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# Fluoride exposure from infant formula and child IQ in a Canadian birth cohort

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ABSTRACT

*Background:* Infant consumption of formula reconstituted with fluoridated water can lead to excessive fluoride intake. We examined the association between fluoride exposure in infancy and intellectual ability in children who lived in fluoridated or non-fluoridated cities in Canada.
*Methods:* We examined 398 mother-child dyads in the Maternal-Infant Research on Environmental Chemicals cohort who reported drinking tap water. We estimated water fluoride concentration using municipal water reports. We used linear regression to analyze the association between fluoride exposure and IQ scores, measured by the Wechsler Primary and Preschool Scale of Intelligence-III at 3–4 years. We examined whether feeding status (breast-fed versus formula-fed) modified the impact of water fluoride and if fluoride exposure during fetal development attenuated this effect. A second model estimated the association between fluoride intake from formula and child IQ.
*Results:* Thirty-eight percent of mother-child dyads lived in fluoridated communities. An increase of 0.5 mg/L in water fluoride concentration (approximately equaling the difference between fluoridated and non-fluoridated regions) corresponded to a 9.3- and 6.2-point decrement in Performance IQ among formula-fed (95% CI: −13.77, −4.76) and breast-fed children (95% CI: −10.45, −1.94). The association between water fluoride concentration and Performance IQ remained significant after controlling for fetal fluoride exposure among formula-fed ($B = -7.93$, 95% CI: −12.84, −3.01) and breastfed children ($B = -6.30$, 95% CI: −10.92, −1.68). A 0.5 mg increase in fluoride intake from infant formula corresponded to an 8.8-point decrement in Performance IQ (95% CI: −14.18, −3.34) and this association remained significant after controlling for fetal fluoride exposure ($B = -7.62$, 95% CI: −13.64, −1.60).
*Conclusions:* Exposure to increasing levels of fluoride in tap water was associated with diminished non-verbal intellectual abilities; the effect was more pronounced among formula-fed children.

## 1. Introduction

Fluoride can occur naturally in water and, in some communities, is added to water supplies to reach the recommended concentration of 0.7 mg/L for the prevention of tooth decay (Health Canada, 2010). About 74% of Americans and 38% of Canadians on municipal water are supplied with fluoridated drinking water. Water fluoridation has been reported to reduce the prevalence of tooth decay by 26% to 44% (Iheozor-Ejiofor et al., 2015; National Health and Medical Research Council (NHMRC), 2017) in youth and by 26% (Iheozor-Ejiofor et al.,

*Abbreviations:* BF, breastfed; FF, formula fed; CI, confidence intervals; HOME, home observation for measurement of the environment; IQ, intelligence quotient; FSIQ, full scale IQ; PIQ, performance IQ; VIQ, verbal IQ; MIREC, maternal-infant research on environmental chemicals; MUF, maternal urinary fluoride; SD, standard deviation

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2015) to 27% (NHMRC, 2017) in adults. Infants who are fed formula reconstituted with fluoridated water have approximately three to four times greater exposure to fluoride than adults (National Research Council (NRC), 2006) on a per body-weight basis. Formula-fed infants residing in fluoridated areas have an approximate 70-fold higher fluoride intake than exclusively breastfed infants (Ekstrand, 1981; Zohoori et al., 2018; United States Environmental Protection Agency, 2010)

The prevalence of enamel fluorosis, a discoloration of enamel resulting from chronic, excessive ingestion of fluoride during tooth development (Brothwell and Limeback, 2003; Buzalaf et al., 2001), is higher among formula-fed infants than breastfed infants (Buzalaf et al., 2001; Do et al., 2012; Fv et al., 2012; Hong et al., 2006; Walton and Messer, 1981). While enamel fluorosis develops from excess fluoride exposure during the first four years of life, (Levy et al., 2010) the first 12 months are the most vulnerable period (Hong et al., 2006). The risk of fluorosis increases with higher levels of fluoride in the water supply for formula-fed infants (Hujoel et al., 2009).

Breastmilk contains extremely low concentrations of fluoride (0.005–0.01 mg/L) due to the limited transfer of fluoride in plasma into breastmilk (Dabeka et al., 1986; Ekstrand, 1981; Ekstrand and Hardell, 1984; Esala et al., 1982; Faraji et al., 2014; Zohoori et al., 2018). Exclusive breastfeeding for six months, which is recommended by current practice guidelines (Critch, 2013; Eidelman, 2012), is reported by 25% of mothers in the United States (Breastfeeding Report Card. United States, 2018) and Canada (Health Canada, 2001). Ninety percent of bottle-fed infants are fed powdered formula (Infant Feeding Practices Survey II) and 75% of mothers report using tap water to reconstitute formula (Van Winkle et al., 1995). Thus, reconstituted formula is the major source of nutrition for many infants in the United States and Canada.

Despite growing concerns about excessive exposure to fluoride during infancy and the vulnerability of the developing brain (Rice and Barone, 2000; Grandjean and Landrigan, 2006), no studies have tested the potential neurotoxicity of using optimally fluoridated drinking water to reconstitute formula during infancy (Harriehausen et al., 2019). Increased fluoride exposure during fetal brain development was associated with diminished IQ scores in two birth cohort studies (Bashash et al., 2017; Green et al., 2019; Valdez Jiménez et al., 2017), among a number of recent studies conducted in endemic fluorosis areas (Karimzade et al., 2014; Dong et al., 2018; Zhang et al., 2015), as well as a 2012 meta-analysis of 27 ecologic studies (Choi et al., 2012). Increased fluoride exposure has also been linked with ADHD-related behaviors in children (Malin and Till, 2015; Bashash et al., 2018; Riddell et al., 2019).

We investigated the association between water fluoride concentration and intellectual abilities of Canadian children who were formula-fed or breastfed. In addition, we tested whether postnatal effects of fluoride exposure on child IQ remained after controlling for fetal exposure.

## 2. Materials and methods

### 2.1. Study population

Between 2008 and 2011, the Maternal-Infant Research on Environmental Chemicals (MIREC) program recruited 2001 pregnant women from ten Canadian cities to participate in a longitudinal pregnancy cohort study. Women who could communicate in English or French, were > 17 years, and were < 14 weeks gestation were recruited from prenatal clinics. Participants were excluded if there was a known fetal abnormality, if they had any medical complications, or if there was known illicit drug use during pregnancy. Additional details are in the cohort profile description (Arbuckle et al., 2013).

Of the 610 children who were recruited to participate in the developmental follow-up phase of the study (MIREC-Child Development Plus), 601 completed all testing. Children were recruited from six of the cities in the original cohort (Vancouver, Toronto, Hamilton, Halifax, Kingston, Montreal); approximately half of the children lived in non-fluoridated cities and half lived in fluoridated cities.

This study received ethics approval from Health Canada and York University.

### 2.2. Infant feeding assessment

When children were between 30 and 48 months of age, mothers completed an infant feeding questionnaire asking, “How old was your baby when you ceased breastfeeding exclusively? At what age did you introduce other type of milk or food to your baby?”. Women who breastfed exclusively for six months or longer were included in the breastfeeding (BF) group; those who reported introducing formula within the first six months (never breastfed or partial breastfeeding) were included in the formula-feeding (FF) group.

To explore the possibility of recall or response bias of mothers completing the questionnaire, we compared information reported by mothers when their children were between 30 and 48 months of age (i.e. time when the questionnaire was completed for classifying the BF and FF groups) with information reported by a subset of women at an earlier visit when their children were between 6 and 8 months of age. Information about infant feeding was only available for 11% of the sample at the infant visit (note that responses could only be matched for women who had stopped breastfeeding at the time the questionnaire was completed at the infant visit). Among women who provided information at both occasions, the median difference for when breastfeeding was reported to be ceased was 0 months; responses were within 1.5 months of each other for two-thirds of this subsample.

We dichotomized feeding status at six months because the Canadian Pediatric Society and American Academy of Pediatrics both recommend exclusive breastfeeding for six months (Critch, 2013; Eidelman, 2012). Moreover, formula-fed infants who are younger than six-months derive most of their nutrition from formula, placing this group at highest risk of exceeding the recommended upper limit (0.7 mg/d) for fluoride (Harriehausen et al., 2019; Institutes of Medicine, 1997; National Research Council (NRC), 2006). Finally, fluoride intake differences become less evident when other dietary sources of fluoride are introduced at around six months (Zohoori et al., 2018).

### 2.3. Infant fluoride exposure

We estimated fluoride concentrations in drinking water by accessing daily or monthly reports provided by water treatment plants. Water reports were first linked with mothers' postal codes and the daily or weekly amounts were averaged over the first six-months of the child's life. We only included participants whose postal codes could be linked to a water treatment plant that provided water fluoride measurements. We also excluded participants who reported that their primary drinking source was from a well or ‘other’ (e.g. bottled water) (Table S1). Further details can be found in our previous report (Till et al., 2018).

To obtain a continuous fluoride exposure estimate collapsed across the BF and FF groups, we estimated fluoride intake from formula (in mg F/day) by multiplying water fluoride concentration by the amount of time that the infant was not exclusively breastfed in the first year using the following equation:

*Fluoride intake from formula = (water_F mg/L) * (1 − #mo_excl_BF/11.99) * 0.80 L/day*

where *water_F mg/L* refers to the average water fluoride concentration and *1-#mo_excl_BF/11.99* represents the proportion over the 12-month period the infant was not exclusively breastfed. A value near one indicates that an infant was primarily formula-fed over the 12 months whereas a value near zero indicates an infant primarily breastfed. We estimated fluoride intake based on an average of 0.80 L of water used to reconstitute powdered formula as suggested by an infant food diary completed for infants in a prior study (Carignan et al., 2015); the average milk intake at 3 months of age is 0.812 L per day, ranging from 0.523 to 1.124 L (Dewey et al., 1991). Because we did not know the type of formula used (i.e. soy- or milk-based), we did not add fluoride derived from formula to our fluoride intake estimate. Previous studies have indicated that fluoride from water used in formula is a greater source of fluoride than fluoride found in formula (Buzalaf et al., 2004).

### 2.4. Fetal fluoride exposure

We used maternal urinary fluoride (MUF) adjusted for specific gravity as a proxy of fetal fluoride exposure. MUF, which was derived by averaging three spot samples collected across all three trimesters of pregnancy, was considered our most reliable measure of exposure (Till et al., 2018). Urinary fluoride concentrations were analyzed at the Indiana University School of Dentistry using a modification (Martínez-Mier et al., 2011) of the hexamethyldisiloxane (Sigma Chemical Co., USA) micro-diffusion procedure previously described (Green et al., 2019).

### 2.5. Intelligence assessment

We assessed children's intellectual abilities between ages 3.0 and 4.0 years with the Wechsler Preschool and Primary Scale of Intelligence-III (Wechsler, 2002) using United States population-based normative data (*mean* = 100, *SD* = 15). Outcomes included Full Scale IQ (FSIQ), a measure of global intellectual functioning, Verbal IQ (VIQ), a measure of verbal reasoning, and Performance IQ (PIQ), a measure of non-verbal reasoning and visual-motor coordination skills.

### 2.6. Covariates

We adjusted for potential confounding by selecting covariates *a priori* that have been associated with fluoride, breastfeeding, and children's intellectual abilities. Final covariates included child's sex and age at testing, maternal education (dichotomized as either a bachelor's degree or higher versus trade school diploma or lower), maternal race (white or not), second-hand smoke in the home (yes, no), and quality of the child's home environment (measured at time of testing using the Home Observation for Measurement of the Environment (HOME) - Revised Edition (Caldwell and Bradley, 1984). For each analysis, a covariate was retained in the final model if its *p*-value was $< 0.20$ or its inclusion changed the regression coefficient of water fluoride concentration or fluoride intake from formula by more than 10% (Kleinbaum et al., 1982). City was not included as a covariate in Model 1 because it was strongly multi-collinear with water fluoride concentration (VIF $>$ 20). City was also excluded from Model 2 because fluoride intake from formula is a function of water fluoride concentration and was therefore deemed redundant.

### 2.7. Statistical analyses

We used linear regression to model differences in child IQ by water fluoride concentration while controlling for covariates. In our first model, we examined whether feeding status (BF or FF) modified the impact of water fluoride. In our second model, we estimated the association between fluoride intake from formula and child IQ. We controlled potential confounders by including them simultaneously with predictors.

In secondary analyses, we controlled for MUF during pregnancy in both models to account for fetal exposure. We also tested for sex-specific effects because we previously found that MUF concentration was only associated with diminished FSIQ in males (Green et al., 2019).

Regression diagnostics indicated no assumption violations pertaining to linearity, normality, or homogeneity of variance. Specifically, QQ-plots of residuals were consistent with a normal distribution and plots of residuals against fitted values did not suggest any assumption violations. Two observations were investigated based on a plot of Cook's D that suggested they may be influential; these cases had extremely low IQ scores that were more than 2.5 standard deviations from the sample mean. In a sensitivity analyses, we re-estimated the models after removing these two observations. Finally, variance inflation factors indicated no concerns with excessive multicollinearity.

To aid interpretation, we divided all regression coefficients by 2 so that they represent the predicted IQ difference per 0.5 mg/L of fluoride in tap water or 0.5 mg fluoride from formula; 0.5 mg/L corresponds to the approximate difference between mean water fluoride level in fluoridated versus non-fluoridated regions in our sample.

## 3. Results

Of the 601 children who completed neurodevelopmental testing, 591 (99%) mother–child pairs completed the infant feeding questionnaire and IQ testing (BF: *n* = 296; FF: *n* = 295). Of these, 398 (67.3%) pairs reported drinking tap water, had water fluoride data and complete covariate data (BF: *n* = 200; FF: *n* = 198). The demographic characteristics of women included in the current analyses (*n* = 398) were not substantially different from the original MIREC cohort (*N* = 1945) or the subset without complete water fluoride and covariate data (*n* = 203) (Table S2, Mcknight-hanes et al., 1988).

Among the BF group, more women who lived in a fluoridated region had a bachelor's degree or higher compared with those in a non-fluoridated region (86 vs. 74%, $p = .001$) (Table 1). Compared with the FF group, women in the BF group were more educated, more likely to be married or common law, and had higher HOME scores (all *ps* $<$ 0.05). The BF group had significantly higher FSIQ and VIQ scores relative to the FF group (Table 1; Fig. S1). Children living in a fluoridated region had a significantly lower PIQ score, but higher VIQ score, relative to children living in a non-fluoridated region (Table 1; Fig. S1).

Water fluoride concentration was correlated with MUF (r = 0.37, $p < .001$) and estimated fluoride intake from formula (r = 0.79, $p < .001$); MUF was correlated with fluoride intake from formula (r = 0.55, $p < .001$).

### 3.1. Feeding status

The mean duration of exclusive breastfeeding was 4.98 months (*SD* = 3.48); 54 (13.6%) women reported never breastfeeding, 32 (8%) reported discontinuing breastfeeding after the first three months, and 200 (50.2%) reported continuing to breastfeed at six months or longer. Water fluoride concentration did not significantly differ between the BF (*M* = 0.32 mg/L) and FF groups (*M* = 0.29 mg/L; $p = .18$).

### 3.2. Model 1: IQ scores and water fluoride concentration by feeding status

A 0.5 mg/L increase in water fluoride concentration was associated with a decrease of 4.4 FSIQ points (95% CI: −8.34, −0.46, $p = .03$) in the FF group, but it was not significantly associated with FSIQ in the BF group ($B = -1.34$, 95% CI: −5.04, 2.38, $p = .48$) (Table 2; Fig. 1A); the interaction between water fluoride and feeding status was not statistically significant ($p = .26$). Controlling for fetal exposure by adding MUF to the model resulted in non-significant associations between water fluoride concentration and FSIQ in both the FF ($B = -3.58$, 95% CI: −7.83, 0.66, $p = .098$) and BF groups ($B = -1.69$, 95% CI: −5.66, 2.27, $p = .40$). Removing two cases with extreme IQ scores from the models resulted in non-significant associations between water fluoride concentration and FSIQ in both groups (Table S3).

Water fluoride concentration was significantly associated with lower PIQ in the FF ($B = -9.26$, 95% CI: −13.77, −4.76, $p < .001$) and the BF groups ($B = -6.19$, 95% CI: −10.45, −1.94, $p = .004$)

**Table 1**
Demographic characteristics and exposure outcomes for mother-child pairs by infant feeding status.

| Characteristic | Breastfed ≥ 6 mo. (n = 200) | | Formula-fed (n = 198) | | |
|---|---|---|---|---|---|
| | Fluoridated (n = 83)<br>Mean (SD)/% | Non-fluoridated (n = 117)<br>Mean (SD)/% | Fluoridated (n = 68)<br>Mean (SD)/% | Non-fluoridated (n = 130)<br>Mean (SD)/% | *p* value comparing BF and FF groups |
| **Maternal characteristics** | | | | | |
| Years of age at delivery | 32.54 (3.64) | 32.86 (4.79) | 32.91 (4.42) | 32.39 (5.11) | .73 |
| Net household income > $70 K | 70.3 | 72.9 | 79.7 | 68 | .88 |
| Caucasian | 88 | 93 | 88 | 84 | .11 |
| Maternal education | | | | | |
| Trade school diploma/high school | 14 | 26* | 28 | 42* | < .001 |
| Bachelor's degree or higher | 86 | 74* | 72 | 58* | < .001 |
| Employed at time of pregnancy | 92 | 90 | 94 | 84* | .40 |
| Married/common-law (at time of testing) | 100 | 99 | 96 | 92 | .001 |
| Smoked in trimester 1 | 0 | 1.7 | 2.9 | 3.8 | .17 |
| Parity (first birth) | 45 | 51 | 43 | 47 | .61 |
| Number of months exclusively breastfeeding | 7.54 (2.95) | 7.45 (2.46) | 2.63 (2.08) | 2.37 (2.13) | < .001 |
| **Child characteristics** | | | | | |
| Years of age at IQ testing | 3.48 (0.29) | 3.34 (0.31)* | 3.53 (0.28) | 3.37 (0.3)* | .32 |
| Female sex | 51 | 53 | 54 | 47 | .32 |
| HOME total score | 48.71 (3.42) | 48.09 (3.86) | 47.59 (4.33) | 46.55 (4.76) | < .001 |
| Second hand smoke in home | 2.5 | 3.4 | 4.4 | 5.4 | .43 |
| Gestational age in weeks | 39.22 (1.55) | 39.17 (1.52) | 38.68 (2.48) | 39.15 (1.53) | .24 |
| Birth weight (kg) | 3.42 (0.50) | 3.49 (0.46) | 3.43 (0.62) | 3.46 (0.52) | .75 |
| Full Scale IQ | 109.9 (12.4) | 108.9 (13.6) | 106.1 (15.8) | 106.8 (13.5) | .03[a] |
| Verbal IQ[b] | 115.1 (11.3) | 110.4 (12.4)* | 110.9 (14.9) | 107.1 (13.3) | .00[a] |
| Performance IQ[b] | 102.0 (15.2) | 105.6 (15.8) | 99.7 (15.1) | 105.6 (13.4)* | .69 |
| **Exposure variables** | | | | | |
| Water fluoride concentration (mg/L) | 0.58 (0.08) | 0.13 (0.06)* | 0.59 (0.07) | 0.13 (0.05)* | .18 |
| % living in fluoridated region | 41.5 | | 34.3 | | 14 |
| Infant fluoride intake (mg F/day) | 0.12 (0.07) | 0.02 (0.02)* | 0.34 (0.12) | 0.08 (0.04)* | < .001 |
| MUF concentration (mg/L) | 0.70 (0.39) | 0.42 (0.28)* | 0.64 (0.37) | 0.38 (0.27)* | .07 |

Abbreviations: HOME = Home Observation for Measurement of the Environment; MUF = Maternal urinary fluoride, adjusted for specific gravity; SD = standard deviation.

* $p < .05$ for comparing participants in the breastfed or formula-fed group living in a fluoridated versus non-fluoridated region.

[a] *p*-value reported for main effect of feeding status from 2 × 2 ANCOVA, adjusting for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), second-hand smoke status in the child's house (yes, no), and water fluoridation status (fluoridated versus non-fluoridated).

[b] Main effect of fluoridation status, adjusting for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), second-hand smoke status in the child's house (yes, no), and feeding status (BF vs. FF); VIQ: $p = .02$; PIQ: $p < .001$.

**Table 2**
Adjusted difference in IQ scores at 3–4 years of age per 0.5 mg/L water fluoride concentration and 0.5 mg infant fluoride intake from formula per day, with and without adjusting for maternal urinary fluoride (MUF).

| Exposure variable | N | FSIQ<br>B (95% CI) | N | PIQ<br>B (95% CI) | N | VIQ<br>B (95% CI) |
|---|---|---|---|---|---|---|
| *Model 1* | | | | | | |
| Water Fl (mg/L) | 398 | | 393 | | 397 | |
| Formula-fed | | −4.40 (−8.34, −0.46)* | | −9.26 (−13.77, −4.76)* | | 0.89 (−2.87, 4.65) |
| Breastfed | | −1.34 (−5.04, 2.38) | | −6.19 (−10.45, −1.94)* | | 3.06 (−0.49, 6.61) |
| Water Fl (mg/L) adjusted for MUF[a] | 350 | | 345 | | 349 | |
| Formula-fed | | −3.58 (−7.83, 0.66) | | −7.93 (−12.84, −3.01)* | | 2.60 (−1.98, 7.16) |
| Breastfed | | −1.69 (−5.66, 2.27) | | −6.30 (−10.92, −1.68)* | | 4.20 (−0.06, 8.45) |
| *Model 2* | | | | | | |
| Fluoride intake from formula | 398 | −2.69 (−7.38, 2.01) | 393 | −8.76 (−14.18, −3.34)* | 397 | 3.08 (−1.40, 7.55) |
| Fluoride intake from formula adjusted for MUF[b] | 350 | −1.94 (−7.09, 3.21) | 345 | −7.62 (−13.64, −1.60)* | 349 | 3.05 (−1.89, 7.98) |

Abbreviations: Fl = fluoride; MUF = maternal urinary fluoride; Regression model adjusted for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), and second-hand smoke status in the child's house (yes, no).

* $p < .05$.

[a] MUF was not significantly associated with FSIQ score ($B = -1.08$, 95% CI: −1.54, 0.47, $p = .29$), PIQ score ($B = -1.31$, 95% CI: −3.63, 1.03, $p = .27$), or VIQ score ($B = -0.34$, 95%CI: −2.21, 1.59, $p = .73$). Note: regression coefficients represent the predicted IQ difference per 0.5 mg/L MUF; effect for both sexes is reported. Variance inflation factor (VIF) for water Fl is 2.41 for FSIQ, 2.41 for PIQ, and 2.40 for VIQ when MUF is entered in the model.

[b] MUF is significantly associated with PIQ score ($B = -2.38$, 95% CI: −4.62, −0.27, $p = .04$), but not FSIQ score ($B = -1.50$, 95% CI: −3.41, 0.43, $p = .13$) or VIQ score ($B = -0.11$, 95% CI: −1.94, 1.74, $p = .91$); Note: regression coefficients represent the predicted IQ difference per 0.5 mg/L MUF; effect for both sexes is reported. Variance inflation factor (VIF) for infant fluoride intake is 1.10 for FSIQ, 1.12 for PIQ, and 1.10 for VIQ when MUF is entered in the model

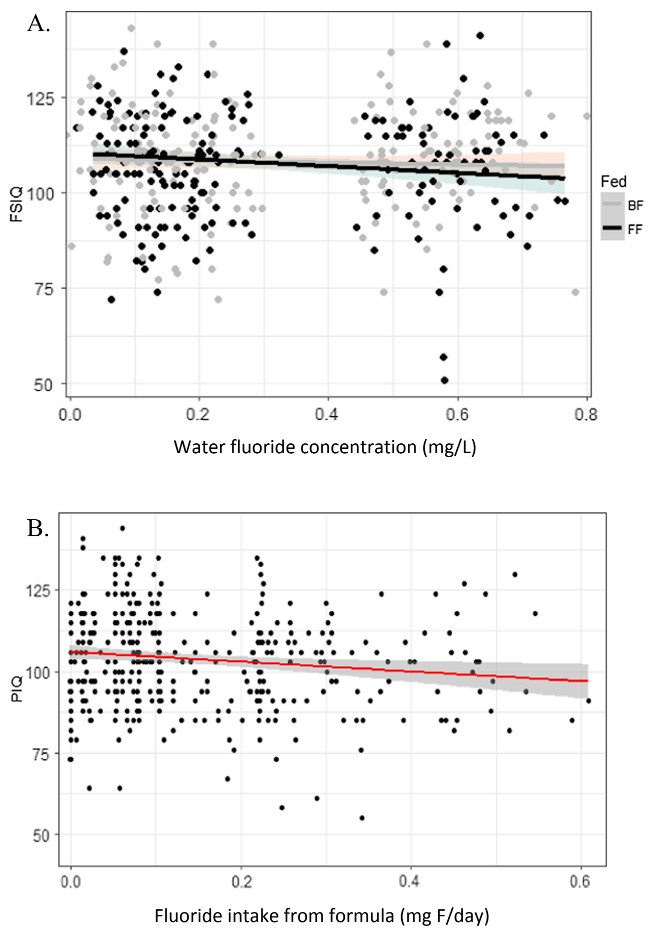


**Fig. 1.** A. Water fluoride concentration as a predictor of Full Scale IQ with an interaction by formula-fed (FF) vs. breastfed (BF) group. Black data points represent the FF group and grey data points represent the BF group. B. Fluoride intake from formula (mg F/day) as a predictor of Performance IQ score.

(Table 2); the interaction was not significant ($p$ = .26). Controlling for MUF, water fluoride concentration remained significantly associated with PIQ in the FF ($B$ = −7.93 95% CI: −12.84, −3.01, $p$ = .002) and BF groups ($B$ = −6.30, 95% CI: −10.92,-1.68, $p$ = .008). Likewise, the associations between water fluoride concentration and PIQ remained significant for both groups after removing two cases with extreme IQ scores (Table S3).

In contrast, water fluoride concentration was not associated with VIQ in the FF ($B$ = 0.89, 95% CI: −2.87, 4.65, $p$ = .64) or BF group ($B$ = 3.06, 95% CI: −0.49, 6.61, $p$ = .09); these associations remained non-significant after controlling for MUF (Table 2) and removing two cases with extreme IQ scores (Table S3).

### *3.3. Model 2: IQ scores and fluoride intake from formula*

Fluoride intake from formula was not significantly associated with FSIQ ($B$ = −2.69, 95% CI: −7.38, 2.01, $p$ = .26) or VIQ ($B$ = 3.08, 95% CI: −1.40, 7.55, $p$ = .18) (Table 2). In contrast, a 0.5 mg increase in fluoride intake predicted an 8.76-point decrement in PIQ score (95% CI: −14.18, −3.34, $p$ = .002; Fig. 1B). Adding MUF to the PIQ model slightly attenuated the association between fluoride intake and PIQ ($B$ = −7.62, 95% CI: −13.64, −1.60, $p$ = .01) (Table 2). Removing two cases with extreme IQ scores did not appreciably alter the association between fluoride intake and PIQ score, with and without adjustment for MUF (Table S3).

## 4. Discussion

For each 0.5 mg/L increase in water fluoride concentration, we found a decrease of 4.4 FSIQ points among preschool children who were formula-fed in the first six months of life; 0.5 mg/L is the approximate difference in mean water fluoride level between fluoridated (0.59 mg/L) and non-fluoridated (0.13 mg/L) regions. In contrast, we did not find a significant association between water fluoride concentration and FSIQ among exclusively breastfed children. The association between water fluoride concentration and FSIQ must be interpreted with caution, however, because the association became non-significant when two outliers were removed. We observed an even stronger association between water fluoride and PIQ (non-verbal intelligence). A 0.5 mg/L increase in water fluoride level predicted a decrement in PIQ in both the formula-fed (9.3-points) and the breastfed groups (6.2-points). Adjusting for fetal exposure or removing two extreme scores did not appreciably alter these results.

We observed converging results using fluoride intake from formula, which is a continuous, time-weighted exposure estimate. For each 0.5 mg/day of fluoride intake, we found an 8.8-point decrement in PIQ; adjusting for fetal exposure using MUF attenuated the association only slightly (7.6-point decrement in PIQ). MUF was also negatively associated with PIQ (2.4-point decrement for each 0.5 mg/L increase in MUF). The fluoride intake estimate may reflect a more refined measure of exposure in infancy because it captures differences in both water fluoride level and the proportion of time each child was given formula over the first year of life. Yet, our binary classification of whether a child was exclusively breastfed for 6 months may better capture children who are most vulnerable to neurotoxic effects of fluoride because it subsets those exposed to fluoride during the early infancy period when the brain undergoes significant development (Huttenlocher and Dabholkar, 1997; Kostovic, 2006). Taken together, these findings suggest that using optimally fluoridated water (0.7 mg/L) to reconstitute infant formula may diminish the development of intellectual abilities in young children, particularly for non-verbal abilities. The findings also suggest that both prenatal and postnatal fluoride exposure affect the development of non-verbal intelligence to a greater extent than verbal intelligence. Prior studies examining prenatal exposure to fluoride and IQ showed a similar pattern (Bashash et al., 2017; Green et al., 2019).

Consistent with prior studies showing a positive effect of breastfeeding on cognition (Horta et al., 2015), children in the breastfed group had higher FSIQ and VIQ scores relative to the formula-fed group, regardless of fluoridation status (Table 1); higher education and income levels in the breastfed group likely accounts for part of this association (Walfisch et al., 2013). In contrast, the breastfed group did not differ significantly from the formula-fed group with respect to PIQ score. Children who lived in non-fluoridated regions showed higher PIQ scores than children who lived in fluoridated regions, though this difference was significant only for the formula-fed group, perhaps reflecting a higher vulnerability of nonverbal abilities to fluoride exposure in infancy.

Most studies of fluoride exposure from infant formula consumption have focused on risk for later development of dental enamel fluorosis (Brothwell and Limeback, 2003; Hong et al., 2006; Berg et al., 2011). Beyond fluorosis, the safety of fluoride exposure from infant formula has not been rigorously tested, despite warnings of overexposure (Diesendorf and Diesendorf, 1979). A recent study showed that up to 59% of infants younger than four months exceed the upper limit (0.1 mg/kg/day) (Institutes of Medicine, 1997) when optimally fluoridated water is used to reconstitute infant formula (Harriehausen et al., 2019); 33% and 14.3% of six- and nine-month old infants exceeded the upper limit threshold, respectively. Conversely, breastfed infants receive very low fluoride intake (generally less than 0.01 mg/L), even in communities with fluoridated water (Dabeka et al., 1986; Ekstrand, 1981; Fomon et al., 2000). Our estimate of fluoride intake (0.34 mg F/day) among formula-fed infants who live in a fluoridated region is an underestimate of actual fluoride intake because we did not include fluoride from other sources, such as the fluoride found in the formula or foods; thus, the association between fluoride intake and IQ scores among formula-fed infants may be stronger than the association obtained in our analysis.

Our results, which showed that higher fluoride exposure in infancy was associated with diminished IQ scores in young children, are consistent with two longitudinal birth cohort studies. In one study involving 299 mother–child pairs living in Mexico City, there was a decrement of 3.2 IQ points in preschool aged children for every 0.5 mg/L of MUF level during pregnancy (Bashash et al., 2017). In the other study, which we conducted using the same Canadian cohort, we reported a decrement of 2.2 IQ points among preschool aged boys for every 0.5 mg/L of MUF level during pregnancy (Green et al., 2019). When MUF was included as a covariate in the current study, the association between MUF and FSIQ was not significant (see Table 2, note a). This discrepancy arises because (1) Green et al. (2019) did not include fluoride exposure in infancy as a covariate and (2) Green et al. (2019) estimated sex-specific MUF effects whereas the current study estimated an overall MUF effect.

The beneficial effects of fluoride predominantly occur at the tooth surface, after teeth have erupted (Limeback, 1999). Fluoride contributes to the prevention of dental caries primarily when it is topically applied to teeth, such as brushing with fluoridated toothpaste (Featherstone, 2001; Limeback, 1999; NRC, 2006; Pizzo et al., 2007; Warren and Levy, 2003). Because fluoride is not essential for growth and development (Scientific Committee on Health and Environmental Risks (SCHER), 2011), there is no recommended intake level of fluoride during fetal development or in the first six months of life before teeth have erupted. Accordingly, the Canadian Pediatric Society recommends administering supplemental fluoride (i.e. systemic exposure) only when primary teeth begin to erupt (American Dental Association) (at approximately 6 months) and only if the child is susceptible to high caries activity and is not exposed to other fluoride-based interventions, such as toothbrushing or water fluoridation (Godel, 2002).

The American Dental Association (Berg et al., 2011; American Dental Association, 2018) advises parents to use optimally fluoridated drinking water to reconstitute concentrate infant formulas, while being cognizant of the potential risk of mild enamel fluorosis development. This recommendation is echoed by the Centers for Disease Control and Prevention (Community Water Fluoridation. Infant Formula) as well as the U.S. Department of Health and Human Services (2015). The Canadian Dental Association (2019) recommends using water with low fluoride concentration (or ready-to-feed formula) when the fluoride level in drinking water is above the optimal level. In addition to tap water, which is reportedly used by 93% of caregivers who feed formula to infants (Brothwell and Limeback, 2003), “nursery” water (which may contain up to 0.7 mg F/L) is marketed for reconstituting formula and sold in Canada and the United States. The availability of fluoridated nursery water gives the false impression that fluoride exposure during early infancy is beneficial prior to teeth eruption.

Formula-fed infants who reside in fluoridated areas have a 70-fold higher intake of fluoride than exclusively breastfed infants (Ekstrand, 1981; Zohoori et al., 2018; United States Environmental Protection Agency, 2010). Formula-fed infants also retain more fluoride than breastfed infants (Zohoori et al., 2018; Ekstrand and Hardell, 1984) because infants have a limited capacity to excrete fluoride before renal function reaches its full capacity at about two years of age (National Research Council (NRC), 2006; Zohoori et al., 2018). Fluoride absorption also depends on the presence of other nutrients (Health Canada, 2010); when fluoride intake is exclusively from reconstituted formula, the bioavailability of fluoride is 65%, whereas a varied diet reduces fluoride absorption in tissues and bone to about 47% (Ekstrand and Ehrnebo, 1979). These factors place formula-fed infants at an even higher risk of fluoride toxicity.

Our study has some limitations. First, infant formulas vary in fluoride content. Ready-to-use formulas typically have less fluoride than powdered formula (Dabeka and McKenzie, 1987; Fomon et al., 2000); information about formula type was only available for 100 of 198 (50.5%) participants in the formula group; of those, 75% reported using powdered formula, which is the most common type of formula used by the general population (Infant Feeding Practices Survey II; Fomon et al., 2000). Variability in fluoride content is also seen across different types of powdered formula (United States Environmental Protection Agency, 2010; Harriehausen et al., 2019; Mahvi et al., 2010). Additionally, soy-based formula reconstituted with distilled water has more fluoride (0.24–0.30 mg/L depending on whether it is ready-to-feed or concentrated) than milk-based powdered formulas (0.12–0.17 mg/L) (Harriehausen et al., 2019; Van Winkle et al., 1995). Although we lacked data on brand of formula, we have no reason to expect that use of powdered versus ready-to-feed or soy- versus milk-based formula would differ by fluoridation status. Moreover, our effects were primarily based on water fluoride content, which is the major source of fluoride (Buzalaf et al., 2001). Second, we did not have specific information on the type of water (bottled versus tap) used to reconstitute formula. However, mothers typically report using tap water for reconstituting formula (Van Winkle et al., 1995) and we only included children of women who reported drinking tap water in our analyses. Third, there is potential for non-differential misclassification of the feeding status variable because mothers may have been confused by the definition of exclusive breastfeeding on the questionnaire or the responses may have been affected by recall or response bias. As with any survey, women could be confused by the question, but given the demographic of the sample – highly educated, English speaking, and non-teenage mothers – confusion seems less likely. Fourth, our method of estimating infant fluoride intake has not been validated. Finally, children were tested between 3 and 4 years of age and we have no information regarding other possible sources of fluoride that occurred between post-weaning and the age of testing. Thus, other sources of fluoride (e.g. dental products) or more frequent brushing, might differ between participants who lived in fluoridated versus non-fluoridated communities or among those in the breastfeeding versus formula-feeding group. To control for these potential differences, we included maternal education in all models. In addition, the design of our study compares water fluoride level and IQ scores in the formula-fed children using the breast-fed children as a control.

In summary, fluoride intake among infants younger than 6 months may exceed the tolerable upper limits if they are fed exclusively with formula reconstitued with fluoridated tap water. After adjusting for fetal exposure, we found that fluoride exposure during infancy predicts diminished non-verbal intelligence in children. In the absence of any benefit from fluoride consumption in the first six months, it is prudent to limit fluoride exposure by using non-fluoridated water or water with lower fluoride content as a formula diluent.

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The authors have no financial disclosures.

## Contributors statement

Dr Till conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Ms Green designed the study, curated the data, carried out the initial data analysis, reviewed and revised the manuscript. Drs Flora and Hornung supervised data analysis, reviewed and revised the manuscript. Ms. Farmus assisted with data analysis, reviewed and revised the manuscript. Dr Martinez-Mier reviewed and revised the manuscript and supervised the analysis of maternal urinary fluoride. Mr Blazer collected the water fluoride data from water treatment plants and reviewed the manuscript. Drs Ayotte and Muckle assisted with initial data collection, and critically reviewed and revised the manuscript. Dr Lanphear conceptualized the study, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105315.

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