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Fluoride exposure during pregnancy from a community water supply is associated with executive function in preschool children: A prospective ecological cohort study

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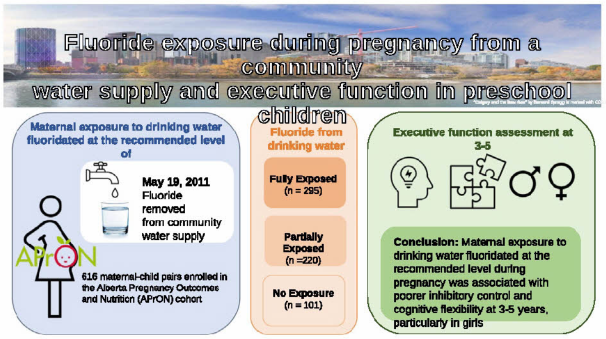
HIGHLIGHTS

- Maternal fluoride exposure from drinking water was associated with executive function.
- Poorer inhibitory control and cognitive flexibility were found, particularly in girls.
- Maternal fluoride exposure was not associated with lower intelligence in children.
- Water fluoridated at the recommended level of 0.7 mg/L may adversely affect executive function.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: On May 19, 2011, Calgary, Canada stopped fluoridating its drinking water. This prospective ecological study examined if maternal exposure to fluoride during pregnancy from drinking water that was fluoridated at the recommended level of 0.7 mg/L was associated with children's intelligence and executive function at 3–5 years of age.
Methods: Participants were 616 maternal-child pairs enrolled in the Calgary cohort of the Alberta Pregnancy Outcomes and Nutrition (APrON) study between 2009 and 2012. Maternal-child pairs were classified as fully exposed to fluoridated drinking water throughout pregnancy ($n = 295$); exposed to fluoridated drinking water for at least part of the pregnancy plus an additional 90 days ($n = 220$); or not exposed to fluoridated drinking water during pregnancy plus the 90 days prior to pregnancy ($n = 101$). Children's Full Scale IQs were assessed using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition: Canadian (WPPSI-IV^{CDN}). Children's executive functions were also assessed: working memory (WPPSI-IV^{CDN} Working Memory Index), inhibitory control (Gift Delay, NEPSY-II Statue

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Abbreviations: APrON, Alberta; DCCS, Dimensional Change Card Sort; FSIQ, Full Scale IQ; NEPSY-II, Developmental NEuroPSYchological Assessment- Second Edition; VCI, Verbal Comprehension Index; VSI, Visual Spatial Index; WMI, Working Memory Index; WPPSI-IV^{CND}, Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition: Canadian.

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subtest), and cognitive flexibility (Boy-Girl Stroop, Dimensional Change Card Sort (DCCS)).
Results: No associations were found between exposure group and Full Scale IQ. However, compared to no exposure, full exposure to fluoridated drinking water throughout pregnancy was associated with poorer performance on the Gift Delay ($B = 0.53$, *95 % CI* = 0.31, 0.93). Sex-specific analyses revealed that girls in the fully exposed (*AOR* = 0.30, *95 % CI* = 0.13, 0.74) and partially exposed groups (*AOR* = 0.42, *95 % CI* = 0.17, 1.01) performed more poorly than girls in the not exposed group. Sex effects were also found on the DCCS; girls in the fully exposed (*AOR* = 0.34, *95 % CI* = 0.14, 0.88) and partially exposed groups (*AOR* = 0.29, *95 % CI* = 0.12, 0.73) performed more poorly.
Conclusion: Maternal exposure to drinking water throughout pregnancy fluoridated at the level of 0.7 mg/L was associated with poorer inhibitory control and cognitive flexibility, particularly in girls, suggesting a possible need to reduce maternal fluoride exposure during pregnancy.

1. Introduction

Fluoridation of community water supplies is a common primary prevention method used to prevent tooth decay. Current rates of community water fluoridation range from 3 % in regions of Western Europe to over 70 % in the USA and Australia (Centers for Disease Control, 2018; Cheng et al., 2007; National Health and Medical Research Council. Public Statement, 2017). In 2017, 38.7 % of the Canadian population had access to a fluoridated water supply (Public Health Agency of Canada, 2017). In fluoridated communities, it is estimated that 60 % to 80 % of daily fluoride intake comes from tap water and beverages made with tap water (United States Environmental Protection Agency, 2010), and strong associations have been found between fluoride levels in community water supplies and urinary fluoride concentrations in pregnant women (Till et al., 2018).

In animal models, fluoride exposure has been associated with memory and learning impairment, and alterations in monoamine levels in the hippocampus, cortex, striatum and amygdala, and neurodegenerative changes in rats (Pereira et al., 2011; Jiang et al., 2014). In human populations, maternal fluoride exposure during pregnancy could influence children's neurodevelopment as fluoride passes across the placenta and the fetal blood-brain barrier (Gupta et al., 1993). Many studies have investigated associations between prenatal exposure to fluoride and child neurodevelopmental outcomes using ecological cross-sectional designs. Fluoride exposure was estimated by measuring fluoride concentrations in drinking water where high fluoride (0.9–11.0 mg/L) occurs naturally such as in India, Iran, and China, and the neurodevelopmental outcomes of children living in these areas were compared with those of children living in areas in the same countries with low levels of fluoride exposure from drinking water (Aravind et al., 2016; Choi et al., 2012; Sebastian and Sunitha, 2015; Karimzade et al., 2014; Grandjean, 2019; Khan, 2015). These studies reported that higher levels of fluoride exposure from drinking water were associated with adverse neurocognitive outcomes in children (Aravind et al., 2016; Choi et al., 2012; Sebastian and Sunitha, 2015; Karimzade et al., 2014; Grandjean, 2019; Khan, 2015). In Canada, where high levels of fluoride are typically not endemic in drinking water, the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort study estimated maternal daily intake of fluoride in nonfluoridated and fluoridated communities and examined the association with child intelligence at 3–4 years of age (Green et al., 2019). Results revealed that an estimated daily increase of 1 mg/L of fluoride was associated with a 3.66 point decrease in Full Scale IQ (FSIQ) in children at 3–4 years of age. Ridell et al., using data from the Canadian Health Measures Survey, reported that in a national sample of Canadian youth aged 6 to 17 years a 1 mg/L increase in tap water fluoride level was associated with 6.1 times higher odds of a diagnosis of attention deficit/hyperactivity disorder (ADHD) (Riddell et al., 2019). The results of these studies suggest that exposure to fluoride from drinking water could adversely impact children's cognitive development and behavior.

Most studies that have investigated the association between prenatal fluoride exposure and children's neurodevelopment have focused on general cognitive development as assessed by the Bayley Scales of Infant and Toddler Development or intelligence (e.g., Wechsler Scales, Raven's Progressive Matrices). The influence of fluoride exposure on children's executive functions have not been examined. Executive functions are required to carry out goal-directed behaviours (Dajani et al., 2016) and include abilities such as working memory, inhibitory control, and cognitive flexibility (Diamond, 2016). They are critical for the academic, psychological, and social development and associated with mental and physical health outcomes (Diamond, 2016; Blair and Razza, 2007; Moffitt et al., 2011). Although executive functions are not fully developed until adulthood, children's performance on executive functioning tasks in early childhood are highly predictive of academic success and economic achievement later in life (Diamond, 2016; Diamond, 2013; Isquith-Dicker et al., 2021). Further, executive function deficits are consistently associated with behavioural and neurodevelopmental disorders such as ADHD, autism spectrum disorder (ASD), intellectual disability, and specific learning disorders (Canfield et al., 2003; Willcutt et al., 2005; Corbett et al., 2009; Otterman et al., 2019; Crisci et al., 2021). Therefore, it is essential to move beyond examining only the influence of prenatal exposure to fluoride on intelligence to examining associations between prenatal fluoride exposure and other important domains of neurocognitive function such as executive function.

Health Canada and the Public Health Service in the USA recommend a fluoride concentration of 0.7 mg/L in drinking water in community water systems that add fluoride as it provides the best balance of protection from dental caries in children and adults while limiting the risk of dental fluorosis (Centers for Disease Control and Prevention, 2023; Health Canada, 2011). However, the effects of this level of fluoride exposure on prenatal brain development and in turn neurocognitive outcomes in children is not known. Few prospective longitudinal epidemiological studies are able to conduct a naturalistic ecological study examining the association between maternal exposure during pregnancy to fluoridated drinking water at the level of 0.7 mg/L (Government of Canada, 2023) or nonfluoridated drinking water on children's neurodevelopment in comparable populations from the same community. In the Bow and Elbow Rivers, which supply Calgary with its drinking water, fluoride occurs naturally, in concentrations that vary from 0.1 to 0.4 mg/L (Isquith-Dicker et al., 2021). Until May 19, 2011, in the midst of recruitment of pregnant women into the Alberta Pregnancy Outcomes and Nutrition (APrON) study, fluoride levels in Calgary's community water supply were adjusted to 0.7 mg/L (Cheng et al., 2007; Isquith-Dicker et al., 2021). After that time, fluoride levels were not adjusted and varied between 0.1 and 0.4 mg/L. The primary aim of this study was to determine if maternal exposure to fluoride during pregnancy from drinking water that was fluoridated at the level of 0.7 mg/L was associated with children's intelligence and executive function (i.e., working memory, inhibitory control, and cognitive flexibility) at 3–5 years of age.

2. Methods

2.1. Study cohort

Between 2009 and 2012, the APrON study recruited 1969 pregnant women from Calgary, Alberta, Canada. Women were eligible if they could communicate in English, were <27 weeks gestational age and were ≥16 years of age. A subset of 616 maternal-child pairs from Calgary whose children participated in cognitive and executive function assessments at 3 to 5 years of age (M = 4.24 SD = 0.51) participated in this study. The APrON protocol was approved by health research ethics boards at the University of Calgary (Ethics ID: REB14–1702) and University of Alberta (Study ID: Pro00002954). Women provided written informed consent at time of recruitment and prior to their children's neurodevelopmental assessment.

2.2. Fluoride exposure during pregnancy

As of May 19, 2011, fluoride was not added to Calgary's community water supply. This likely resulted in a decrease, but not an elimination of fluoride exposure, due to other sources of exposure (e.g., food, toothpaste, natural levels of fluoride in water). Further, when fluoride levels in Calgary's community water supply were not adjusted to 0.7 mg/L, plasma levels may not have dropped immediately (Maheshwari et al., 1982). To our knowledge, the time required to reach a “quasi-steady state” in plasma fluoride levels after removal of fluoride from a community water supply has not been determined; therefore, based on expert advice (William Maas, unpublished communication, 15 June 2020), we conservatively estimated that 90 days was required.

The effects of maternal exposure to fluoride on children's intelligence and executive functions were examined in three groups: a) women exposed to recommended levels of fluoride (i.e., 0.7 mg/L) from drinking water throughout pregnancy, i.e., “fully” exposed group (47.9 %; *n* = 295); b) women exposed to recommended levels of fluoride from drinking water for at least part of their pregnancy (range = 1 day to 270 days gestation) plus an additional 90 days to ensure that maternal levels of plasma fluoride had reached a “steady state” after removal of fluoride from the community water supply, i.e., “partially” exposed group (35.7 %; *n* = 220); and c) women not exposed to recommended levels of fluoride from drinking water during pregnancy plus the 90 days prior to pregnancy, i.e., “not exposed” group (16.4 %; *n* = 101). The fully exposed group included women whose children were born before May 19, 2011; the partially exposed group included women whose children were born between May 19, 2011 and May 13, 2012 (accounts for 270 days gestation plus an additional 90 days); the not exposed group included women whose children were born after May 13, 2012 (accounts for no exposure to fluoride from drinking water during the entire pregnancy plus the 90 days prior to pregnancy) (Fig. 1).

2.3. Children's intelligence and executive function measures

Children',s Full Scale IQ (FSIQ) on the Wechsler Preschool and Primary Scale of Intelligence Fourth Edition: Canadian (WPPSI-IV^{CND}) was our primary outcome. Children's performance on the WPPSI-IV Verbal Comprehension Index (VCI) and Visual Spatial Index (VSI) were also assessed. Higher scores on the WPPSI-IV^{CND} indicate better performance.

Measures of working memory, inhibitory control, and cognitive flexibility were used to assess executive function. Working memory was assessed using the Working Memory Index (WMI) of the WPPSI-IV^{CND}; Gift Delay (i.e., no peek versus peek) and the NEPSY-II Statue subtest were used to assess inhibitory control. Cognitive flexibility was assessed with Boy-Girl Stroop (i.e., number of correct responses out of 16) and Dimensional Change Card Sort (DCCS) (i.e., pass/fail pass was the correct performance on at least 5 of 6 post-switch trials). Higher scores on the executive function tasks indicated better performance.

2.4. Covariates

Potential covariates were selected from established factors associated with children's intellectual abilities and executive functioning (i.e., maternal age, sociodemographic factors, maternal pre-pregnancy BMI, maternal pre-pregnancy smoking, maternal depression, child sex, and infant gestational age at birth). As performance on the Gift Delay, DCCS, and Boy-Girl Stroop were not age standardized, child age was included as a covariate. The covariates were coded as follows: maternal education (i.e., bachelor's degree or higher, trade school diploma or lower), maternal marital status (i.e., married/living with a partner, single/separated/divorced/widowed), annual household income (i.e., <$70,000, > $70,000), maternal birthplace (i.e., born in Canada or not), maternal parity

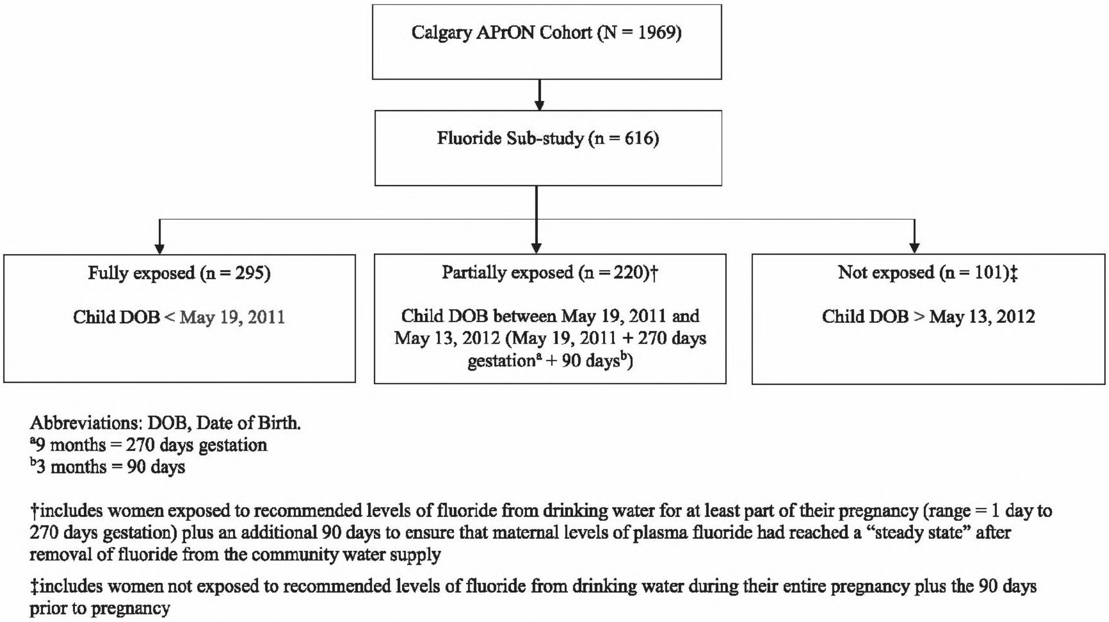

Fig. 1. Abbreviations: DOB, Date of Birth.
[a]9 months = 270 days gestation
[b]3 months = 90 days
†includes women exposed to recommended levels of fluoride from drinking water for at least part of their pregnancy (range = 1 day to 270 days gestation) plus an additional 90 days to ensure that maternal levels of plasma fluoride had reached a “steady state” after removal of fluoride from the community water supply
‡includes women not exposed to recommended levels of fluoride from drinking water during their entire pregnancy plus the 90 days prior to pregnancy.

status (i.e., primiparous, multiparous), maternal pre-pregnancy BMI (i.e., underweight/normal, overweight/obese), and maternal pre-pregnancy smoking (i.e., yes, no). Maternal depression was measured using the Edinburgh Depression Scale (Bergink et al., 2011; Matthey, 2016) and coded as either probable no or mild depression (score < 10) or probable moderate or severe depression (score ≥ 10). Infant gestational age at birth was recorded in weeks.

2.5. Statistical analysis

Analyses were performed in R (version 4.1.3). The missingness of data varied (i.e., fluoride exposure group data were 100 % complete; covariates were >98 % complete; child neurodevelopmental data were between 93 % and 99 % complete). Incomplete data were imputed by chained equations using predictive mean matching and classification and regression trees (using *pmm* and *cart* for from the *mice* package) (van Buuren, 2021; van Buuren and Groothuis-Oudshoorn, 2011). Five datasets were imputed and estimates were evaluated in all multiple imputation datasets and combined by pooling (using *with.mids* and *pool* from the *mice* package) (van Buuren, 2021; van Buuren and Groothuis-Oudshoorn, 2011).

Analysis of variance and chi-square tests were used to examine differences in sample characteristics between fluoride exposure groups (using *mi.anova* and *micombine.chisquare* from the *miceadds* package) (van Buuren and Groothuis-Oudshoorn, 2011; Robitzsch et al., 2022). Most of the children's intellectual functioning and executive function scores violated the assumptions of a normal distribution (i.e., skewed), which is common in typically developing samples of young children (Albers and Grieve, 2007; Skogan et al., 2016). For this reason, robust multivariable regressions (using *rlm* from the *MASS* package) (Lourenço et al., 2011; Venables, 2002) and robust logistic binomial regressions were used (using *glmrob* from the *robustbase* package) (Maechler et al., 2022), as these techniques are robust to violations of normality and outliers. Adjusted robust linear models examined associations between fluoride exposure group and children's scores on the WPPSI-IV$^{\text{CND}}$, NEPSY-II Statue subtest, and Boy-Girl Stroop. Adjusted robust logistic models examined associations between fluoride exposure group and children's performance on the Gift Delay and DCCS. Child sex and sample characteristics that differed significantly among exposures groups were included as covariates if *p* values were < 0.05 (Table 1). Sex-stratified models investigated associations separately for girls ($n = 300$) and boys ($n = 316$).

Sensitivity analyses, removing potential outlier values of the FSIQ (i.e., values ± 2SD from standard score of 100) and removing children with low birthweights (i.e., birthweight < 2500 g), assessed the robustness of results for FSIQ. For all statistical analyses, statistical significance tests with an alpha of 5 % were used; 95 % confidence intervals were used to estimate uncertainty.

3. Results

Few differences in sample characteristics were found between the overall sample and the fluoride exposure groups (Table 1). In the overall sample, the mean age of the mothers at enrollment was 32.24 (SD = 3.99) years. Most mothers were born in Canada (82.14 %) and just over half of the children were boys (51.3 %). The not exposed group had a lower prevalence of women born in Canada (71.29 %) compared to the partially (83.64 %) and fully exposed (84.75 %) groups, and a lower proportion of women who reported smoking prior to pregnancy (13.86 %) compared to the partially (25.0 %) and fully exposed (27.12 %) groups. Descriptive statistics of the children's performance on the intellectual and executive functioning measures are reported in Table A.1.

Table 1
Sample characteristics for the overall sample and by fluoride exposure group.

Variables	Overall Sample ($n = 616$)	Fully Exposed Group ($n = 295$)	Partially Exposed Group ($n = 220$)	Not Exposed Group ($n = 101$)	Test of Group Differences (*P*-value[a])
Women					
Age, M (SD)	32.24 (3.99)	32.36 (4.12)	32.12 (3.93)	32.17 (3.72)	0.79
Marital status, n (%)					0.18
Married/living with a partner	599 (97.24 %)	285 (96.61 %)	213 (96.82 %)	101 (100 %)	
Single/separated/divorced/widowed	17 (2.76 %)	10 (3.39 %)	7 (3.18 %)	0 (0.0 %)	
Born in Canada n (%)					0.01*
Yes	506 (82.14 %)	250 (84.75 %)	184 (83.64 %)	72 (71.29 %)	
No	110 (17.86 %)	45 (15.25 %)	36 (16.36 %)	29 (28.71 %)	
Education n (%)					0.26
Trade school diploma/high school	153 (24.84 %)	74 (25.08 %)	60 (27.27 %)	19 (18.81 %)	
University degree or higher	463 (75.16 %)	221 (74.92 %)	160 (72.73 %)	82 (81.19 %)	
Household income, n (%)					0.88
<$70,000 CAD	104 (16.88 %)	52 (17.63 %)	35 (15.91 %)	17 (16.83 %)	
≥ $70,000 CAD	512 (83.12 %)	243 (82.37 %)	185 (84.09 %)	84 (83.17 %)	
Pre-pregnancy smoking, n (%)					0.03*
No	467 (75.81 %)	215 (72.88 %)	165 (75.0 %)	87 (86.14 %)	
Yes	149 (24.19 %)	80 (27.12 %)	55 (25.0 %)	14 (13.86 %)	
Parity, n (%)					0.97
Primiparous	340 (55.19 %)	164 (55.59 %)	120 (54.55 %)	56 (55.45 %)	
Multiparous	276 (44.81 %)	131 (44.41 %)	100 (45.45 %)	45 (44.55 %)	
Depression, n (%)					0.69
Probable no or low (EDS < 10)	448 (72.73 %)	210 (71.19 %)	164 (74.55 %)	74 (73.27 %)	
Probable moderate or severe (EDS ≥10)	168 (27.27 %)	85 (28.81 %)	56 (25.45 %)	27 (26.73 %)	
Pre-pregnancy BMI, n (%)					0.86
Under/ normal Weight	409 (66.4 %)	198 (67.12 %)	143 (65.0 %)	68 (67.33 %)	
Overweight/Obese	207 (33.6 %)	97 (32.88 %)	77 (35.0 %)	33 (32.67 %)	
Children					
Child sex, n (%)					0.32
Boy	316 (51.3 %)	157 (53.22 %)	114 (51.82 %)	45 (44.55 %)	
Girl	300 (48.7 %)	138 (46.78 %)	106 (48.18 %)	56 (55.45 %)	
Gestational age at birth, M (SD), weeks	39.31 (1.48)	39.26 (1.51)	39.41 (1.29)	39.25 (1.79)	0.45
Birth weight, M (SD), grams	3368.81 (500.0)	3363.39 (464.54)	3402.97 (515.76)	3310.23 (560.6)	0.29

Abbreviations: M, Mean; SD, Standard Deviation; EDS; Edinburgh Depression Scale; BMI, Body Mass Index.

[a] *P*-values for one-way analysis of variance (ANOVA) and chi-square test (x^2) statistics for differences between groups on continuous and categorical variables using pooled results from multiple imputed datasets.

* $p < 0.05$.

3.1. Intelligence

No associations were found between the fully exposed ($B = 0.36$, 95 % CI: −2.69, 3.41) and partially exposed ($B = 0.06$, 95 % CI: −3.10, 3.23) fluoride groups and the not exposed group for WPPSI-IV^{CND} FSIQ in the overall sample (Table 2). Similarly, no associations were found for scores on the VCI and VSI indexes (Table 2). Sex-stratified analyses did not reveal any associations (Table 2).

3.2. Executive functions

3.2.1. Working memory

No associations were noted between the fully exposed ($B = 2.36$, 95 % CI: −0.85, 5.57) and partially exposed ($B = 0.68$, 95 % CI: −2.65, 4.01) fluoride groups and the not exposed group on the WMI of the WPPSI-IV^{CND} for the overall group. Sex-stratified analyses also revealed no associations (Table 2).

3.2.2. Inhibitory control

On the Gift Delay, children in the fully exposed fluoride group had lower odds of passing than children in the not exposed group (*AOR* = 0.53, *95 % CI* = 0.31, 0.93) indicting poorer inhibitory control. In contrast, for the NEPSY-II Statue subtest, no associations were found between exposure group and children's scores (Table 3). Sex-stratified models showed that girls in the fully exposed group (*AOR* = 0.30, *95 % CI* = 0.13, 0.74) displayed lower odd of passing the Gift Delay compared to girls in the not exposed group; a similar association was noted for girls in the partially exposed group compared to those in the non-exposed group (*AOR* = 0.42, *95 % CI* = 0.17, 1.01). For boys, the pattern of results suggested that partial exposure to fluoride compared to no exposure may be associated with better performance on Gift Delay (*AOR* = 2.05, *95 % CI* = 0.99, 4.22).

3.2.3. Cognitive flexibility

For the DCCS, no associations were found between fluoride exposure group and odds of passing the DCCS in the overall group or for boys. However, girls in the fully (*AOR* = 0.34, *95 % CI* = 0.14, 0.88) and partially exposed groups (*AOR* = 0.29 *95 % CI* = 0.12, 0.73) were approximately one third less likely to pass the DCCS compared to girls in the not exposed group (Table 3). No associations were found between fluoride exposure group and scores on Boy-Girl Stroop (Table 3).

Table 2
Adjusted associations estimated from robust linear models of fluoride exposure and child performance on the WPPSI-IV.

	FSIQ B (95 % CI)	VCI B (95 % CI)	VSI B (95 % CI)	WMI B (95 % CI)
Overall (n = 616)				
Fully exposed	0.36 (−2.69, 3.41)	−1.40 (−4.62, 1.82)	−0.51 (−4.06, 3.04)	2.36 (−0.85, 5.57)
Partially exposed	0.06 (−3.10, 3.23)	−2.02 (−5.36, 1.33)	−1.57 (−5.26, 2.12)	0.68 (−2.65, 4.01)
Non-exposed	Ref	Ref	Ref	Ref
Girls (n = 300)				
Fully exposed	1.36 (−2.54, 5.26)	−0.91 (−5.11, 3.29)	−0.74 (−5.23, 3.75)	3.81 (−0.19, 7.81)
Partially exposed	−0.62 (−4.67, 3.43)	−3.59 (−7.95, 0.78)	−1.08 (−5.74, 3.59)	1.17 (−2.99, 5.32)
Non-exposed	Ref	Ref	Ref	Ref
Boys (n = 316)				
Fully exposed	−0.71 (−5.46, 4.04)	−1.88 (−6.81, 3.05)	−0.74 (−6.25, 4.76)	0.35 (−4.93, 5.63)
Partially exposed	0.51 (−4.41, 5.44)	−0.66 (−5.77, 4.46)	−2.41 (−8.12, 3.30)	−0.43 (−5.91, 5.05)
Non-exposed	Ref	Ref	Ref	Ref

Abbreviations: WPPSI-IV, Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition; FSIQ, Full scale IQ; VCI, Verbal Comprehension Index; VSI, Visual Spatial Index; WMI, Working Memory Index; CI, Confidence Interval; Ref, Reference category.

All models are adjusted for whether or not mothers were born in Canada and pre-pregnancy smoking. Overall models are also adjusted for child sex. Unstandardized coefficients are presented.

Table 3
Adjusted associations estimated from robust linear models and logistic regression models of fluoride exposure and child performance on the executive function tasks.

	Gift Delay AOR (95 % CI)	NEPSY-II Statue[a] B (95 % CI)	Boy-Girl Stroop B (95 % CI)	DCCS AOR (95 % CI)
Overall (n = 616)				
Fully exposed	0.53 (0.31, 0.93)*	0.38 (−0.34, 1.11)	0.70 (−0.35, 1.75)	0.70 (0.38, 1.30)
Partially exposed	0.99 (0.57, 1.69)	−0.03 (−0.78, 0.73)	−0.01 (−1.02, 1.00)	0.65 (0.36, 1.17)
Non-exposed	Ref	Ref	Ref	Ref
Girls (n = 300)				
Fully exposed	0.30 (0.13, 0.74)*	0.49 (−0.41, 1.39)	−0.13 (−1.32, 1.07)	0.34 (0.14, 0.88)*
Partially exposed	0.42 (0.17, 1.01)	0.15 (−0.78, 1.09)	−0.56 (−1.71, 0.60)	0.29 (0.12, 0.73)*
Non-exposed	Ref	Ref	Ref	Ref
Boys (n = 316)				
Fully exposed	0.83 (0.40, 1.73)	0.18 (−1.00, 1.35)	1.56 (−0.29, 3.41)	1.22 (0.54, 2.75)
Partially exposed	2.05 (0.99, 4.22)	−0.24 (−1.46, 0.98)	0.54 (−1.24, 2.32)	1.27 (0.58, 2.77)
Non-exposed	Ref	Ref	Ref	Ref

Abbreviations: OR, Odds Ratio; DCCS, Dimensional Change Card Sort; CI, Confidence Interval; Ref, Reference category.

All models are adjusted for maternal birthplace, maternal pre-pregnancy smoking, and child age. Overall models are also adjusted for child sex. Unstandardized coefficients and ORs are presented.

[a] NEPSY-II Statue subtest scores are standardized, so child age was not included as a covariate in these models.

* $p < 0.05$.

3.3. Sensitivity analyses

Removal of children whose FSIQ scores were ±2 standard deviations from the sample mean did not alter the associations with FSIQ (Table A.2). However, removal of children with low birthweight (<2500 g) did alter the magnitude of some of the associations with FSIQ (Table A.3).

4. Discussion

In this prospective ecological study, no associations were found between exposure to drinking water from a community water supply fluoridated at 0.7 mg/L throughout pregnancy and measures of intelligence at 3–5 years of age. However, maternal exposure to fluoride throughout pregnancy was associated with poorer inhibitory control, particularly in girls, at 3 to 5 years of age compared to children who were not exposed. Further, exposure to fluoride throughout or for part of pregnancy was associated with poorer cognitive flexibility in girls at 3–5 years of age. These findings suggest that exposure to levels of fluoride recommended for dental health in a community water supply during pregnancy may be associated with adverse effects on executive function abilities in young children, particularly girls.

To our knowledge, no previous research has examined the influence of exposure to fluoride from a community water supply fluoridated at 0.07 mg/L on neurocognitive outcomes in children. However, a study conducted in the MIREC cohort reported that a 1 mg/L daily increase in estimated fluoride intake from drinking water was associated with a 3.66 point decrement in IQ in boys and girls 3–4 years of age (Green et al., 2019). Research that has measured maternal urinary concentrations of fluoride has reported that an increase in maternal urine fluoride was associated with decreased scores on measures of cognitive ability (Green et al., 2019; Bashash et al., 2017). However, a recent study by Ibarluzea et al. using data from the Infancia y Medio Ambiente (Childhood and Environment, INMA) birth cohort reported a positive association between maternal urinary fluoride and cognitive outcomes in boys (Ibarluzea et al., 2022). The difference between our findings and those of previous studies that have investigated the association between maternal fluoride exposure and intellectual outcomes in children could be due to differing levels of maternal exposure, how fluoride exposure was assessed, differences in the measures used to assess cognitive outcomes, and sociodemographic differences among the populations studied.

Our results suggest that the children of mothers who were fully or partially exposed to drinking water that was fluoridated to 0.7 mg/L displayed poorer executive functions than children who were exposed to drinking water that had not been fluoridated to this level. Specifically, we found poorer performance on measures of inhibitory control and cognitive flexibility in children, particularly girls, whose mothers were fully or partially exposed to drinking water fluoridated to 0.7 mg/L during pregnancy. Difficulties in inhibitory control and cognitive flexibility are commonly reported in children with ADHD and ASD (Schachar et al., 1995; Martinussen et al., 2005; Rubia et al., 2007; Geurts et al., 2009; Van Eylen et al., 2011). A recent study with the ELEMENT cohort reported that higher maternal urinary fluoride was associated with higher global ratings of ADHD and more parent-reported symptoms of inattention at 6–12 years of age (Bashash et al., 2018). Further, a growing body of research supports a link between chronic fluoride exposure both prenatally and in childhood to the increasing prevalence of ASD (Strunecka and Strunecky, 2019). Overall, our findings and those of the ELEMENT cohort suggest that higher levels of fluoride exposure during pregnancy may be associated with an increased risk of ADHD symptoms (i.e., inattention, poorer inhibitory control) and symptoms associated with ASD (i.e., poorer cognitive flexibility) in children and youth, which in turn could be associated with an increased risk of a diagnosis of ADHD or ASD.

Limited research has investigated whether the associations between maternal exposure to fluoride during pregnancy and child outcomes differ by sex. Green et al. reported that higher maternal urinary fluoride was associated with lower FSIQ scores in boys (Green et al., 2019). We did not find sex-specific associations between maternal fluoride exposure and measures of intelligence for boys or girls. However, our finding of poorer performance on measures of inhibitory control and cognitive flexibility in girls who were exposed to fluoride throughout or for part of pregnancy suggests that prenatal fluoride exposure could affect neurocognitive development in boys and girls differently. Prospective longitudinal studies are required to determine if adverse effects of exposure to fluoride during pregnancy manifest differently in boys and girls, in different cognitive and behavior functions, and at different developmental stages, as shown with studies that have examined other neurotoxicants (Hyland et al., 2019; England-Mason et al., 2020; Desrochers-Couture et al., 2018).

Because fluoride was not added to the drinking water in Calgary after May 19, 2011, we were able to use this naturalistic experiment to examine if maternal exposure to fluoride in drinking water at levels recommended for dental health (i.e., 0.7 mg/L) were associated with intelligence and executive function outcomes in preschool-aged children. Our findings suggest that maternal exposure to tap water that has been fluoridated to the level of 0.7 mg/L may have adverse effects on executive function development. Water fluoridation was introduced to prevent tooth decay; however, a systematic review of the literature concluded that there is no benefit of systematic exposure to fluoride during pregnancy for the prevention of dental caries in offspring (Maechler et al., 2022). Further, fluoride is not an essential nutrient required for normal body function and growth (*EFSA J.*, 2013). Executive function difficulties in early childhood have been associated with poorer academic, psychological, and social development, and mental and physical health (Diamond, 2016; Blair and Razza, 2007; Moffitt et al., 2011) and the findings of this study and previous research suggest that maternal exposure to fluoride, even at what is considered the recommended level for dental health, may have long-term effects on children's cognition and behavior. Prospective longitudinal studies are needed to determine if there is a "safe" level of fluoride that can be added to drinking water for dental health that is not associated with adverse neurodevelopmental effects.

4.1. Strengths and limitations

This prospective ecological study has several strengths including its longitudinal design, large sample size, comparable groups from the same community, and assessment of children's intelligence and executive functions using measures validated in preschool children. Further, our criteria for assigning maternal-child pairs to the various fluoride exposure groups were very conservative (see Fig. 1). This study also has some limitations. We did not measure maternal urinary fluoride concentrations, which would have provided a potentially more precise proxy measure of each child's exposure at one specific time during pregnancy. However, strong associations have been found between fluoride levels in community water supplies and urinary fluoride concentrations in pregnant women (Till et al., 2018). Further, urinary fluoride has a short half-life (5 h) and can be affected by behaviors such as consumption of fluoride-free bottled water or black tea prior to urine sampling, or other factors such as diet or dental product use; therefore, a single or even serial urine samples may not accurately estimate maternal exposure levels over the course of pregnancy. We also did not estimate maternal fluoride exposure from dietary sources as the main source of human fluoride exposure is water (United States Environmental Protection Agency, 2010; Guth et al., 2020). Typically, food contains low concentrations of fluoride (*EFSA J.*, 2013), and unlike some countries in Europe and Latin America (e.g., Mexico, Columbia, Hungary, Switzerland, Germany), fluoridated salt is not used in Canada. Further, we did not estimate maternal fluoride exposure from oral hygiene products. Fluoride containing toothpaste, gels, and rinses may increase intake; however, this is relatively negligible. The European Food Safety Authority estimated that average intake of fluoride from toothpaste was approximately 1.4 μg/kg/day for adults and 11.5 μg/kg/day in children (*EFSA J.*, 2013). Postnatal fluoride exposure was not examined, and thus its impact on the present associations is unclear. However, a study conducted in New Zealand that examined preschool fluoride exposure found no significant differences in intelligence from 7 to 13 years of age and at 38 years of age between participants who had or had not resided in areas with community water fluoridation, used fluoride toothpaste, or used fluoride tablets (Broadbent et al., 2015). Further, whether there are periods during development in which exposure has stronger effects is not known. However, a recent Canadian study reported that in a large cohort of children and youth, those exposed to higher levels of fluoride from tap water had a higher risk of a diagnosis of ADHD and reported more symptoms of inattention and hyperactivity, particularly in adolescence (Riddell et al., 2019). Also, chronic exposure throughout pregnancy and childhood may be associated with an increased risk of neurodevelopmental disorders (Strunecka and Strunecky, 2019). Future research that examines the associations between prenatal and childhood exposure to fluoride, and neurocognitive outcomes and developmental disorders such as ADHD and ASD is needed. Another limitation is that our analyses did not control for maternal FSIQ; however, our exposure groups were not found to differ on maternal education or household income, both of which are associated with FSIQ, and we controlled for covariates that differed among our exposure groups (i.e., whether or not mothers were born in Canada and pre-pregnancy smoking) to adjust for the potential effect of these demographic differences on child neurodevelopmental outcomes. Despite the number of potential covariates examined, our study cannot address the possibility that other unmeasured confounders could have influenced our findings, such as the timing of pregnancy, which could influence exposure levels; it is possible that spring and summer mountain-fed water supplies could contain higher levels of naturally occurring fluoride. Further, we did not measure the actual fluoride concentrations in tap water in participants' homes; however, the tap water for all participants came from the same community water system.

5. Conclusion

In this prospective ecological pregnancy cohort study, maternal exposure to fluoridated drinking water from a community water supply was associated with poorer executive functions, specifically inhibitory control and cognitive flexibility, in preschool aged children, particularly girls. No adverse associations were found for intelligence. Our findings support the importance of future research that investigates associations between maternal exposure to the recommended fluoride concentration of 0.7 mg/L from community drinking water supplies and neurocognitive outcomes, particularly executive functions, in children. The results of this study are of public health significance given the large number of pregnant people exposed to fluoride from drinking water and the potential effects that such exposure could have on their children's long-term neurocognitive development.

CRediT authorship contribution statement

Drs. Dewey and England-Mason had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All Authors

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Dewey, England-Mason

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Dewey, England-Mason, Ntanda

Funding: Dewey, Giesbrecht, Letourneau, APrON Study Team

Administrative, technical, or material support: All Authors

Supervision: Dewey, Letourneau

Data availability

Data is available from the APrON study (https://apronstudy.ca) upon request.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.164322.

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