1.28)	−0.64 (−1.69 to 0.42)	−1.36 (−3.58 to 0.90)
Boys	−5.01 (−9.06 to −0.97)	−4.49 (−8.38 to −0.60)	−1.48 (−2.76 to −0.19)	−3.14 (−5.86 to −0.42)
Girls	2.23 (−2.77 to 7.23)	2.40 (−2.53 to 7.33)	0.79 (−0.83 to 2.42)	1.68 (−1.77 to 5.13)
Fluoride intake[d,e]	−3.19 (−5.94 to −0.44)	−3.66 (−7.16 to −0.15)	−2.26 (−4.45 to −0.09)	−3.80 (−7.46 to −0.16)

Abbreviations: FSIQ, Full Scale IQ; HOME, Home Observation for Measurement of the Environment; MUF_{SG}, maternal urinary fluoride adjusted for specific gravity.

[a] Adjusted estimates pertain to predicted FSIQ difference for a value spanning the interquartile range (25th to 75th percentiles) and 80th central range (10th to 90th percentiles): (1) MUF_{SG}: 0.33 mg/L, 0.70 mg/L, respectively; (2) fluoride intake: 0.62 mg, 1.04 mg, respectively.

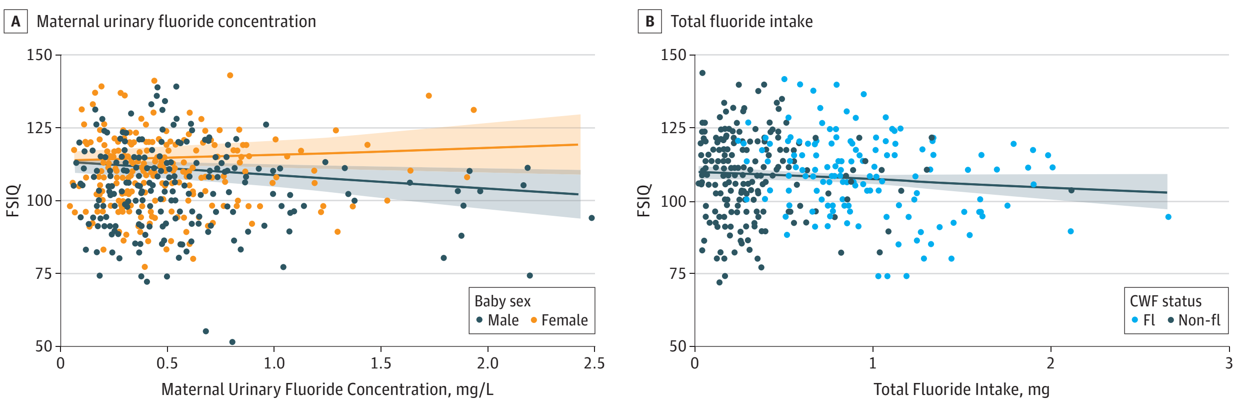
[b] n = 512.

[c] Adjusted for city, HOME score, maternal education, race/ethnicity, and including child sex interaction.

[d] n = 400.

[e] Adjusted for city, HOME score, maternal education, race/ethnicity, child sex, and prenatal secondhand smoke exposure.

Figure 3. Covariate Results of Multiple Linear Regression Models of Full Scale IQ (FSIQ) from Maternal Urinary Fluoride Concentration by Child Sex (n = 512) and Total Fluoride Intake Estimated from Daily Maternal Beverage Consumption (n = 400)



B, Community fluoridation status (CWF) is shown for each woman; black dots represent women living in nonfluoridated (non-Fl) communities and blue dots represent women living in fluoridated (Fl) communities.

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* for interaction = .66).

Sensitivity Analyses

Adjusting for lead, mercury, manganese, perfluorooctanoic acid, or arsenic concentrations did not substantially change the overall estimates of MUF_{SG} 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 MUF_{SG} among boys or girls.

Estimates for determining the association between MUF_{SG} and PIQ showed a similar pattern with a statistically significant interaction between MUF_{SG} and child sex (*P* for interaction = .007). An increase of 1 mg/L MUF_{SG} 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 MUF_{SG} 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 MUF_{SG} and child sex was not statistically significant (*P* for interaction = .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 13.79 (95% CI, −18.82 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 MUF_{SG} spanning the interquartile range for the entire sample (ie, 0.33 mg/L), which is roughly the difference in

MUF_{SG} concentration for pregnant women living in a fluoridated vs a nonfluoridated community, was associated with a 1.5-point IQ decrement among boys. An increment of 0.70 mg/L in MUF_{SG} concentration was associated with a 3-point IQ decrement in boys; about half of the women living in a fluoridated community have a MUF_{SG} equal to or greater than 0.70 mg/L. These results did not change appreciably after controlling for other key exposures such as lead, arsenic, and mercury.

To our knowledge, this study is the first to estimate fluoride exposure 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 IQ in preschool-aged children compared with a 4.5 decrement for boys in our study for every 1 mg/L of MUF.[10] The findings of the current study are also concordant with ecologic studies that have shown an association between higher levels of fluoride exposure and lower intellectual abilities in children.[7,8,26] Collectively, these findings support that fluoride exposure during pregnancy may be associated with neurocognitive deficits.

In contrast with the Mexican study,[10] the association between higher MUF_{SG} concentrations and lower IQ scores was observed only in boys but not in girls. Studies of fetal and early childhood fluoride exposure and IQ have rarely examined differences by sex; of those that did, some reported no differences by sex.[10,27-29] Most rat studies have focused on fluoride exposure in male rats,[30] although 1 study[31] showed that male rats were more sensitive to neurocognitive effects of fetal exposure to fluoride. Testing whether boys are potentially more vulnerable to neurocognitive effects associated with fluoride exposure requires further investigation, especially considering that boys have a higher prevalence of neurodevelopmental disorders such as ADHD, learning disabilities, and intellectual disabilities.[32] Adverse effects of early exposure to fluoride may manifest differently for girls and boys, as shown with other neurotoxicants.[33-36]

The estimate of maternal fluoride intake during pregnancy in this study showed that an increase of 1 mg of fluoride was associated with a decrease of 3.7 IQ points across boys and girls. The finding observed for fluoride intake in both boys and girls may reflect postnatal exposure to fluoride, whereas MUF primarily captures prenatal exposure. Importantly, we excluded women who reported that they did not drink tap water and matched water fluoride measurements to time of pregnancy when estimating maternal fluoride intake. None of the fluoride concentrations measured in municipal drinking water were greater than the maximum acceptable concentration of 1.5 mg/L set by Health Canada; most (94.3%) were lower than the 0.7 mg/L level considered optimal.[37]

Water fluoridation was introduced in the 1950s to prevent dental caries before the widespread use of fluoridated dental products. Originally, the US Public Health Service set the optimal fluoride concentrations in water from 0.7 to 1.2 mg/L to achieve the maximum reduction in tooth decay and minimize the risk of enamel fluorosis.[38] Fluorosis, or mottling, is a symptom of excess fluoride intake from any source occurring during the period of tooth development. In 2012, 68% of adolescents had very mild to severe enamel fluorosis.[39] The higher prevalence of enamel fluorosis, especially in fluoridated areas,[40] triggered renewed concern about excessive ingestion of fluoride. In 2015, in response to fluoride overexposure and rising rates of enamel fluorosis,[39,41,42] the US Public Health Service recommended an optimal fluoride concentration of 0.7 mg/L, in line with the recommended level of fluoride added to drinking water in Canada to prevent caries. However, the beneficial effects of fluoride 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.

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Author Affiliations: Faculty of Health, York University, Toronto, Ontario, Canada (Green, Flora, Neufeld, Till); Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada (Lanphear); Child and Family Research Institute, British Columbia Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada (Lanphear); Pediatrics and Environmental Health, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Hornung); School of Dentistry, Indiana University, Indianapolis (Martinez-Mier); Department of Social and Preventive Medicine, Laval University, Québec City, Québec, Canada. (Ayotte); Centre de Recherche du CHU de Québec, Université Laval, Québec City, Québec, Canada (Ayotte, Muckle); School of Psychology, Laval University, Québec City, Québec, Canada (Muckle).

Author Contributions: Ms Green and Dr Till had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Green, Lanphear, Martinez-Mier, Ayotte, Muckle, Till.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Green, Flora, Martinez-Mier, Muckle, Till.
Critical revision of the manuscript for important intellectual content: All authors.
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Supplementary Online Content

Green R, Lanphear B, Hornung R, et al. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. Published online August 19, 2019. *JAMA Pediatr.* doi:10.1001/jamapediatrics.2019.1729

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1: Comparison of current sample to other MIREC samples

Variable	Participants in the MIREC cohort with:		
	Live births[a]	**Women with 3 urine samples and child IQ scores**	**Women with <3 urine samples and child IQ scores**
n	1983	512	70
Mean (SD) age of mother at enrollment (years)	32.2 (5.1)	32.51 (4.46)	32.43 (5.29)
Caucasian, No. (%)	1651 (85)	463 (90)	56 (80)
Married or Common-law, No. (%)	1890 (95.3)	497 (97)	63 (90)
Born in Canada, No. (%)	1569 (79)	426 (83)	53 (76)
Maternal Education, No. (%)			
High school or less	158 (9)	24 (5)	4 (6)
Some college	100 (5)	17 (3)	5 (7)
College diploma	412 (24)	121 (24)	20 (29)
University degree	1246 (62)	348 (68)	40 (57)
Employed at time of pregnancy, No. (%)	1647 (83)	452 (88)	87.0
Net household income >$70,000, No. (%)	1269 (64)	364 (71)	65.2

Abbreviations: SD = standard deviation

[a]from a total of 2001 women who were recruited

Note: Differences between the analytic sample (n=512), live births sample (n=1983), and excluded participants (n=70) were all considered small (i.e. Cohen's effect size *h* of ≤0.30).

eTable 2: Sensitivity analyses predicting Full Scale IQ (FSIQ).

MLR Models	***N***	***B (SE)* of predictor**	***p***	**95% CI**
Model $_{A}$	512	-4.49 (1.98)	.02	-8.38, -0.60
Model $_{A+lead}$	504	-4.61 (1.98)	.02	-8.50, -0.71
Model $_{A+mercury}$	456	-5.13 (2.05)	.01	-9.16, -1.10
Model $_{A+PFOA}$	503	-4.57 (1.97)	.02	-8.21, -0.50
Model $_{A+arsenic}$	512	-4.44 (1.99)	.03	-8.35, -0.54
Model $_{A+manganese}$	502	-4.55 (1.97)	.02	-8.42, -0.69
Model $_{A+second\ hand\ smoke\ exposure}$	512	-4.18 (1.98)	.03	-8.06, -0.30
Model $_{B}$	510	-4.11 (1.92)	.03	-7.89, -0.33
Model $_{C}$	407	-4.96 (1.83)	.007	-8.56, -1.36
Model $_{D}$	369	-6.25 (2.70)	.02	-11.56, -0.94

Abbreviations: HOME = Home Observation for Measurement of the Environment; PFOA = perfluorooctanoic acid; MLR = multiple linear regression; MUF = maternal urinary fluoride

Model $_{A}$ – MUF_{SG} coefficient for boys controlling for city, HOME total score, race and maternal level of education with baby sex as an interaction term

Model $_{B}$ – Model $_{A}$ without two boys with FSIQ lower than 60

Model $_{C}$ – MUF coefficient for boys adjusted for creatinine with same covariates as Model $_{A}$

Model $_{D}$ – using water fluoride concentration as a predictor for those women who have MUF values only

eTable 3. Unadjusted and adjusted effect estimates from linear regression models of fluoride exposure variables predicting Verbal IQ and Performance IQ scores.

	Performance IQ		Verbal IQ	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Predictor	***B* (95% CI)**	***B* (95% CI)**	***B* (95% CI)**	***B* (95% CI)**
MUF_{SG}[a]	-5.81* (-9.31, -2.30)	-1.24 (-4.88, 2.40)	1.28 (-1.87, 4.43)	-1.60 (-4.74, 1.55)
Boys	-8.81* (-13.29, -4.32)	-4.63* (-9.01, -0.25)[d]	-0.21 (-4.19, 3.77)	-2.82 (-6.62, 0.98)[c]
Girls[b]	-0.56 (-6.09, 4.97)	4.51 (-1.02, 10.05)[d]	4.78 (-0.14, 9.70)	0.50 (-4.32, 5.33)[c]
Fluoride intake[c]	-5.75* (-8.74, -2.76)	-2.74 (-6.82, 1.34)[e]	-0.03 (-2.71, 2.64)	-3.08 (-6.40, 0.25)[d]

Abbreviations: MUF_{SG} = maternal urinary fluoride adjusted for specific gravity; HOME = Home Observation for Measurement of the Environment

[a] N=507 for PIQ; N=509 for VIQ

[b] Girls had significantly higher scores on VIQ ($p < .001$) and PIQ ($p = .03$) compared with boys

[c] N=395 for PIQ; N=399 for VIQ; Missing data due to incomplete questionnaire responses to beverage consumption

[d] adjusted for city, HOME score, maternal education, race and including child sex interaction

[e] adjusted for HOME score, maternal education, race, child sex, prenatal second-hand smoke exposure, and city

*$p < .05$

eTable 4: Unadjusted and adjusted effect estimates from linear regression models of water fluoride concentration (mg/L) predicting FSIQ scores.

		Adjusted estimates[b]		
	Unadjusted (FSIQ)	**Full Scale IQ**	**Performance IQ**	**Verbal IQ**
Predictor	***B* (95% CI)**	***B* (95% CI)**	***B* (95% CI)**	***B* (95% CI)**
Water fluoride concentration[a]	3.49 (-9.04, 2.06)	-5.29* (-10.39, -0.19)[b]	-13.79* (-18.82, -7.28)	3.37 (-1.50, 8.24)

[a] N=420

[b] adjusted for HOME score, maternal education, race, child sex, and prenatal second-hand smoke exposure; because city was strongly multi-collinear with water fluoride concentration (VIF >20), it was excluded from the model

*p < .05

August 19, 2019

expert reaction to study looking at maternal exposure to fluoride and IQ in children

Research, published in *JAMA Pediatrics*, reports that maternal exposure to fluoride in pregnancy can lead to lower IQ scores in young children.

Prof Thom Baguley, Professor of Experimental Psychology, Nottingham Trent University, said:

"First, the claim that maternal fluoride exposure is associated with a decrease in IQ of children is false. This finding was non-significant (but not reported in the abstract). They did observe a decrease for male children and a slight increase in IQ (but non-significant) for girls. This is an example of subgroup analysis – which is frowned upon in these kinds of studies because it is nearly always possible to identify some subgroup which shows an effect if the data are noisy. Here the data are very noisy. A further issue is that the estimate of the decrease in IQ for male offspring is unfeasibility large – at 4-5 IQ points. This level of average deficit would be readily detectable in previous studies and is likely a reflection of bias or very noisy data (the interval estimate here is very wide). As high fluoride areas are not randomly assigned there are also countless uncontrolled confounders. While they did correct for a limited set of covariates, the overall effect was non-significant with and without covariates. In summary it is not correct to imply that the data here show evidence of a link between maternal fluoride exposure and IQ. The average change in IQ is not statistically significant."

Dr Oliver Jones, Associate Professor of Analytical Chemistry, RMIT University, said:

"While this paper's title (which hints that high fluoride may affect your children's intelligence) might at first sound scary I think there are several factors that should be kept in mind when reading it.

"The key words in the paper are "higher levels". The authors state that an increase of 1 milligram per liter (1 mg/L) increase in fluoride was associated with a 4.49 point lower IQ score but fluoride intake appears to have been below 1 mg/L for most people in the study, even for those with fluoridated water, and nearly everyone (bar a few outliers) had a fluoride intake of less than 2 mg/L (which multiple previous studies have shown is safe) . There is also a Lot of variation in the data – which makes drawing firm conclusions/ predictions from it difficult.

"There are also a number of potential confounding factors including the fact that the water intake was self-reported and, as the authors admit, some of the methods used are not validated. One observed association also only seems to occur in boys and not girls but no explanation is given as to why this should be the case?

"In conclusion, while the work in interesting and the authors have tried to be thorough, in the end they only claim to have shown an association between two factors – not prove they are linked; the "possibility" of an effect justifying future research is not the same as concluding that there is an effect and; nearly everyone in this study had low levels of fluoride intake anyway. So, although the work is interesting, I don't think there is a need to worry."

Dr Joy Leahy, Statistical Ambassador, Royal Statistical Society, said:

"This study aimed to specifically assess the impact of maternal fluoride exposure during pregnancy and IQ scores in offspring. However, we should expect that fluoride exposure during pregnancy will be strongly associated with fluoride exposure in children after birth. For example, if a woman is living in an area with fluoridated water during pregnancy, then her child is likely to grow up drinking this same fluoridated water. Therefore, it is difficult to say whether any association found is driven by the fluoride consumption in pregnancy, or an assumed fluoride consumption in the infant after birth."

Prof Alastair Hay, Professor (Emeritus) of Environmental Toxicology, University of Leeds, said:

"The Green et al. study looks at the association between maternal exposure to fluoride during pregnancy and IQ at ages 3 and 4 in the children. The authors find an association between maternal intake of fluoride and reduced IQ in boys, but not girls.

"I have a range of concerns about this paper.

"Firstly, as the authors acknowledge maternal intake of fluoride has not been validated. I see this as a crucial failure. For a substance with a short half-life, such as fluoride, urine concentrations vary hugely and are really only representative of the last drink. Validation of intake is something you must do before looking at associations.

"The authors look at mid-stream urine concentrations in pregnancy and base findings largely on these and the association with IQ at ages 3 to 4. Whilst the authors correct for changes in urine concentration (early morning urine is more concentrated than later samples in the day, for example) the half-life of fluorine is going to have a much greater impact on concentrations of the chemical than any adjustment to take account of urine dilution.

“Although the authors adjust for a range of substances (including lead in maternal blood and say this has no effect on findings, for me, the major serious gap is the range of exposure to multifarious substances, including lead, that the children would have had between birth and IQ assessment at ages 3 or 4. We know that lead exposure has devastating effects on IQ in children and this study takes no account of postnatal lead exposure.

“A curious finding is that the link between maternal urine fluoride and IQ decrements is only seen in boys and not girls. And the IQ decrement is not present for verbal IQ in boys. Whilst the authors are just reporting what they found I find these sex differences difficult to explain. With a neurotoxicant you might expect both sexes to be affected.

“There are many limitations which could affect the findings reported in this paper and until these are addressed, I regard the results as interesting, but not something to alter fluid or food intake by mothers.”

Prof Rick Cooper, Professor of Cognitive Science, Birkbeck, University of London, said:

“Green et al.’s headline claim that “maternal exposure to higher levels of fluoride during pregnancy [is] associated with lower IQ scores in children aged 3 to 4 years” is not supported by the data. In fact, when using the more reliable measure of fluoride exposure, a significant decrease in IQ was found only in boys – girls showed a non-significant increase in IQ. The negative effect was driven by a small number of boys whose mothers had extreme levels of fluoride exposure, but even these children had IQ in the normal range.

“There are numerous other complicating factors that limit the interpretability of the results. For example:

“While attempts were made to control for various chemical toxins, no attempt was made to take account of socio-economic status.

“There was no attempt to assess whether the fluoride estimate measure is accurate (yet there is opportunity to do so). Relative to the fluoride urine test, this estimate produces lower levels of fluoride in non-fluoride water areas, but higher levels of fluoride in fluoride water areas, so the accuracy of this estimate is questionable.

“The male sample includes a couple of extremely low IQ scores (below 70 would be special needs, but they have two boys with IQ in the 50s). The results would be more convincing if it were shown that they did not depend on these children.

“The fluoride distribution is not homogenous. There are very few children/observations at high levels and most at low levels, so the assumptions of the statistical test are not met, and any conclusions must be interpreted with caution.

"There is no consideration of whether an effect, if present, might be non-linear. For example, it appears that there is no effect at low concentrations, with the effect only arising at extreme levels. The chosen statistical approach does not allow consideration of this possibility.

"Lastly, one cannot tell if any effect (if present) is due to prenatal exposure or postnatal exposure."

Prof Kevin McConway, Emeritus Professor of Applied Statistics, The Open University, said:

"This question would need to be researched in a lot more detail, in my view, before any clear conclusions can be drawn. I think that there are far too many questions to be answered before pregnant women should feel they must reduce their fluoride intake, or public health authorities should change their advice of policies. The reduction in average IQ scores in young children, associated with higher fluoride intake during their mothers' pregnancies, is really fairly small, and there are reasons to doubt whether the reduction is entirely caused by fluoride intake anyway.

"The researchers used two different measures of the amount of fluoride the mothers consumed during pregnancy. One was based on the fluoride in the mothers' urine. The researchers point out that such readings can change quite rapidly over time and be affected by things like drinking fluoride-free bottled water shortly before the urine samples were taken, or swallowing fluoridated toothpaste. So, their measure (based on only three urine samples across the whole pregnancy) may not be a very accurate measure of the exposure of the unborn baby to fluoride. The other method used an estimate of daily fluoride intake in the mothers. This measurement method was developed by this research team and they make it clear that it has not been validated. It is based on what the mothers recalled and told the researchers about their consumption of water and of tea (which contains some fluoride), on two occasions during pregnancy, but couldn't take into account the actual brand of tea (because the fluoride content varies), and didn't take into account any fluoride from food (which depends on exactly what was eaten) or from swallowing some toothpaste after teeth-cleaning. So, the accuracy is not known and may or may not be low.

"This is an observational study – the women were not allocated to particular levels of fluoride intake by the researchers, but just did what they would have done anyway. Therefore, there are likely to be several differences between mothers with high and low fluoride intake, apart from the levels of fluoride. They will tend to live in different places, if nothing else. Maybe these other differences (called confounders) are the real cause for any differences in the children's IQ levels, and not their mothers' fluoride consumption at all. It's possible to make statistical adjustments to allow for the effect of these differences, though these adjustments aren't perfect. The researchers did make some such adjustments, for things like the town the mother lived in, the mother's age and number of previous pregnancies, a very simple measure of the mother's educational level (was it above or below degree level), and a standard measure of the home environment that is often used in studies of learning and child development (but does not really relate to the physical environment of the home). But adjustments cannot be made for possible confounders on which there is no data. The researchers point out that they could not adjust for the mother's IQ, and there may well be other important confounders that weren't dealt with. In particular, apart from the home environment measure, nothing was taken into account that occurred between birth and the age of 3 or 4 when the child's IQ was measured. A child's IQ certainly isn't completely determined before birth, and any coincidental difference in early childhood between children of mothers with different measured fluoride intakes could explain some or all of the observed IQ differences.

"The researchers reported the size of the associations between fluoride in the mothers' urine, or their estimate of fluoride intake, and the children's IQ in several different ways, but arguably none of the associations is actually very sizeable. Perhaps the most useful measure is the difference in average IQ between children whose mother's fluoride intake or urine concentration was just in the lowest quarter of fluoride levels (the lower quartile), and children whose mother's fluoride level was just in the top quarter (the upper quartile). For boys, in terms of the mother's urine fluoride, the IQ for those at this lower quartile fluoride level had an IQ on average 1.5 points above those whose mothers were at the upper quartile level. Now 1.5 IQ points isn't much, given the variation that exists between people in IQ anyway. Imagine we could get 100 pairs of boys, matched up in terms of the quantities used for statistical adjustment in this research, but with, in each pair, one boy whose mother was at the lower quartile of urine fluoride and one whose mother was at the upper quartile. Then in about 53 of those pairs, the boy whose mother had the lower fluoride level would have the higher IQ, but in the other 47 pairs, it would be the other way round and the boy whose mother had the lower fluoride level would have the lower IQ. Even if the difference was entirely caused by the fluoride – and we definitely don't know that it is – it's certainly not the case that children's lives are being blighted on a large scale. In girls, those whose mothers had lower levels of fluoride in their urine actually had lower average IQs in this study, not higher, though the difference was not statistically significant and so might well have been due entirely to chance variation. Looking at the measure of maternal fluoride intake, there were slightly larger effects (averaged across both boys and girls), but again not huge. Again making the comparison on the basis of the quartiles (of the mothers' fluoride intake measure), the difference was on average about 2.3 IQ points, but again looking at 100 pairs of children where one child's mother had the lower fluoride intake and the other had the higher, in about 54 pairs the child whose mother had a lower fluoride intake would have the higher IQ, but in the other 46 pairs it would be the other way round.

"I think that differences of this sort of size could well be largely, or even entirely, due to residual confounding. That doesn't mean that fluoride during pregnancy definitely has no effect on IQ – just that it's far from clear that it's even the main explanation for these relatively small IQ differences."

Dr Stuart Ritchie, Lecturer, Institute of Psychiatry Psychology & Neuroscience, King's College London (IoPPN), said:

"This study comprises two analyses – the first one is about the maternal urinary fluoride content, and the second is about the self-report of how much fluoride the mother had ingested. Some points to highlight about the results are:

- In the first analysis, there's only a statistically significant result if they split the sample up into boys and girls: the effect only exists in boys. In the second, there's an overall effect, but it's no stronger in boys than girls. So those two results are inconsistent.
- Not only that, but as far as I can see there's no pre-registration of the study, so we can't know whether the decision to split it by sex was done post hoc. Doing further analyses on the same data makes it more likely a false positive result will be found. No theoretical reason for there being an effect in boys but not girls is given, which is further evidence that the split wasn't done for a reason set out at the start of the study, before the data was analysed.
- For the second analysis, where there's an overall effect, the p-value is .04 – that is, it's JUST below the standard threshold used for declaring something to be significant (0.05). Given that they ran lots of other hypothesis tests in the paper, and didn't correct for how many times they did so, I wouldn't have much confidence in this finding being robust or replicable.
- The same point can be made for the sex difference in the first analysis – the p-value there (for the interaction, which is the critical test of whether the effect is bigger in one sex than another) is only .02, which I'd suggest is nothing to write home about either.

"So overall, I think the findings here are pretty weak and borderline. They might be interesting as part of a larger set of studies on this question, but alone they shouldn't move the needle much at all on the question of the safety of fluoride."

Prof Grainne McAlonan, Professor of Translational Neuroscience, Sackler Centre for Translational Neurodevelopment, King's College London, said:

"I would be very cautious about over interpreting this data. Statistical significance does not equal 'importance'.

"This is a large sample and although a statistically significant relationship is reported, any shift in IQ said to be elicited by exposure to more fluoride is not very dramatic. The authors describe the relationship between urinary fluoride and IQ in terms of a 1mg/L increase in urinary fluoride levels in pregnancy being associated with an almost 4.5 point reduction in IQ, but in reality the average difference in fluoride levels between the majority living in low and high fluoride areas is no-where near 1mg/L. The average urinary fluoride levels in non-fluoridated areas is 0.4mg/L while in higher areas it is almost 0.7mg/L. A difference of only 0.3mg/L.

"Also, if you look at average IQ in the children from fluoridated and non-fluoridated groups these are virtually the same: 108.07 vs. 108.21 respectively. I was therefore surprised that the study went on to look for a relationship between fluoridation and IQ, given these figures.

"If you look at the figures it's only the individuals which have the very highest levels of fluoride whose children have any IQ lowering and it's a pretty small drop in IQ score with a range of error that includes the average of the non-fluoridated children's' IQ.

"IQ, like many other measurements, contains a degree of error. Taking a test at different times or in different environments, with different administrators all might give a score difference. A few points difference in IQ may not necessarily be meaningful within the average range – that's why we tend to talk about IQ in terms of ranges instead – low, average, high."

'Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada' by Rivka Green *et al.* was published in *JAMA Pediatrics* at 16:00 UK time on Monday 19 August.

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Declared interests

Dr Oliver Jones: I have no conflicts of interest to declare.

Prof Kevin McConway: Prof McConway is a member of the SMC Advisory Committee, but his quote above is in his capacity as a professional statistician.

Prof Alastair Hay: I have no conflicts of interest.

Dr Stuart Ritchie: No conflicts of interest

Prof Grainne McAlonan: No relevant conflicts of interest

None others received.