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Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth

Julia K. Riddell[a,*], Ashley J. Malin[b], David Flora[a], Hugh McCague[c], Christine Till[a]

[a] Faculty of Health, York University, Ontario, Canada
[b] Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[c] Institute for Social Research, York University, Ontario, Canada

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ABSTRACT

Background: Exposure to fluoride has been linked with increased prevalence of attention deficit hyperactivity disorder (ADHD) in the United States and symptoms of inattention in Mexican children. We examined the association between fluoride exposure and attention outcomes among youth living in Canada.

Method: We used cross-sectional data collected from youth 6 to 17 years of age from the Canadian Health Measures Survey (Cycles 2 and 3). Urinary fluoride concentration adjusted for specific gravity (UFSG) was available for 1877 participants. Water fluoride concentration measured in tap water samples was available for 980 participants. Community water fluoridation (CWF) status was determined by viewing reports on each city's website or contacting the water treatment plant. We used logistic regression to test the association between the three measures of fluoride exposure and ADHD diagnosis. Linear regression was used to examine the relationship between the three measures of fluoride exposure and the hyperactivity/inattention score on the Strengths and Difficulties Questionnaire (SDQ).

Results: UF_{SG} did not significantly predict ADHD diagnosis or hyperactive/inattentive symptoms. A 1 mg/L increase in tap water fluoride level was associated with a 6.1 times higher odds of an ADHD diagnosis (95% CI = 1.60, 22.8). A significant interaction between age and tap water fluoride level ($p = .03$) indicated a stronger association between tap water fluoride and hyperactivity/inattention symptoms among older youth. A 1 mg/L increase in water fluoride level was associated with a 1.5 SDQ score increase (95% CI: 0.23, 2.68, $p = .02$) for youth at the 75th percentile of age (14 years old). Similarly, there was a significant interaction between age and CWF. At the 75th percentile of age (14 years old), those living in a fluoridated region had a 0.7-point higher SDQ score (95% CI = 0.34, 1.06, $p < .01$) and the predicted odds of an ADHD diagnosis was 2.8 times greater compared with youth in a non-fluoridated region (aOR = 2.84, 95% CI: 1.40, 5.76, $p < .01$).

Discussion: Exposure to higher levels of fluoride in tap water is associated with an increased risk of ADHD symptoms and diagnosis of ADHD among Canadian youth, particularly among adolescents. Prospective studies are needed to confirm these results.

1. Introduction

Fluoride is beneficial in the prevention of dental caries (Health Canada, 2010). It can naturally occur in water, but often at levels that are too low to prevent tooth decay. In the middle of the 20th century, the concept of adding fluoridation chemicals (usually hexafluorosilicic acid) to water supplies was introduced. Currently, approximately 38% of Canadians on public water supplies receive community water fluoridation (CWF; Public Health Agency of Canada, 2017) compared with 74% of Americans and only 3% of Europeans (Centers for Disease Control and Prevention, 2014). Consumption of optimally fluoridated water (i.e., 0.7 mg fluoride per liter of water) accounts for approximately 40 to 70% percent of daily fluoride ingestion (United States Environmental Protection Agency, 2010).

Fluoride has been classified as a developmental neurotoxin (Grandjean and Landrigan, 2014) – a claim that is uncontested at high exposure levels, but remains debated at the exposure levels associated with water fluoridation. Epidemiological studies conducted in endemic fluorosis areas (i.e., naturally occuring water fluoride concentrations > 1.5 mg/L) have reported a negative association between fluoride concentrations in drinking water and intellectual ability in children (Das and Mondal, 2016; Rocha-Amador et al., 2007; Seraj

* Corresponding author at: Department of Psychology, York University, 4700 Keele Street, M3J 1P3 Toronto, ON, Canada.
E-mail address: jriddell@yorku.ca (J.K. Riddell).

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et al., 2012; Xiang et al., 2003; Zhao et al., 1996). A *meta*-analysis of 27 studies concluded that children who lived in areas with high fluoride exposure had IQ scores that were approximately seven points lower than those who lived in low-exposure areas (Choi et al., 2012). Most of the studies included in this review were cross-sectional and had deficient reporting of key information; however, the consistency of their findings supports the potential for fluoride-mediated developmental neurotoxicity at elevated levels of exposure. Recently, three longitudinal birth cohort studies addressed these limitations by examining the associations between maternal fluoride exposure indicators in pregnancy and offspring cognitive abilities. These prospective studies reported a negative association between prenatal fluoride exposure and cognitive development in infants (Jiménez et al., 2017), children living in Mexico (Bashash et al., 2017), and children living in Canada (Green et al., 2019).

Experimental and epidemiologic studies have also reported an association between early-life fluoride exposure and adverse behavioural outcomes. One study demonstrated that prenatal fluoride exposure caused greater hyperactivity in male rat pups whereas females were more sensitive to postnatal exposures (Mullenix et al., 1995). In an ecological study, higher prevalence of water fluoridation was associated with increased prevalence of Attention Deficit Hyperactivity Disorder (ADHD) diagnoses among youth in the United States (Malin and Till, 2015). In a cohort study, higher levels of fluoride exposure during pregnancy were associated with more inattentive symptoms and total ADHD symptoms in Mexican children aged 6 to 12 years (Bashash et al., 2018). In contrast, a study using data from the Canadian Health Measures Survey (CHMS; Statistics Canada, 2013; 2015) did not report an association between urinary fluoride corrected for dilution and a diagnosis of a learning disability in children aged 3 to 12 years (Barberio et al., 2017).

We examined the relationship between urinary and tap water fluoride concentrations and attention-related outcomes in a national sample of Canadian youth aged 6 to 17 years. We hypothesized that higher levels of urinary and water fluoride would be associated with increased odds of an ADHD diagnosis and more symptoms of hyperactivity and inattention.

2. Methods

2.1. Data source and participants

We used data from Cycle 2 (2009–2011) and Cycle 3 (2012–2013) of the CHMS collected by Statistics Canada. All aspects of the CHMS were reviewed and approved by Health Canada's Research Ethics Board (Day et al., 2006); the current study was approved by the York University Research Ethics Board.

The CHMS randomly selected participants aged 3 to 79 years who lived in private households across Canada. A total of 6395 people participated in Cycle 2 of the CHMS, with 2520 people providing urine samples analyzed for fluoride concentration. Among those who provided urine samples, 909 (36%) were between 6 and 17 years of age. For Cycle 3, a total of 5785 people were enrolled, with 2667 people providing urine samples analyzed for fluoride concentration; 968 (36%) were between 6 and 17 years of age. In Cycle 3 only, 980 youth ages 6 to 17 were selected to provide a tap water sample to be analyzed for fluoride content. Full details about the survey can be found at www.statcan.gc.ca.

Approximately half of the sites included in Cycles 2 and 3 received CWF, which was determined by viewing reports on each city's website or contacting the water treatment plant (see Supplemental Table 1). In total, 13 of 25 sites received CWF (eight from Cycle 2 and five from Cycle 3), corresponding to approximately 1400 (51.9%) of 2700 participants included in the study (rounded due to Statistics Canada data release requirements). Nine additional sites were considered to have mixed fluoridation status, corresponding to approximately 650 (24.0%) participants. A site was classified as mixed for one of five reasons: unclear site boundaries (n = 150), having some municipalities within the site add fluoride while others did not (n = 250), and stopping CWF during the period spanning CHMS data collection (n = 50). We excluded all mixed sites from any analysis using city fluoridation status as a variable. We also excluded sites which were labeled as fluoridated or non-fluoridated, but had an average water fluoride level that was either 2.5 times lower (n = 100) or higher (n = 100) than other fluoridated or non-fluoridated sites, respectively.

We utilized three participant samples for our analyses; see Fig. 1 for a participant flow chart. The first sample, collapsed across both cycles, included 1877 youth ages 6 to 17 who had urinary fluoride measurements. The second sample categorized 1722 youth who were on a municipal water system (instead of a well) as either living in a fluoridated region (n = 932; 54.1%) or a non-fluoridated region (n = 790; 45.9%). This sample only included youth who primarily drank tap water (instead of bottled water), did not have a home filtration system that removes fluoride (i.e., reverse osmosis or distillation), and have lived in their current residence for three or more years. The third sample consisted of 710 youth from Cycle 3 who primarily drank tap water (instead of bottled water) and had fluoride levels measured in their tap water.

2.2. Measurement of urinary fluoride concentration

Urine spot samples were collected under normal (non-fasting) conditions and were not standardized with respect to collection time. Fluoride concentrations in spot urine samples were analyzed using an Orion PH meter with a fluoride ion selective electrode after being diluted with an ionic adjustment buffer (Statistics Canada, 2013). Urinary analyses were performed at the Human Toxicology Laboratory of the Institut National de Santé Publique du Québec (INSPQ; accredited under ISO 17025) under standardized operating procedures (Statistics Canada, 2013; 2015). The precision and accuracy of the fluoride analyses, including quality control measures and quality assurance reviews, are described in previous publications (Health Canada, 2015). The limit of detection (LoD) for urinary fluoride was 20 μg/L for Cycle 2 and 10 μg/L for Cycle 3 (Health Canada, 2015). No urinary fluoride values in the Cycle 2 or Cycle 3 samples were below the LoD. Urinary fluoride concentrations were adjusted for specific gravity (UF_{SG}; mg/L); specific gravity shows no systematic variation within a day and is less dependent on body size, age, and gender than creatinine (Barr et al., 2005; Nermell et al., 2008; Moriguchi et al., 2005; Suwazono et al., 2005).

2.3. Measurement of water fluoride concentration

Tap water samples were collected at respondents' homes and were available for Cycle 3 only. Samples were analyzed for fluoride concentrations (mg/L) via a basic anion exchange chromatography procedure with a LoD of 0.006 mg/L. Concentrations at the LoD were assigned a missing value code by Statistics Canada, and these values were subsequently replaced with an imputed value of LoD/√2 (Hornung and Reed, 1990); 150 of 980 (16%) water samples had fluoride levels below the LoD.

2.4. Measurement of attention-related outcomes

Primary outcomes included the hyperactivity/inattention subscale score from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001) and a physician-made diagnosis of ADHD; these outcomes were measured in both Cycles 2 and 3. Data are presented for youth ages 6 to 17 because the SDQ was only administered to youth under age 18 and 90% of youth with ADHD are diagnosed after age 6 (Kessler et al., 2005). For children aged 6 to 11 years, information about ADHD diagnosis and SDQ ratings were provided by parents or guardians, whereas youth aged 12 to 17 years completed the questionnaire

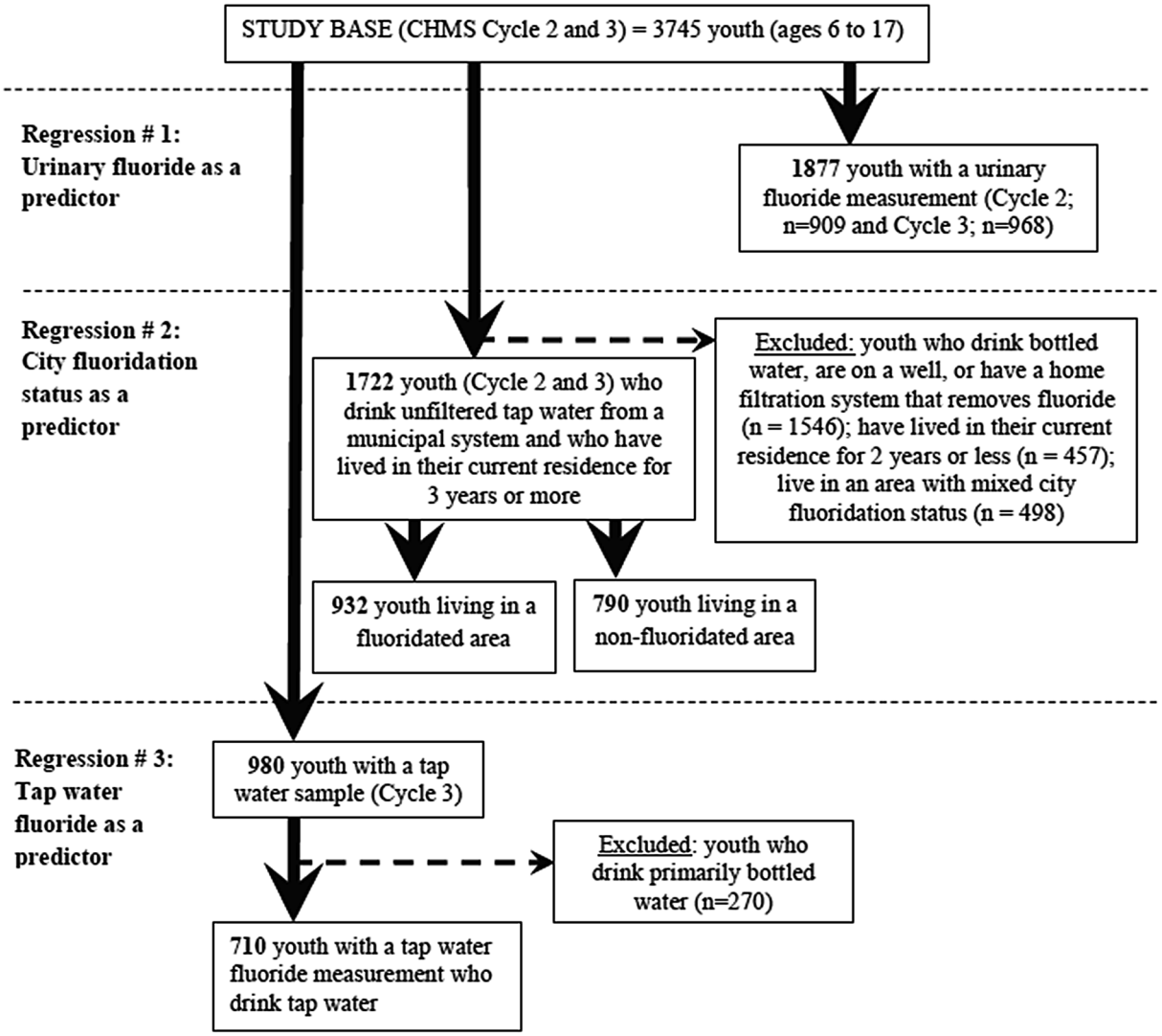

Fig. 1. Subject inclusion in each regression analysis.

themselves, including the question about having a diagnosis of ADHD.

The SDQ consists of 25 items with a 3-point response scale (0 = *not true*, 1 = *somewhat true*, and 2 = *certainly true*). These items are divided among five subscales: emotional problems, conduct problems, hyperactivity-inattention, peer problems, and prosocial behaviour. Possible scores on each subscale range from 0 to 10. The five-item hyperactivity-inattention subscale was used in the current study to test the association between fluoride and ADHD-like symptoms.

The item pertaining to a physician-made diagnosis of ADHD differed between Cycles 2 and 3. In Cycle 2, respondents were asked *Do you have a learning disability?*, and if they responded *yes*, they were asked to specify the type of learning disability from among four options: (1) Attention Deficit Disorder, no hyperactivity [ADD]; (2) Attention Deficit Hyperactivity Disorder [ADHD]; (3) Dyslexia; and (4) Other. In Cycle 3, parents of children aged 6 to 11 were asked directly whether their child had ADHD, and if so, which subtype. Similarly, youth age 12 or older were asked whether they have received a physician-diagnosis of ADHD, and if so, which subtype. Across both cycles, all subtypes were combined into a single dichotomous variable of ADHD diagnosis (*no* = 0, *yes* = 1) as per current diagnostic classification schemes (American Psychiatric Association, 2013).

2.5. Covariates

Covariates related to ADHD diagnosis and to fluoride metabolism were selected based on literature review and consultation with an ADHD expert. The following covariates were included in each regression model: sex, age of child at household interview, ethnicity (white or ethnic minority), Body Mass Index (BMI), highest level of education obtained by either parent (less than a bachelor's degree vs. bachelor's degree or greater), total household income (Canadian dollars), exposure to cigarette smoke inside the home (yes or no), and $\log_{10}$-transformed value of concurrent level of blood lead (μg/dL).

2.6. Statistical analysis

Outliers that had high Studentized residuals, leverage, or Cook's distance values were removed from all analyses with UF_{SG} as a predictor; these outliers (0.27% of values) represented individuals with urinary fluoride levels that were over 30 times the mean UF_{SG} level, likely representing an acute fluoride ingestion (e.g., swallowing toothpaste). Further, individuals with the highest incomes were identified as extreme observations; these values were replaced with the next highest income value (only 0.01% of income values were adjusted).

We used robust logistic regression to examine the associations between each fluoride exposure measure (UF_{SG}, CWF status, tap water

fluoride) and ADHD diagnosis with the same set of covariates in each model. Box-Tidwell tests were used to check the linearity of the relationship between the log-odds of the dependent variable (ADHD diagnosis) and all continuous predictors; none of the non-linear terms were significant. Next, we used robust linear regression models with the same set of covariates to examine the associations between the three measures of fluoride exposure and the SDQ hyperactivity/inattention subscale score. Because the regression models produced heteroscedastic and non-normal residuals, all significance tests and confidence intervals were based on robust Huber-White standard errors. No issues with multicollinearity were detected from variance inflation factor (VIF) statistics. All regression analyses tested interactions between age and fluoride and between sex and fluoride, as hyperactivity is more common in younger boys and sex-dependent fluoride effects have been previously reported (Mullenix et al., 1995; Green et al., 2019). If an interaction with age was significant, we probed the interaction by calculating the predicted association between fluoride and the outcome at the 25th and 75th percentiles of age. When a tested interaction was non-significant, the model was re-estimated without the interaction term and the overall associations were interpreted. Finally, we conducted sensitivity analyses to test whether the associations between the fluoride exposure variables and ADHD diagnosis differed between cycles given that the question about ADHD diagnosis was posed differently across the two cycles. A two-tailed $\alpha = 0.05$ was used as the threshold for statistical significance.

3. Results

3.1. Descriptive statistics

Of all variables included in the CHMS, missing data were highest for household income (missing among 29% and 23% of CHMS respondents in Cycle 2 and 3, respectively); however, Statistics Canada provided imputed estimates for all participants missing the household income variable. Across Cycle 2 and 3 combined, most demographic variables (including sex, age, ADHD diagnosis, SDQ score, and length of residence) had less than 2% missing data. For highest household education, 2.6% of data were missing, and 7.4% of participants did not report their height or weight, which are needed to calculate BMI.

Table 1 presents descriptive statistics for the different samples used for the regression models. Among the 1877 youth in Cycles 2 and 3 with a urinary fluoride measurement, 51.2% were male, 72.6% were white, and 47.0% had at least one parent with a university degree or higher. In this sample, 137 (7.3%) reported having received a diagnosis of ADHD; the mean for the SDQ Hyperactivity-Inattention subscale score was 2.7 ($SD = 2.7$; range: 0 to 10) with 201 (11.4%) youth having scores in the clinical range (i.e., above 90th percentile; Goodman, 2001). As expected, participants with an ADHD diagnosis had significantly higher scores on the SDQ Hyperactivity-Inattention subscale ($M = 6.5$, $SD = 2.5$) than those without a diagnosis ($M = 2.5$, $SD = 2.4$), $t = 24.8$, $p < .01$. Table 2 provides descriptive statistics for the 1877 youth aged 6 to 17 years with and without an ADHD diagnosis.

3.2. Fluoride measurements

The mean UF_{SG} concentration was 0.61 mg/L ($Mdn = 0.51$; $SD = 0.39$; 10th to 90th percentile range = 0.27–1.06 mg/L) among the 1877 youth from Cycles 2 and 3. Mean UF_{SG} concentration was significantly higher among youth who lived in communities with fluoridated drinking water ($M = 0.82$ mg/L, $SD = 0.54$) than among youth who lived in communities without fluoridated drinking water ($M = 0.46$ mg/L, $SD = 0.32$), $t = 15.1$, $p < .01$. The mean water fluoride concentration was 0.23 mg/L ($Mdn = 0.12$; $SD = 0.24$; 10th-90th percentile = 0.01–0.65 mg/L) among the 710 youth for whom tap water measures were available, excluding those who reported drinking bottled water as their main source of water. As expected, water fluoride levels were significantly higher among those living in a fluoridated region ($M = 0.49$ mg/L, $SD = 0.22$) than non-fluoridated region ($M = 0.04$ mg/L, $SD = 0.06$), $t = 34.9$, $p < .01$. Table 3 presents the urinary fluoride and water fluoride levels across demographic characteristics, fluoride exposure variables, and attention outcomes.

Table 1
Demographic characteristics, fluoride exposure variables, and attention outcomes for youth included in the three different samples.

Variable	Participants in Cycles 2 and 3 with:		Participants in Cycle 3 with:
	Urinary fluoride Mean (SD) or %	CWF status† Mean (SD) or %	Water fluoride Mean (SD) or %
N	1877	1722	710
Child sex			
Male	51.2	50.8	52.7
Female	48.8	49.2	47.3
Child age at interview (years)	11.3 (3.4)	11.3 (3.3)	11.2 (3.5)
Ethnicity			
White	72.6	67.6	69.0
Non-white	27.3	32.5	31.0
Parental Education			
High School/College	53.0	43.4	44.9
University or higher	47.0	56.6	55.1
Smoking in the home			
Yes	11.5	7.7	8.3
No	88.5	92.4	91.7
Household income (per $1000 CDN)	91.7 (82.7)	97.3 (70.6)	104.0 (134.6)
Body Mass Index	19.8 (4.7)	19.7 (4.7)	19.6 (4.6)
Blood lead (μg/dL)	0.83 (0.41)	0.83 (0.41)	0.83 (0.41)
Lived in residence			
2.99 years or less	19.2	Excluded	21.1
3.00 years or more	80.8	100.0	78.9
Fluoride measures			
UF_{SG} (mg/L)	0.61 (0.39)	0.64 (0.45)	0.62 (0.48)
Water fluoride (mg/L)	0.23 (0.24)	0.26 (0.26)	0.23 (0.24)
Site adds fluoride			
Yes	50.9	53.3	53.7
No	48.1	46.7	46.3
Outcome Variables			
Diagnosis of ADHD	7.3	5.5	6.3
SDQ H/I Subscale Score	2.8 (2.7)	2.6 (2.6)	2.9 (2.6)

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; BMI = Body Mass Index; SD = standard deviation; UF_{SG} = urinary fluoride adjusted for specific gravity; SDQ H/I = Strengths and Difficulties Questionnaire Hyperactivity Inattention.
† Youth who drink tap water and have a stable residence.

3.3. Association between fluoride exposure and ADHD diagnosis

No planned interactions were significant in the logistic regression of ADHD diagnosis on UF_{SG} concentration; thus, the final model did not include interaction terms. UF_{SG} did not significantly predict an ADHD diagnosis (adjusted Odds Ratio [aOR] = 0.96; 95% CI: 0.63, 1.46, $p = .84$) adjusting for covariates (Table 4). In the regression of ADHD diagnosis on CWF, there was a significant interaction between age and CWF ($B = 0.19$, $p = .02$), such that the association between CWF and the odds of an ADHD diagnosis was stronger among older youth. Specifically, at the 75th percentile of age (14 years old), the predicted odds of an ADHD diagnosis was 2.8 times greater among youth in a fluoridated region compared with youth in a non-fluoridated region (aOR = 2.84, 95% CI: 1.40, 5.76, $p < .01$), whereas among youth at the 25th percentile of age (9 years old), the predicted odds of an ADHD

Table 2
Comparison of youth with a urinary and water fluoride measurement with and without a diagnosis of ADHD.

Variable	ADHD Diagnosis (n = 137) *Mean (SD)/%*	No ADHD Diagnosis (n = 1740) *Mean (SD)/%*
Sex		
Male	69.7	49.6
Female	30.3	50.4
Ethnicity		
White	85.1	72.4
Non-white	14.9	27.6
Parental Education		
High School/College	68.7	53.1
University or higher	31.3	46.9
Smoking in the home		
Yes	26.9	10.0
No	73.1	90.0
Age	12.0 (3.2)	11.2 (3.5)
Household income (per $1000 CND)	70.6 (54.1)	97.9 (95.4)
BMI	19.4 (4.1)	19.9 (4.8)
Blood lead (μg/dL)	0.83 (0.41)	0.83 (0.41)
Fluoride measures		
Tap water fluoride concentration[†](mg/L)	0.29 (0.28)	0.22 (0.24)
UF_{SG} (mg/L)	0.57 (0.32)	0.62 (0.45)
Site adds fluoride – Yes	47.1	52.8
Site adds fluoride – No	52.9	47.2
Outcome		
SDQ H/I Subscale Score	6.74 (2.5)	2.51 (2.4)

ADHD = Attention Deficit Hyperactivity Disorder; BMI = Body Mass Index; SD = standard deviation; UF_{SG} = urinary fluoride adjusted for specific gravity concentration; SDQ H/I = Strengths and Difficulties Questionnaire Hyperactivity-Inattention.
[†] Cycle 3 only.

diagnosis was similar across CWF status (aOR = 0.91, 95% CI: 0.41, 1.99, p = .81; Table 4). Finally, tap water fluoride concentration was significantly associated with having an ADHD diagnosis, adjusting for covariates; this effect did not significantly interact with sex or age. Specifically, a 1 mg/L increase in tap water fluoride was associated with a 6.1 times higher odds of ADHD diagnosis (95% CI: 1.60, 22.8, $p < .01$; Table 4).

Estimating the models with UF_{SG} and CWF for Cycle 2 and 3 separately showed a similar pattern (Supplemental Table 2). For the regression with CWF, the interaction with age was not significant using Cycle 2 data only (B = 0.12, p = .35), but was significant using data from Cycle 3 only (B = 0.30, p = .03).

3.4. Association between fluoride exposure and SDQ hyperactive/inattentive scores

No planned interactions were significant in the regression of SDQ hyperactive/inattentive subscale scores on UF_{SG} concentration; thus, the final model did not include interaction terms. UF_{SG} did not significantly predict SDQ hyperactive/inattentive subscale scores (B = 0.31, 95% CI = −0.04, 0.66, p = .08; Table 4).

Next, there was a significant interaction between age and CWF status (B = 0.11, p = .01) such that the association between CWF and hyperactivity/inattention scores was stronger among older youth. Specifically, the regression model predicted that for youth at the 75th percentile of age (14 years old), living in a fluoridated region was associated with a 0.7-point higher SDQ hyperactivity/inattention score (95% CI = 0.34, 1.06, $p < .01$). In contrast, among youth at the 25th percentile of age (9 years old), CWF status was not significantly associated with SDQ hyperactivity/inattention scores (B = 0.04, 95% CI = −0.38, 0.46, p = .85).

Table 3
Urinary fluoride and tap water fluoride levels across binary demographic characteristics and fluoride exposure variables.

Variable	UF_{SG} (mg/L) Mean (SD)	Water fluoride (mg/L) Mean (SD)
Child sex		
Male	0.61 (0.36)	0.23 (0.24)
Female	0.63 (0.51)	0.23 (0.24)
Ethnicity		
White	0.60 (0.42)	0.21 (0.23)
Non-white	0.68 (0.51)	0.28 (0.26)
Parental Education		
High School/College	0.62 (0.49)	0.21 (0.23)
University or higher	0.61 (0.38)	0.24 (0.25)
Smoking in the home		
Yes	0.57 (0.36)	0.17 (0.21)
No	0.63 (0.45)	0.24 (0.24)
Lived in residence		
2.99 years or less	0.64 (0.50)	0.23 (0.24)
3.00 years or more	0.61 (0.42)	0.23(0.24)
Type of water consumed		
Tap water	0.62 (0.44)	0.23 (0.24)
Bottled water	0.62 (0.45)	0.22 (0.23)
Source of water		
Municipal water system	0.63 (0.45)	0.25 (0.25)
Private well	0.54 (0.34)	0.13 (0.13)
Fluoride measures		
Site adds fluoride		
Yes	0.82 (0.54)	0.49 (0.22)
No	0.46 (0.32)	0.05 (0.06)

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; SD = standard deviation; UF_{SG} = urinary fluoride adjusted for specific gravity.

Table 4
Adjusted Odds Ratio (aOR) and effect estimates for the association between fluoride exposure, ADHD diagnosis, and attention symptoms.

	ADHD diagnosis		SDQ H/I subscale score	
	aOR[a]	95% CI	aOR[a]	95% CI
UF_{SG} (mg/L)[b]	0.96	0.63, 1.46	0.31	−0.04, 0.66
Fluoride in tap water (mg/L)[c]	6.10*	1.60, 22.8	0.31*	0.04, 0.58
75th percentile age	–[d]	–	1.52*	0.23, 2.80
25th percentile age	–	–	−0.33	−1.51, 0.84
CWF status[e]	1.21*	1.03, 1.42	0.11*	0.02, 0.20
75th percentile age	2.84*	1.40, 5.76	0.70*	0.34, 1.06
25th percentile age	0.91	0.41, 1.99	0.04	−0.38, 0.46

Abbreviations: ADHD = Attention Deficit/Hyperactivity Disorder; CWF = community water fluoridation; aOR = adjusted odds ratio; SDQ H/I = Strengths and Difficulties Questionnaire Hyperactivity-Inattention.
* $p < .05$.
[a] Adjusted for child's sex, age at interview, ethnicity (white or other), body mass index, highest level of parental education, total household income, exposure to cigarette smoke inside the home (yes/no), concurrent blood lead level (log_{10}-transformed).
[b] Non-significant main effect of urinary fluoride level predicting ADHD diagnosis (B = −0.04, p = .84) or SDQ subscale score (B = 0.31, p = .08).
[c] Interaction between age and water fluoride level predicting SDQ subscale score (B = 0.31, p = .03).
[d] Since the interaction between age and water fluoride was not significant, only the main effects are presented for the logistic regression predicting ADHD diagnosis from fluoride in tap water (mg/L).
[e] Significant interaction between age and CWF status predicting ADHD diagnosis (B = 0.19, p = .03) and SDQ subscale score (B = 0.11, p = .01).

Finally, the interaction between age and tap water fluoride level was also significant (B = 0.31, p = .03) such that the association between tap water fluoride and SDQ hyperactivity/inattention score was

stronger among older youth. In particular, among youth at the 75th percentile of age (14 years old), an increase of 1 mg/L in water fluoride level was associated with a 1.52 increase in the SDQ hyperactivity/inattention subscale score (95% CI: 0.23, 2.68, $p = .02$). However, for youth at the 25th percentile of age (8 years old), the association between water fluoride level and SDQ hyperactivity/inattention subscale score was not significant ($B = -0.33$, 95% CI: -1.51, 0.84, $p = .58$).

4. Discussion

We found that Canadian youth exposed to higher tap water fluoride levels had a higher risk of receiving an ADHD diagnosis and reported more symptoms of hyperactivity and inattention. Specifically, an increase of 1.0 mg/L in water fluoride concentration was associated with a 6.1 times higher odds of an ADHD diagnosis after accounting for potential confounding variables, such as exposure to second-hand smoke, household income, and blood lead level. Likewise, water fluoride concentration was positively associated with hyperactive/inattentive symptoms, especially among older youth. To contextualize these results, the difference in water fluoride concentration between cities with and without fluoridation is approximately 0.5 mg/L. Our finding of a 1.5-point increase in the SDQ hyperactive/inattentive symptom subscale for each increase of 1 mg/L in water fluoride level implies a 0.75-point increase per 0.5 mg/L water fluoride; this result is remarkably consistent with our finding of a 0.7-point increase on the SDQ's hyperactivity/inattention subscale observed among older youth living in a fluoridated versus non-fluoridated region.

In contrast, urinary fluoride levels were not significantly associated with a diagnosis of ADHD or hyperactive/inattentive symptoms. Water fluoride concentration and CWF status may be more strongly associated with attention-related outcomes than urinary fluoride levels because fluoride concentrations in municipal water supplies vary within a limited range and therefore may serve as a proxy for early-life and chronic fluoride exposure. In contrast, urinary fluoride levels in spot samples are more likely to fluctuate due to the rapid elimination kinetics of fluoride. Additionally, urinary fluoride values may capture acute exposures due to behaviours that were not controlled in this study, such as professionally applied varnish, consumption of beverages with high fluoride content (e.g., tea), or swallowing toothpaste prior to urine sampling. Finally, the association between urinary fluoride and attention-related outcomes could be obscured due to reduced fluoride excretion (i.e., increased fluoride absorption) during a high growth spurt stage (Jha et al., 2011; World Health Organization, 1997). Despite these limitations, use of individualized biomarkers is considered an improvement over past ecologic studies (Malin and Till, 2015) examining the association between ADHD and fluoride exposure and it has the advantage of examining all sources of fluoride exposure, not just from drinking water.

Our findings are consistent with earlier studies showing a relationship between fluoride exposure and ADHD. In particular, Malin and Till (2015) found that a 1% increase in community water fluoridation prevalence in 1992 was associated with approximately 67,000 to 131,000 additional ADHD diagnoses from 2003 to 2011 among children and adolescents in the United States. Conversely, Barberio and colleagues (2017) did not find a significant relationship between fluoride exposure and learning disabilities (including ADHD) using data from the CHMS Cycles 2 and 3. A direct comparison of our results to the results found by Barberio and colleagues is challenged by the differences in how the data were analyzed between the two studies. Our sample included youth between ages 6 and 17, whereas Barberio and colleagues restricted their sample to youth ages 3 to 12. Further, Barberio and colleagues included participants with learning disabilities instead of selecting only those with a diagnosis of ADHD. Finally, the current study accounted for whether youth in both Cycles 2 and 3 drank unfiltered municipal tap water. It may be that the effects of fluoride exposure are most pronounced in older youth, or that fluoride is specifically associated with ADHD-related behaviours as opposed to learning disabilities. Finally, inclusion of learning disabilities may also introduce selection bias due to differences in how learning disabilities and ADHD are diagnosed in Canada.

Our findings showed that age modified the association between fluoride exposure and the likelihood of ADHD diagnosis and symptoms of hyperactivity and inattention, such that the associations were stronger among older youth. The method used in the CHMS may not be as sensitive for young children who are at risk of an ADHD diagnosis but have not yet been diagnosed; given that 90% of youth with ADHD are diagnosed after age 6 (Kessler et al., 2005), we restricted our minimum age to 6 years. Cumulative exposure to fluoride over time may also impact neurobehavioural development such that youth show more symptoms as they age. Alternatively, because the developing brain is highly sensitive to environmental toxins (Grandjean and Landrigan, 2006; 2014) and because gene expression later in life is impacted by epigenetic changes that occur earlier in development (Roth, 2012), changes produced by early exposure to environmental toxins may manifest later in development.

While ADHD is known to have a strong genetic component with an estimated heritability of 70% to 80% (Larsson et al., 2014), environmental risk factors are also believed to contribute to the development of ADHD. Prenatal substance exposures, heavy metal and chemical exposures, and nutritional factors have been proposed to contribute to the rise in ADHD in the United States (Xu et al., 2018; Sciberras et al., 2017) and an increase in behavioural difficulties as assessed by the SDQ (Philippat et al., 2017; Oulhote et al., 2016; Luk et al., 2018). A recent systematic review (Donzelli et al, 2019) reported a significant association between lead exposure and risk of ADHD in 12 out of 17 studies; the adjusted odds ratios ranged from 1.09 to 7.25, which is within the range of the current study findings. Although the precise mechanism by which fluoride affects neurodevelopment is unclear, several possible mechanisms have been proposed. Animal studies have shown alterations in acetylcholine or cholinergic receptors due to fluoride exposure (Chouhan et al., 2010; Liu et al., 2010; Reddy et al., 2014). In particular, both nicotinic acetylcholine receptors and cholinesterase expression appear to play a role in attentional processes (Levin et al., 2011). Other studies have shown morphological changes in neurons (Bhatnagar et al., 2011), mitochondria (Zhao et al., 2019), increased catalase immunoreactivity (Güner et al., 2016), more oxidative stress (Zhang et al., 2015), and increases in apoptotic neurons and abnormal mitochondrial dynamics (Lou et al., 2013, 2014). Further, some studies have suggested that fluoride may suppress thyroid function (Trabelsi et al., 2001); subclinical hypothyroidism during pregnancy has been linked with increased risk for attention disorders (Modesto et al., 2015; Päkkilä et al., 2014).

Our study has some limitations. First, tap water fluoride was measured in Cycle 3 only, which decreased the sample size for analyses using this predictor. However, we were able to determine CWF status for participants in both Cycle 2 and 3, which permitted examining the concordance between the effects associated with tap water fluoride level, CWF status, and urinary fluoride level. Second, use of exposure metrics obtained at the same time as the outcome of interest (cross-sectional data) is limited for making conclusions about the causal association between fluoride and attention-related outcomes. Exposure misclassification may have occurred for some participants due to changes in a city's water fluoridation status over the youth's lifetime. Tap water samples were collected between 2012 and 2013 when approximately 37.4% of Canadians had access to fluoridated water as compared with 42.6% in 2007 (Public Health Agency of Canada, 2017). Thus, water fluoride measures obtained at the time of CHMS data collection may not be consistent with water fluoride levels that were antecedent to the outcomes in our study. Because the CHMS only measured postnatal fluoride exposure, we were not able to distinguish the effects of fluoride exposure during different developmental periods (e.g., prenatal versus postnatal). Recent studies have identified

pregnancy as a critical period during which fluoride exposure is linked to lowered IQ (Bashash et al., 2017; Green et al., 2019) and attention-related behaviours (Bashash et al., 2018) in offspring. Third, the method used by CHMS may not completely capture true ADHD prevalence. Because of the way that the CHMS items were phrased, the Cycle 2 sample may identify youth with a comorbid learning disability and ADHD, but not those who have ADHD and no learning disability. Nonetheless, the prevalence of ADHD in the current study (7.3%) is similar to the prevalence rate found in other studies. A *meta*-analysis including 175 studies from across the world obtained an overall ADHD prevalence rate of 7.2% (Thomas et al., 2015). In a 2012 sample of Canadian youth under age 24, the prevalence of ADHD was 5.4% (Hauck et al., 2017). Relatedly, the number of youth with ADHD in our study was relatively small, ranging from approximately 45 to 140 depending on the sample used for a given analysis, which limited statistical power and precision. Finally, the SDQ relies on youth or parent perceptions of symptoms. Future studies would benefit from prospective designs and more rigorous symptom assessment, particularly a structured diagnostic interview that assesses DSM-5 criteria for ADHD.

In conclusion, we found that higher tap water fluoride levels and fluoridation of municipal water supplies were associated with a higher risk of an ADHD diagnosis as well as increased symptoms of hyperactivity and inattention, especially among adolescents. These findings, which point to a potential cumulative effect of fluoride exposure, highlight the need for further investigation of the potential for fluoride-mediated developmental neurotoxicity in populations with water fluoridation.

Declaration of Competing Interest

None.

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Appendix A. Supplementary material

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