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Abbreviations

CI	Confidence interval
CWF	Community water fluoridation
FSIQ	Full Scale IQ
HOME	Home Observation for Measurement of the Environment
HTA	Health technology assessment
IQ	Intelligence quotient
MA	Meta-analysis
MIREC	Maternal-Infant Research on Environment Chemicals
MUF	Maternal urine fluoride
NR	Not reported
PIQ	Performance IQ
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SD	Standard deviation
SR	Systematic review
VIQ	Verbal IQ

Context and Policy Issues

In Canada, community water fluoridation (CWF) is the process of monitoring and controlling fluoride levels (by adding or removing fluoride) in the public water supply to reach the optimal level of 0.7 part per million (ppm) and not to exceed the maximum concentration of 1.5 ppm, as recommended in the 2010 *Health Canada Guidelines for Drinking Water Quality*.[1] CWF has been identified as a cost-effective method of delivering fluoride to the population and reducing dental caries in children and adults.[2,3] The Centers for Disease Control and Prevention recognized CWF as one of 10 great public health achievements of the 20th century because of its contribution to the prevention of tooth decay and improvement in oral health over the past 70 years.[4] CWF is endorsed by over 90 national and international governments and health organizations around the world.[5,6]

Despite the endorsement of governments and health organizations, and a large body of empirical evidence on the preventive effect of CWF on dental caries, a number of municipalities across Canada have not implemented or have discontinued water fluoridation.[7] In 2017, 38.7% of the Canadian population were exposed to community water systems having recommended optimal fluoride levels to protect their teeth.[7] Different factors contributed to CWF cessation including concerns about the potential harmful side effects of water fluoride to human health, including fluorosis, skeletal fractures, cancer, reproduction and development, thyroid function, and children's intelligence quotient (IQ).[1]

Multiple studies have been published showing that exposure to higher levels of fluoride in drinking water may be associated with lower intelligence among children.[8-11] However, the generalizability of the findings from those studies to the Canadian context is unlikely given they were conducted in rural areas and areas of low socioeconomic status in countries, such as China, India, Iran, or Mexico, which also include other sources of fluoride such as fluoridated salts or naturally occurring water fluoride levels that are many folds higher than the current Canadian levels.[8-11] Multiple methodological limitations were identified in these studies including the lack of control for important confounding variables such as exposure to known neurotoxicants (e.g., lead, arsenic, or iodine), socioeconomic status, nutritional status, and parental education that could be related to fluoride exposure and also potentially affect children's IQ.[12] The CADTH CWF Review of Dental Caries and Other Health Outcomes reviewed studies from countries with comparable water fluoride levels and socioeconomic parameters, and found no evidence for an association between water fluoridation at recommended Canadian levels and IQ or cognitive function.[12] A study published by a group of researchers in Canada and the US after the CADTH HTA concluded that exposure to higher levels of fluoride during pregnancy is associated with lower IQ scores in children aged 3 to 4 years in Canada.[13] The findings of that study prompted a further review on this topic.

The aim of this report is to review recent evidence on the effects of fluoride exposure through CWF at levels that are relevant to the Canadian context on the neurological or cognitive development in children and adolescents less than 18 years of age.

In this report, gender-neutral language has been used where possible in order to be inclusive of all gender identities. When reporting results from the published manuscript, gender-neutral language was not used in order to be consistent with the terms used in the source material.

Research Question

What are the neurological or cognitive effects of community water fluoridation, compared with non-fluoridated or different fluoride levels in drinking water, in individuals less than 18 years of age?

Key Findings

This review identified one prospective birth cohort study[13] examining the association between fluoride exposure of mothers during pregnancy and subsequent children's intelligence quotient scores at age 3 to 4 years. Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L in mother urine fluoride and Full Scale intelligence quotient score in the total sample of boys and girls, or in girls. Adjusted estimates also showed no statistically significant association between an increase of 1 mg/L in mother urine fluoride and performance intelligence quotient or verbal intelligence quotient in all children. In boys, every 1 mg/L increased in mothers' urine fluoride levels was associated with a 4.49 point lower intelligence quotient score. Every 1 mg increase in daily fluoride intake of mothers corresponded with 3.66 points lower in total children's intelligence quotient score. The interaction between child sex and maternal fluoride intake was not statistically significant. The evidence is weak due to multiple limitations (e.g., non-homogeneous distribution of data, potential errors and biases in the estimation of maternal fluoride exposure and in IQ measurement, uncontrolled potential important confounding factors); therefore, the findings of this study should be interpreted with caution.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were water fluorination and children (<18 years). No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2017 and September 13, 2019. The search dates were selected to identify information published subsequent to a previous search for the CADTH CWF Review of Dental Caries and Other Health Outcomes.[12]

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Persons less than 18 years of age (including *in utero*)
Intervention	Natural or artificial water fluoridation (range between 0.4 ppm to 1.5 ppm with the optimal level being 0.7 ppm)
Comparator	No water fluoridation, low fluoride level (< 0.4 ppm), or different fluoride levels in drinking water
Outcomes	Neurological (e.g., neurotoxicity) or cognitive outcomes (e.g., Intelligence Quotient)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), randomized controlled trials (RCTs), and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2017. Primary studies were also excluded if they had been included in the recent CADTH HTA report on CWF.[12]

Critical Appraisal of Individual Studies

The methodological quality (i.e., internal and external validity) of the included non-randomized study was assessed using the National Institute for Health and Care Excellence (NICE) checklist.[14] Summary scores were not calculated for the included study; rather, a review of the strengths and weaknesses were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 302 citations were identified in the literature search. Following screening of titles and abstracts, 294 citations were excluded and eight potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of the eight potentially relevant articles, seven publications were excluded for various reasons, while one study met the inclusion criteria and was included in this report. **Appendix 1** presents the PRISMA flowchart[15] of the study selection.

Summary of Study Characteristics

The characteristics of the identified study (Table 2) are presented in Appendix 2.

Study Design

The identified study was a prospective, multicentre birth cohort study,[13] which acquired data and frozen urine samples from the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) program. Maternal urine fluoride (MUF) concentrations were measured in urine spot samples collected at each trimester of gestation and adjusted for specific gravity (MUF_{SG}). Information regarding pregnant persons' consumption of tap water and other beverages such as tea and coffee was obtained using a self-reported questionnaire. The water fluoride concentrations in the areas where persons resided during pregnancy were estimated based on the levels of fluoride in the municipal water reported by waste water treatment plants and persons' postal code. Daily fluoride intake was estimated based on a combination of the above measures. IQ of children was assessed once at ages of three to four years.

Country of Origin

The identified study[13] was conducted by authors in Canada and the US.

Population

The MIREC study recruited 2,001 pregnant persons within the first 14 weeks of pregnancy from 10 Canadian cities. A subset of mother-child pairs (n = 610) from six of 10 cities (Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax) were recruited for the measurement of children's IQ. Of 610 children, 601 had complete IQ data. Of 601 mother-child pairs, 369 had complete exposure and covariate data and drink tap water or live in a water treatment zone and were thus included in an analysis of the association between MUF and children's IQ. Further, 400 mother-child pairs had complete data and drink tap water or live in a water treatment zone and were included in a second analysis of the association between daily fluoride intake and children's IQ. Thus, 39.5% and 34.4% of the initial sample (n = 610) were excluded from the first and second analyses, respectively, due to missing data or ineligible exposure.

The mean age of pregnant persons at the time of recruitment was 32.3 years, and mean age of children at IQ testing was 3.4 years. Fifty two percent of children were female. Other characteristics of mothers and children are shown in Table 2 of Appendix 2.

Interventions and Comparators Mean MUF_{SG} value of the total sample of pregnant persons was 0.51 mg/L. The mean MUF_{SG} values of non-fluoridated and fluoridated groups were 0.40 mg/L and 0.69 mg/L, respectively.

Mean daily fluoride intake value of the total sample of pregnant persons was 0.54 mg. The mean daily fluoride intake values of non-fluoridated and fluoridated groups were 0.30 mg and 0.93 mg, respectively.

The average community fluoride level of areas of total sample of pregnant persons was 0.31 ppm. The mean water fluoride levels in the non-fluoridated and fluoridated areas were 0.13 ppm and 0.59 ppm, respectively.

Outcomes

The primary outcome was full scale IQ (FSIQ), a measure of global intellectual functioning, assessed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III).[16] Verbal IQ (VIQ), a measure of verbal reasoning, and performance IQ (PIQ), a measure of non-verbal reasoning, spatial processing and visual-motor skills, were also assessed. The WPPSI-III contains 14 subtests and two age ranges (from 2 years and 6 months to 3 years and 11 months, and from 4 years and 0 months to 7 years and 3 months). For children in the first age range, FSIQ, VIQ and PIQ scores are obtained from four core subtests. Seven core subtests are for children in the second age range. An overall intelligence score between 90 to 109 with a standard deviation of 15 is considered as average.[16,17] The reliability coefficients for WPPSI-III composite scales range from 0.89 to 0.95[16,17] [Reliability coefficient values range from 0.00 (significant error – no reliability) to 1.00 (no error – perfect reliability), and are used to indicate the amount of error in the scores]. The associations between children's IQ and maternal fluoride exposure (e.g., MUF, daily fluoride intake, water fluoride level) were estimated using linear regression analyses.

Summary of Critical Appraisal

The assessment of the methodological quality of the identified study is presented in Table 3 of Appendix 3.

Strengths

The identified study[13] was conducted in Canada with a well described source population.

The study assessed maternal fluoride exposure using a combination of mother urine fluoride, daily fluoride intake, in areas with or without fluoridation.

The study used linear regression analyses with two main measures of fluoride exposure (i.e., maternal fluoride urine and daily fluoride intake) to estimate the association between maternal fluoride exposure and children's IQ. Test statistics and associated *P* values were reported for all analyses.

The study analyzed mother urine fluoride concentration using established methods that were previously published. Children's' IQ (i.e., full scale IQ, verbal IQ and performance IQ) was assessed using a well-established method (i.e., the Wechsler Preschool and Primary Scale of Intelligence, third Edition).

Weaknesses

The recruitment of participants was not defined. It was unclear how 6 of 10 cities (Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax) were chosen. The authors stated that, due to budgetary restraints, those cities were chosen as most participants fell into the age range required. While there was minimal difference between the MIREC sample, the sample of persons included in the analyses and the sample of persons who had incomplete MUF data, the study did not describe the method of selection of participants from the eligible population. There was no report on the percentage of selected individuals who agreed to participate. Thus, there is a potential risk of bias in selection of participants into the study.

The study did not clearly pre-define the level of fluoride exposure that was considered as low or high at start of the study. As participants were not randomly assigned to level of fluoride exposure at the beginning of the study, mother-child pairs were sorted out based on maternal urine fluoride and fluoride intake after maternal fluoride exposure was determined by a combination of maternal urine fluoride, daily fluoride intake and community water fluoride concentrations. This approach, together with the knowledge of children's IQ, might have affected the classification of exposure status of the mothers. The study did not report the period of fluoride exposure. Some persons might have a lifetime exposure, while others might just have exposure during pregnancy. This strategy may result in classification of intervention bias.

The study tried to link fluoride exposure through drinking tap water and IQ in children. However, fluoride exposure may not specifically come solely from CWF, but rather from other sources, including food and toothpaste. Other sources of fluoride were not accounted and controlled in the analyses.

Although the study used appropriate statistical analyses (e.g., multiple linear regression) to control for some confounding variables, other potential important confounding factors during pregnancy and after birth, as well as those between birth and children's age of 3 or 4 when IQ was assessed, were not fully addressed. Some potential important confounders included parental IQ, father's education, socioeconomic status, duration of breast feeding, postnatal exposure to fluoride, postnatal diet and nutrition, and child's health status.[18,19] There is a potential risk of bias due to confounding.

The outcome measures (i.e. FSIQ, PIQ, and VIQ) could have been influenced by the knowledge of intervention received, or fluoride exposure, as the authors were aware of potential correlation and association between higher maternal fluoride exposure and lower children's' IQ from previous studies. Systematic errors might exist in the measurement IQ, MUF and daily fluoride intake. No information was provided regarding IQ measurement, such as the number of times the test was given per child (as a single measure may not capture all cognitive performance),[20] when and where the test took place (different environments and times may give different results),[18] whether the child was comfortable with the examiner before the test,[17] and whether the outcome assessors were blinded (risk of detection bias). For urine fluoride, although the authors corrected for variations in urine dilution (e.g., samples collected in early morning is more concentrated than those collected in later of the day) by adjusting MUF for specific gravity, the accurate measure of true values of MUF that correctly reflect maternal fluoride exposure remains questionable, given the short half life of fluoride (about 5 hours),[21] and only three urine samples, one at each trimester, during the entire pregnancy. The estimation of the maternal daily fluoride intake may inherit inaccuracies due to the fact that the self-reported questionnaire and the estimation/calculation methods of fluoride intake have not been validated. The estimation was subjected to recall bias as it was based on self-reported estimates of the amount of tap water and types of tea (e.g., black tea has more fluoride than green tea) consumed per day, whose data were collected on only two occasions, first and third trimesters, of pregnancy. The daily fluoride intake did not consider other sources of fluoride such as food or swallowing toothpaste after toothbrushing. The accuracy of the estimated fluoride intake levels is questionable given the discrepancies compared with MUF_{SG} values. For example, the difference in values were lower in the non-fluoridated groups (0.30 mg relative to 0.40 mg/L) and higher in the fluoridated groups (0.93 mg relative to 0.69 mg/L).[21] Given the interrelationship between maternal fluoride exposure and IQ in the estimation of the association, any incorrect assessment of fluoride intake, MUF or IQ could have a great impact on the direction of bias due to measurement of outcomes.

The outcome, exposure and covariate data were not available for all, or nearly all, participants. Over one third of initial sample were excluded due to missing data of MUF, water fluoride, and covariates. Of the 601 mother-child pairs, 369 pairs were used for urine fluoride association analysis and 400 pairs for fluoride intake association analysis. There was no information regarding the proportion of participants and reasons for missing data between exposure to higher fluoride level and lower fluoride level. There is a potential risk of bias due to missing data.

The study did not report R-squared values for the regression lines, and *P* values were reported instead, which are known to be misleading.[22] In the first analysis with MUF_{SG}, the *P* value for interaction in boys was 0.02, and the second analysis with daily fluoride intake, the *P* value was 0.04. No sample size calculation was performed. Thus, it is unclear if the study was sufficiently powered to detect a meaningful effect, and whether or not there was a strong association between maternal fluoride exposure and children's IQ.

In summary, multiple methodological weaknesses that potentially affect the internal validity of the study results limit the generalizability of the findings to all pregnant persons in Canada.

Summary of Findings

The main findings and conclusion of the identified study[13] are presented in Table 4 of Appendix 4.

What are the neurological or cognitive effects of community water fluoridation, compared with non-fluoridated or different fluoride levels in drinking water, in individuals less than 18 years of age?

Children's FSIQ

The mean FSIQ score of the total children sample was 107.16 ± 13.26. The mean FSIQ scores of non-fluoridated and fluoridated groups were 108.07 ± 13.31 and 108.21 ± 13.72, respectively.

Boys had mean FSIQ scores of 104.61 ± 14.09 in the total sample, 106.31 ± 13.60 in non-fluoridated group, and 104.78 ± 14.71 in fluoridated group.

Girls had FSIQ scores of 109.56 ± 11.96 in the total sample, 109.86 ± 12.83 in non-fluoridated group, and 111.47 ± 11.89 in fluoridated group.

Associations between MUF_{SG} and FSIQ in children

Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L MUF_{SG} and FSIQ in the total sample of boys and girls, or in girls. In boys, an increase of 1 mg/L MUF_{SG} was associated with a significant reduction of 4.49 FSIQ score (95% confidence interval [CI] -8.38 to -0.60) after adjusting for covariates (city, Home Observation for Measurement of the Environment [HOME] score, maternal education, race/ethnicity, and child sex interaction). Likewise, an increase of 0.33 mg/L MUF_{SG} (a value spanning the interquartile range between 25th to 75th percentiles) or an increase of 0.70 mg/L MUF_{SG} (a value spanning the 80th central range between 10th to 90th percentiles) was associated with a significant reduction of 1.48 (95% CI -2.76 to -0.19) or 3.14 (95% CI -5.86 to -0.42) FSIQ score in boys, respectively.

Sensitivity analyses

Adjusting for maternal blood concentrations of lead, mercury, perfluorooctanoic acid, arsenic, manganese, or maternal secondhand smoke exposure alone did not change the overall estimate for the association between MUF_{SG} and FSIQ in boys or girls. Excluding data from two boys with FSIQ lower than 60 or use of the adjusted MUF for creatinine in the models did not markedly change the regression coefficient in boys.

Associations between maternal daily fluoride intake and FSIQ in children

Both unadjusted and adjusted estimates showed a significant association between daily fluoride intake and FSIQ in the total sample of boys and girls. An increase of 1 mg fluoride intake was associated with a significant reduction of 3.66 FSIQ score (95% CI -7.16 to -0.15) after adjusting for covariates (city, HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). Likewise, an increase of 0.62 mg fluoride intake (a value spanning the interquartile range between 25th to 75th percentiles) or an increase of 1.04 mg fluoride intake (a value spanning the 80th central range between 10th to 90th percentiles) was associated with a significant reduction of 2.26 (95% CI -4.45 to -0.09) or 3.80 (95% CI -7.46 to -0.16) FSIQ score, respectively. A subgroup analysis was not performed here, as the authors stated that the interaction between child sex and maternal fluoride intake was not statistically significant.

Associations between community water fluoride concentration and FSIQ in children

A 1-ppm (or 1-mg/L) increase in fluoride concentration in the community water was associated with a significant reduction of 5.29 FSIQ score in the total sample after adjusting for covariates (city, HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). No subgroup analysis was conducted, or reported, by sex.

Associations between MUF_{SG} and PIQ in children

Adjusted estimates showed no significant association between an increase of 1 mg/L MUF_{SG} and PIQ in total sample of boys and girls, or in girls. In boys, an increase of 1 mg/L MUF_{SG} was associated with a significant reduction of 4.63 PIQ score.

Associations between maternal daily fluoride intake and PIQ in children

Adjusted estimates showed no significant association between an increase of 1 mg daily fluoride intake and PIQ in total sample of boys and girls. Subgroups analyses based on child sex was either not performed or reported.

Associations between community water fluoride concentration and PIQ in children

A 1-ppm (or 1-mg/L) increase in fluoride concentration in the community water was associated with a significant reduction of 13.79 PIQ score (95% CI -18.82 to -7.28) in total sample after adjusting for covariates (HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). The city covariate was excluded from the model because it was strongly multi-collinear with water fluoride concentration. No subgroup analysis was conducted, or reported, by sex.

Associations between MUF_{SG} and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 mg/L MUF_{SG} and VIQ in the total sample, in boys, or in girls.

Associations between maternal daily fluoride intake and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 mg daily fluoride intake and VIQ in the total sample. A subgroup analysis based on child sex was not performed or reported.

Associations between community water fluoride concentration and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 ppm fluoride concentration in the community water and VIQ in the total sample. A subgroup analysis based on child sex was not performed or reported.

Limitations

The study by Green et al., 2019[13] concluded that "*maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years*." (p. E1) This conclusion was not supported by the data. Between nonfluoridated and fluoridated maternal exposure (assessed by MUF_{SG} or daily fluoride intake), the difference in mean FSIQ in total children (108.07 ± 13.31 versus 108.21 ± 13.72) was minimal. The average FSIQ in boys in the non-fluoridated and fluoridated groups were 106.31 ± 13.60 and 104.78 ± 14.71, respectively, and in girls were 109.86 ± 12.83 and 111.47 ± 11.89, respectively. According to the WPPSI test scoring,[17] these numbers were considered as normal, as a score of 90 to 109 represents average intelligence. Given that these values were available during data collection period, it was unclear about the authors' rationale to further explore the associations between maternal fluoride exposure and children's IQ. Indeed, adjusted estimates with a limited set of covariates showed no statistically significant association between an increase of 1 mg/L in MUF_{SG} and FSIQ, PIQ or VIQ in all children. These were not discussed or considered when formulating the conclusion. The authors performed subgroups analysis based on child sex and found that an increase of 1 mg/L MUF_{SG} was significantly associated with a 4.49 point lower (95% CI -8.38 to -0.60) in FSIQ only in boys. In contrast, there was a non-significant increase in IQ scores in girls associated with increase maternal fluoride exposure. No pre-registered protocol was reported as available, and it is possible that the decision to conduct a subgroup analysis based on sex was made post hoc. As indicated by the authors, further investigation is needed examining differences in boys versus girls regarding their vulnerability to neurocognitive effects associated with fluoride exposure. Further, no rationale is provided to suggest why an increase in daily fluoride intake was significantly associated with lower FSIQ in total children, while no association was seen with MUF_{SG}. For the interaction with child sex, the effect on fluoride exposure was seen in analysis with MUF_{SG} but not in analysis with fluoride intake. These results were inconsistent.

The 1-mg/L increase in MUF_{SG} that was used to examine the association between fluoride exposure and childrens' IQ was far larger than the MUF_{SG} difference between fluoridated and nonfluoridated exposure in reality, which was 0.29 mg/L (difference between 0.69 mg/L and 0.40 mg/L), corresponding with a deficit of 1.53 points in FSIQ in boys (difference between 104.78 and 106.31). This was corroborated with the 1.48 point deficit in FSIQ in boys, corresponding to a MUF_{SG} difference spanning the 25^{th} to 75^{th} percentile range, which was 0.33 mg/L. Given that the reliability coefficients of WPPSI test range from 0.89 to 0.95,[17] the 1.5 points or even 4.5 points deficit is within the range of error (i.e., 5% to 11%).

The estimated level of IQ deficit in boys is likely to be reflected by non-homogeneous distribution of data as relative to fluoride intake, or biases due to uncontrolled confounders. Most of the FSIQ data were concentrated in the lower end of the MUF_{SG} concentrations, with few observations at the extreme level; therefore, an assumption for a linear correlation may not be appropriate. It appears that the effect was not observed at low MUF_{SG} concentrations, and the overall association may be driven by some outliers and few points at the extreme MUF_{SG} concentrations. There were some boys in the sample with extremely low IQ with at least two with FSIQ scores in the 50s and five with FSIQ scores below 75, while all the girls' data points were above 80, as shown in Figure 3 of the study report.[13] Although the authors stated that a sensitivity analysis removing two boys with FSIQ scores in the 50s did not substantially change the overall estimate, data of boys below 75 were not taken into consideration in the sensitivity analysis. No attempt was made to control for potential important confounding factors including parental IQ, father's education, socioeconomic status, duration of breast feeding, postnatal exposure to fluoride, postnatal diet and nutrition, child's health status, and other confounders between birth and the children's age of 3 or 4 when IQ was measured.[18,19] Although the authors controlled for and performed sensitivity analysis to test the robustness of association estimates for a number of substances (including lead, mercury, arsenic) in the mothers' blood samples, they did not consider postnatal exposure of children to these substances. Lead, in particular has been found to have a high association with IQ in children.[23] With incomplete control for potential confounders, it remains uncertain to know if the effect is true, and if it is due to prenatal exposure or postnatal exposure.

Conclusions and Implications for Decision or Policy Making

This review identified one prospective birth cohort study[13] examining the association between fluoride exposure of mothers during pregnancy and subsequent children's IQ scores at age 3 to 4 years. Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L in MUF_{SG} and FSIQ in the total sample of boys and girls, or in girls. Adjusted estimates also showed no statistically significant association between an increase of 1 mg/L in MUF_{SG} and PIQ or VIQ in all children. In boys, every 1 mg/L increased in mothers' urine fluoride levels was associated with 4.49 points lower in FSIQ score. Every 1 mg increase in daily fluoride intake of mothers corresponded with 3.66 points lower in total children's FSIQ score. The interaction between child sex and maternal fluoride intake was not statistically significant. Given multiple aforementioned limitations (e.g., non-homogeneous distribution of data, potential errors and biases in the estimation of maternal fluoride exposure and in IQ measurement, uncontrolled potential important confounding factors), the findings of this study should be interpreted carefully.

A recent CADTH Review of Dental Caries and Other Health Outcomes report on CWF[12] found that water fluoridation levels relevant to the Canadian context is associated with reducing dental caries in children and adults, and there was no evidence that water fluoridation is associated with adverse effects on human health outcomes including cancer, hip fracture, Down syndrome, and IQ and cognitive function. For the IQ and cognitive function, the HTA report[12] identified three studies that were relevant to the Canadian context (a prospective cohort study in New Zealand,[24] an ecological study in Sweden,[25] and a cross-sectional study in Canada).[26] The New Zealand study[24] assessed IQ among participants at age 7 to 13 years, and subsequently at age 38 years, who were residents in areas with CWF (0.7 ppm to 1.0 ppm) and areas without CWF (≤ 0.3 ppm). The study found no clear differences in IQ between fluoridated and non-fluoridated groups and concluded that CWF programs at 0.7 ppm to 1.0 ppm is not neurotoxic. The Swedish study[25] investigated the effect of fluoride exposure through the drinking water throughout life on cognitive and non-cognitive ability, as well as math test scores in participants up to age 18 years. Fluoride in the community water supply in Sweden is naturally occurring and its level is kept at or below 1.5 ppm. The study found that water fluoride levels in Swedish drinking water had no effects on cognitive ability, non-cognitive ability, and math test scores. The Canadian study[26] examined the relationship between fluoride exposure (estimated from urine fluoride levels and tap water samples) and reported diagnosis of learning disability among children aged 3 to 12 years. The study found no association between fluoride exposure and reported learning disability (i.e., attention deficit disorder and attention deficit hyperactivity disorder) diagnosis among Canadian children.

The findings reported by the identified study[13] in this review provided weak evidence and should be interpreted carefully, given the multiple aforementioned limitations. This, along with other evidence described in the CADTH Review of Dental Caries and Other Health Outcomes on CWF[12] which demonstrated no association with IQ and cognitive function should be considered. The identified study should be viewed as part of the research effort to investigate possible associations between fluoride exposure and neurological development in children. Together with a larger body of evidence on this topic, further well conducted research is needed to reduce uncertainty.

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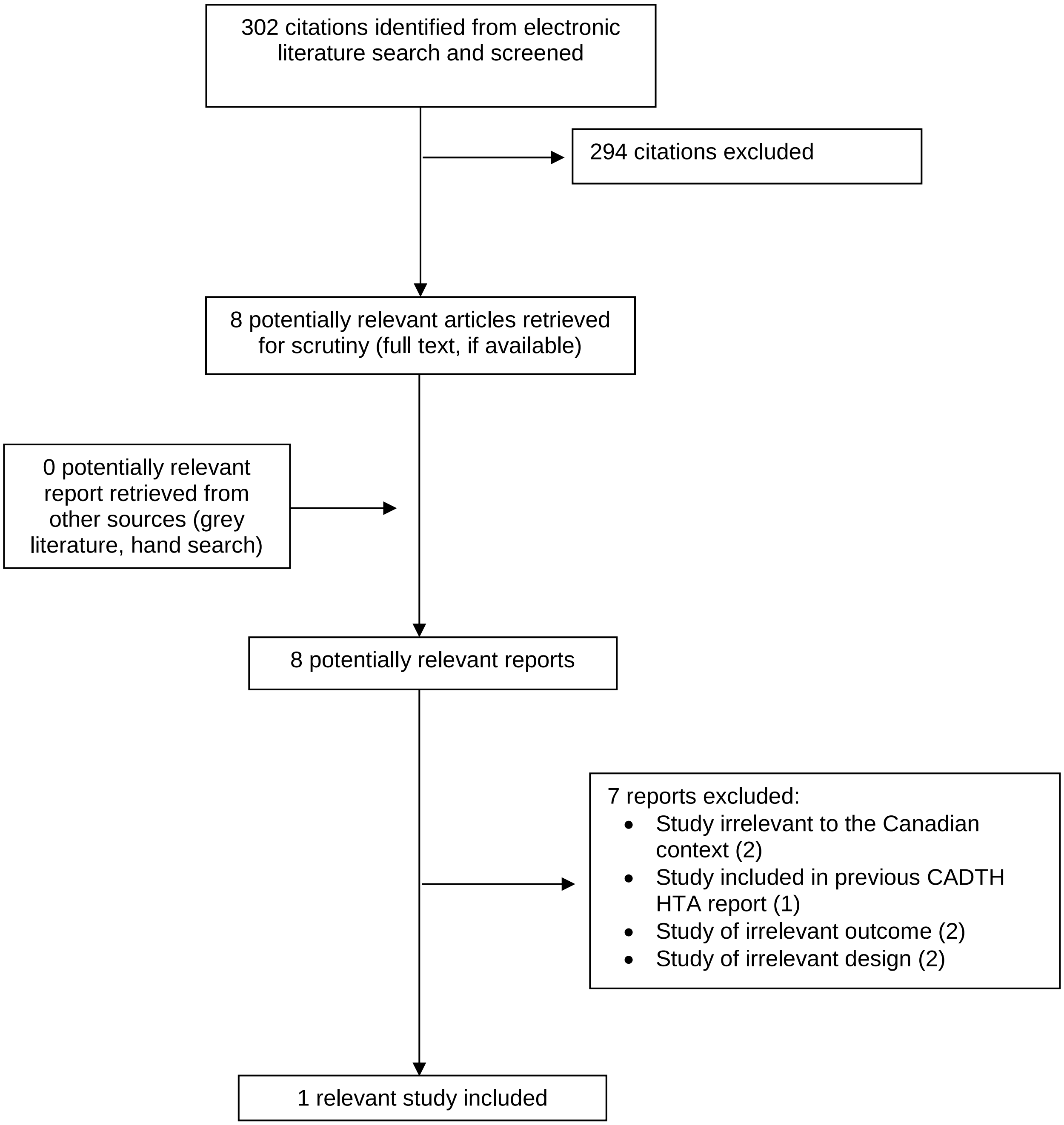
References

1. Health Canada. Guidelines for Canadian drinking water quality: Guideline technical document--Fluoride. 2010; https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/water-fluoride-fluorure-eau/alt/water-fluoride-fluorure-eau-eng.pdf. Accessed 2019 Oct 22.
2. Public Health Agency of Canada and Health Canada. Fact sheet - Community water fluoridation. Ottawa (ON): Her Majesty the Queen in Right of Canada, as represented by the Minister of Health; 2016: https://www.canada.ca/content/dam/canada/health-canada/migration/publications/healthy-living-vie-saine/fluoride-factsheet/community-water-fluoridation-eng.pdf. Accessed 2019 Oct 22.
3. Hannan C, Espinoza L. Statement on the evidence supporting the safety and effectiveness of community water fluoridation. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2018: https://www.cdc.gov/fluoridation/pdf/Scientific-Statement-on-Community-Water-Fluoridation-h.pdf. . Accessed 2019 Oct 22.
4. From the Centers for Disease Control and Prevention. Achievements in public health, 1900-1999: fluoridation of drinking water to prevent dental caries. *JAMA.* 2000;283(10):1283-1286.
5. Canadian Association of Public Health Dentistry. Position paper on fluoridation. 2005; https://www.cpha.ca/sites/default/files/assets/history/achievements/05-caphd_fluoridation_position.pdf. Accessed 2019 Oct 22.
6. Health Canada. Flouride and human health. *It's your health*. Ottawa (ON): Her Majesty the Queen in Right of Canada, represented by the Minister of Health; 2010: http://publications.gc.ca/collections/collection_2010/sc-hc/H50-3-30-2010-eng.pdf. Accessed 2019 Oct 22.
7. Public Health Capacity and Knowledge Management Unit, Quebec Region for the Office of the Chief Dental Officer of Canada. The state of community water fluoridation across Canada. Ottawa (ON): Public Health Agency of Canada 2017; https://www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/community-water-fluoridation-across-canada-2017/community-water-fluoridation-across-canada-2017-eng.pdf. Accessed 2019 Oct 22.
8. Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environ Health Perspect.* 2012;120(10):1362-1368.
9. Duan Q, Jiao J, Chen X, Wang X. Association between water fluoride and the level of children's intelligence: a dose-response meta-analysis. *Public Health.* 2018;154:87-97.
10. Bashash M, Marchand M, Hu H, et al. Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6-12 years of age in Mexico City. *Environ Int.* 2018;121(Pt 1):658-666.
11. Bashash M, Thomas D, Hu H, et al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6-12 Years of Age in Mexico. *Environ Health Perspect.* 2017;125(9):097017.
12. Community water fluoridation programs: a health technology assessment — review of dental caries and other health outcomes. (*CADTH technology review; no. 12)*. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/community-water-fluoridation-programs-health-technology-assessment. Accessed 2019 Oct 22.
13. Green R, Lanphear B, Hornung R, et al. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. *JAMA Pediatr.* 2019;19:19.
14. National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition). London (GB): NICE; 2012: https://www.nice.org.uk/process/pmg4/resources/methods-for-the-development-of-nice-public-health-guidance-third-edition-pdf-2007967445701. Accessed 2019 Oct 21.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
16. Community-University Partnership for the Study of Children, Youth, and Families. Review of the Wechsler Preschool and Primary Scale of Intelligence – Third edition [Canadian] (WPPSIIIICDN). Edmonton (AB); 2011: https://cloudfront.ualberta.ca/-/media/ualberta/faculties-and-programs/centres-institutes/community-university-partnership/resources/tools---assessment/wppsi-iiimay-2012.pdf. Accessed 2019 Oct 22.
17. Present Wechsler IQ Test and PB International. Wechsler Preschool and Primary Scale of Intelligence (WPPSI). 2017; https://wechsleriqtest.com/wppsi/. Accessed 2019 Oct 22.
18. Science Media Centre. Expert reaction to study looking at maternal exposure to fluoride and IQ in children. 2019; https://www.sciencemediacentre.org/expert-reaction-to-study-looking-at-maternal-exposure-to-fluoride-and-iq-in-children/. Accessed 2019 Oct 22.
19. McAdam K, Maheru M. Summary and critical appraisal: Green et al., 2019. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. Region of Peel: Mississauga (ON); 2019.
20. Lee BY. Fluoride and IQ? What is the link, what this study says. *Forbes* 2019 Aug 20; https://www.forbes.com/sites/brucelee/2019/08/20/fluoride-and-iq-what-is-the-link-what-this-study-says/#49512c963cc6. Accessed 2019 Oct 22.
21. Ekstrand J, Ehrnebo M. The relationship between plasma fluoride, urinary excretion rate and urine fluoride concentration in man. *J Occup Med.* 1983;25(10):745-748.
22. Pitak-Arnnop P, Dhanuthai K, Hemprich A, Pausch NC. Misleading p-value:do you recognise it? *Eur J Dent.* 2010;4(3):356-358.
23. Ernhart CB. Effects of lead on IQ in children. *Environ Health Perspect.* 2006;114(2):A85-86; author reply A86-87.
24. Broadbent JM, Thomson WM, Ramrakha S, et al. Community water fluoridation and intelligence: prospective study in New Zealand. *Am J Public Health.* 2015;105(1):72-76.
25. Aggeborn L, Ohman M. The effects of fluoride in the drinking water. Working paper 2017:20. Uppsala (SE): IFAU: Institute for Evaluation of Labour Market and Education Policy; 2017: https://www.ifau.se/globalassets/pdf/se/2017/wp2017-20-the-effects-of-fluoride-in-the-drinking-water.pdf. Accessed 2019 Oct 22.
26. Barberio AM, Quinonez C, Hosein FS, McLaren L. Fluoride exposure and reported learning disability diagnosis among Canadian children: Implications for community water fluoridation. *Can J Public Health.* 2017;108(3):e229-e239.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Primary Study

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Green et al., 2019[13] Canada Funding: Public	Prospective birth cohort study Multicentre Sample size calculation: No Cohort was from the MIREC program that recruited 2,001 pregnant women from 10 cities across Canada A subset of 610 mother-child pairs from 6 out of 10 cities of the MIREC study was selected for neurodevelopment testing of children at ages 3 to 4 years	Mothers: Pregnant women within the first 14 weeks of pregnancy Mean age (SD): 32.33 (5.07) years White: 90 % Married or common law: 97% Bachelor's degree or higher: 68% Employed at time of pregnancy: 88% Net income household > $70,000 CAD: 71%	Exposure to higher levels of fluoride determined by MUF or fluoride intake, and correlated with living area having CWF	Exposure to lower levels of fluoride determined by MUF or fluoride intake, and correlated with living areas having non-CWF	Primary outcome: – FSIQ (measuring global intellectual functioning) Other outcomes: – VIQ (measuring verbal reasoning and comprehension) – PIQ (measuring nonverbal reasoning, spatial processing, and visual-motor skills)

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
	Up to 241 mother-child pairs were excluded due to various reasons, leaving 369 mother-child with MUF, IQ, complete covariates and water fluoride data, and 400 mother-child pairs with fluoride intake, IQ, complete covariates and water fluoride data Two sets of measurements: By MUF By fluoride intake Statistical analysis: Multiple linear regression analyses	Smoked in trimester 1: 2% Secondhand smoke at home: 4% Alcohol consumption (drink/month): None: 83% < 1: 8% ≥ 1: 9 Parity (first birth): 46% Children: Female: 52% Mean age (SD) at testing: 3.42 (0.32) years Mean gestation (SD): 39.12 (1.57) weeks Mean birth weight (SD): 3.47 (0.49) kg	Maternal fluoride exposure[a] measurements: Mean MUF_{SG} (SD) – Total sample: 0.51 (0.36) mg/L – Non-fluoridated areas: 0.40 (0.27) mg/L – Fluoridated areas: 0.69 (0.42) mg/L Mean daily fluoride intake (SD) – Total sample: 0.54 (0.44) mg – Non-fluoridated areas: 0.30 (0.26) mg – Fluoridated areas: 0.93 (0.43) mg Mean water fluoride level (SD) – Total sample: 0.31 (0.23) ppm – Non-fluoridated areas: 0.13 (0.06) ppm – Fluoridated areas: 0.59 (0.08) ppm		

CWF = community water fluoridation; FSIQ = Full Scale IQ; IQ = intelligence quotient; MIREC = Maternal-Infant Research on Environment Chemicals; MUF = maternal urine fluoride; PIQ = performance IQ; VIQ = verbal IQ

[a] Fluoride came from any source, not specifically from CWF

Appendix 3: Quality Assessment of Included Study

Table 3: Quality Assessment of Included Prospective Cohort Study

NICE Checklist[14]	Green et al., 2019[13]	
Question	**Answer**	**Comment**
SECTION 1: POPULATION		
1.1 Is the source population or source area well described?	Yes	The Maternal-Infant Research on Environment Chemicals (MIREC) recruited pregnant persons within the first 14 weeks of pregnancy from 10 cities in Canada. A subset of 610 mother-child pairs in the MIREC study were recruited from 6 of 10 cities: Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax. Children aged 3 to 4 years.
1.2 Is the eligible population or area representative of the source population or area?	Probably no	The recruitment of individuals, clusters or areas was not defined. It was unclear how 6 of 10 cities were chosen.
1.3 Do the selected participants or areas represent the eligible population or area?	Probably no	The method of selection of participants from the eligible population was not described. There was no report on the percentage of selected individuals or clusters who agreed to participate. Risk of selection bias.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)		
2.1 Selection of exposure (and comparison) group. How was selection bias minimized?	Acceptable	Fluoride exposure assessed by areas of fluoridation or non-fluoridation, and by mother urine fluoride and daily fluoride intake. There was no clear pre-defined level of fluoride exposure that was considered as low or high at start of the study. Mother-child pairs were sorted out based on maternal urine fluoride and fluoride intake after mother had been exposed to fluoride, and the knowledge of children's IQ might have affected the classification of exposure status of the mothers.
2.2 Was the selection of explanatory variables based on sound theoretical basis	Probably no	Evidence for the hypothesis that maternal fluoride exposure was associated with lower IQ in children was drawn from studies conducted in countries not applicable to the Canadian context (e.g., use of fluoridated salts, or water fluoride levels many folds higher

NICE Checklist[14]	Green et al., 2019[13]	
		than the current recommended level in Canada)
2.3 Was the contamination acceptable low?	No	Fluoride exposure did not specifically come from CWF; it could be from other sources such as foods or swallowing toothpaste after toothbrushing.
2.4 How well were likely confounding factors identified and controlled?	Partially	Some confounding factors such as city, HOME score, maternal education, race/ethnicity, child sex, and prenatal secondhand smoke exposure were adjusted in the regression analysis.
2.5 Is the setting applicable to the Canadian context?	Yes	The study was conducted in Canada
SECTION 3: OUTCOMES		
3.1 Were the outcome measures and procedures reliable?	Partially	Mother urine fluoride concentration was analyzed using biochemical method previously published. Childrens' IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence, third Edition. The questionnaire used to collect the information on consumption of tap water and other beverages (tea, coffee) and the methods to estimate and calculate fluoride intake were not validated. Self-reported of dietary intake tends to be an unreliable measure.
3.2 Were the outcome measurements complete?	No	Results form all recruited participants were not reported. Over one third were excluded due to missing data. Unclear if missing IQ data from excluded children could affect the findings.
3.3 Were all the important outcomes assessed?	Yes	Full Scale IQ, verbal IQ and performance IQ were measured.
3.4 Was there a similar follow-up time in exposure and comparison groups?	Probably not	Unclear about the period of fluoride exposure of women. Some women might have a lifetime exposure, while others might just have exposure during pregnancy.
3.5 Was follow-up time meaningful?	Yes	All included children had lived in the areas since birth.
SECTION 4: ANALYSES		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?	Not reported	The study did not perform any sample calculation to obtain sufficient power to detect an intervention effect.
4.2 Were multiple explanatory variables considered in the analyses?	Yes	Two measures of fluoride exposure (maternal fluoride urine and fluoride intake) were used in the analyses for the association between fluoride exposure and children's IQ.

NICE Checklist[14]	Green et al., 2019[13]	
4.3 Were the analytical methods appropriate?	Probably Yes	Linear regression analyses were adjusted with some confounding factors. Multiple analyses of the intervention-outcome relationship (both unadjusted and adjusted data) were reported.
4.4 Was the precision of association given or calculable? Is association meaningful?	Probably yes	Test statistics and associated *P* values reported for all analyses. R-squared values for linear regression were not reported. Unclear if association was meaningful.
SECTION 5: SUMMARY		
5.1 Are the study results internally valid (i.e., unbiased)?	No	High risk of bias due to selection of participants, classification of intervention, confounding, missing data, and measurement of outcomes
5.2 Are the findings generalizable to the source population (i.e., externally valid)?	Probably not	Although the study was conducted in Canada, there was a risk of selection bias of the participants into the sample. The findings could not be generalizable to the entire Canadian population.

CWF = community water fluoridation; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Included Primary Study

Main Study Findings	Author's Conclusions
Green et al., 2019[13]	
Children's intellectual ability measurements[a] Mean FSIQ (SD) – Total sample: 107.16 (13.26) Boys: 104.61 (14.09) Girls: 109.56 (11.96) – Non-fluoridated areas: 108.07 (13.31) Boys: 106.31 (13.60) Girls: 109.86 (12.83) – Fluoridated areas: 108.21 (13.72) Boys: 104.78 (14.71) Girls: 111.47 (11.89) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and FSIQ** <u>Measurements with MUF_{SG}</u> Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -2.60 (-5.80 to 0.60) Boys: -5.01 (-9.06 to -0.97) Girls: 2.23 (-2.77 to 7.23) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.95 (-5.19 to 1.28) Boys: -4.49 (-8.38 to -0.60) Girls: 2.40 (-2.53 to 7.33) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.33 mg/L MUF_{SG} (a value spanning the interquartile range between 25th to 75th percentiles) – Total sample: -0.64 (-1.69 to 0.42) Boys: -1.48 (-2.76 to -0.19) Girls: 0.79 (-0.83 to 2.42) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.70 mg/L MUF_{SG} (a value spanning 80th central range between 10th to 90th percentiles) – Total sample: -1.36 (-3.58 to 0.90) Boys: -3.14 (-5.86 to -0.42) Girls: 1.68 (-1.77 to 5.13) *<u>Measurements with daily Fluoride Intake</u>* Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg of daily fluoride intake – Total sample: -3.19 (-5.94 to -0.44) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg of daily fluoride intake – Total sample: -3.66 (-7.16 to -0.15)	*"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."*[13] p. E1

Main Study Findings	Author's Conclusions
Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.62 mg of daily fluoride intake (a value spanning the interquartile range between 25th to 75th percentiles) – Total sample: -2.26 (-4.45 to -0.09) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1.04 mg of daily fluoride intake (a value spanning 80th central range between 10th to 90th percentiles) – Total sample: -3.80 (-7.46 to -0.16) *Measurements with water fluoride concentration* Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: 3.49 (-9.04 to 2.06) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: -5.29 (-10.39 to -0.19) **Sensitivity analyses predicting the associations between an increased of 1 mg/L of MUF_{SG} and FSIQ in boys, regression coefficients *B* (95% CI)** – Model A[d]: -4.49 (-8. 8.38 to -0.60) – Model A adjusting for lead: -4.61 (-8.50 to -0.71) – Model A adjusting for mercury: -5.13 (-9.16 to -1.10) – Model A adjusting for perfluorooctanoic acid: -4.57 (-8.21 to -0.50) – Model A adjusting for arsenic: -4.44 (-8.35 to -0.54) – Model A adjusting for manganese: -4.55 (-8.42 to -0.69) – Model A adjusting for secondhand smoke exposure: -4.18 (-8.06 to -0.30) – Model A excluding two boys with FSIQ lower than 60: -4.11 (-7.89 to -0.33) – Model A adjusting for creatinine: -6.96 (-8.56 to -1.36) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and PIQ** *Measurements with MUF_{SG}* Unadjusted estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -5.81 (-9.31 to -2.30) Boys: -8.11 (-13.29 to -4.32) Girls: -0.56 (-6.09 to 4.97) Adjusted[b] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.24 (-4.88 to 2.40) Boys: -4.63 (-9.01 to -0.25) Girls: 4.50 (-1.02 to 10.05) *Measurements with daily Fluoride Intake* Unadjusted estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg daily fluoride intake – Total sample: -5.75 (-8.74 to -2.76) Adjusted[c] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg daily fluoride intake – Total sample: -2.74 (-6.82 to 1.34) *Measurements with water fluoride concentration*	

Main Study Findings	Author's Conclusions
Adjusted[c] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: -13.79 (-18.82 to -7.28) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and VIQ** *Measurements with MUF_{SG}* Unadjusted estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg/L MUF_{SG} – Total sample: 1.28 (-1.87 to 4.43) Boys: -0.21 (-4.19 to 3.77) Girls: 4.78 (-0.14 to 9.70) Adjusted[b] estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.60 (-4.74 to 1.55) Boys: -2.82 (-6.62 to 0.98) Girls: 0.50 (-4.32 to 5.33) *Measurements with daily Fluoride Intake* Unadjusted estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg daily fluoride intake – Total sample: -0.03 (-2.71 to 2.64) Adjusted[c] estimates, regression coefficient *B* (95% CI) of VIQ for an increased of 1 mg daily fluoride intake – Total sample: -3.08 (-6.40 to 0.25) *Measurements with water fluoride concentration* Adjusted[c] estimates, regression coefficient *B* (95% CI) of VIQ for an increased of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: 3.37 (-1.50 to 8.24)	

CWF = community water fluoridation; FSIQ = full Scale IQ; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient; MUF_{SG} = maternal urine fluoride concentration adjusted for specific gravity; ppm = part per million (or mg/L); PIQ = performance IQ; SD = standard deviation; VIQ = verbal IQ

[a] Children intellectual ability was assessed using the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III)[16] The WPPSI-III contains 14 subtests and two age ranges (from 2 years and 6 months to 3 years and 11 months, and from 4 years and 0 months to 7 years and 3 months). For children in the first age range, FSIQ, VIQ and PIQ scores are obtained from four core subtests. Seven core subtests are for children in the second age range.

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

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