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Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6–12 years of age in Mexico City

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ABSTRACT

Background: Epidemiologic and animal-based studies have raised concern over the potential impact of fluoride exposure on neurobehavioral development as manifested by lower IQ and deficits in attention. To date, no prospective epidemiologic studies have examined the effects of prenatal fluoride exposure on behavioral outcomes using fluoride biomarkers and sensitive measures of attention.

Objective: We aimed to examine the association between prenatal fluoride exposure and symptoms associated with attention-deficit/hyperactivity disorder (ADHD).

Method: 213 Mexican mother-children pairs of the Early Life Exposures to Environmental Toxicants (ELEMENT) birth cohort study had available maternal urinary samples during pregnancy and child assessments of ADHD-like behaviors at age 6–12. We measured urinary fluoride levels adjusted for creatinine (MUF_{cr}) in spot urine samples collected during pregnancy. The Conners' Rating Scales-Revised (CRS-R) was completed by mothers, and the Conners' Continuous Performance Test (CPT-II) was administered to the children.

Results: Mean MUF_{cr} was 0.85 mg/L (SD = 0.33) and the Interquartile Range (IQR) was 0.46 mg/L. In multivariable adjusted models using gamma regression, a 0.5 mg/L higher MUF_{cr} (approximately one IQR higher) corresponded with significantly higher scores on the CRS-R for DSM-IV Inattention (2.84 points, 95% CI: 0.84, 4.84) and DSM-IV ADHD Total Index (2.38 points, 95% CI: 0.42, 4.34), as well as the following symptom scales: Cognitive Problems and Inattention (2.54 points, 95% CI: 0.44, 4.63) and ADHD Index (2.47 points; 95% CI: 0.43, 4.50). The shape of the associations suggested a possible celling effect of the exposure. No significant associations were found with outcomes on the CPT-II or on symptom scales assessing hyperactivity.

Conclusion: Higher levels of fluoride exposure during pregnancy were associated with global measures of ADHD and more symptoms of inattention as measured by the CRS-R in the offspring.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; cm^3, cubic centimeters; CNS, Central Nervous System; CPT-II, Conners' Continuous Performance Test – Second Edition; CRS-R, Conners' Rating Scale – Revised; CUF_{sg}, specific gravity adjusted child urinary fluoride; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition; ELEMENT, Early Life Exposures in Mexico to Environmental Toxicants; EPA, U.S. Environmental Protection Agency; HOME, Home Observation for Measurement of the Environment; L, liter; mg, milligram; MUF_{cr}, creatinine adjusted maternal urinary fluoride; SD, Standard Deviation; SE, Standard Error

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1. Introduction

Fluoride, the ionized form of the halogen element fluorine, exists widely in the environment and is the most electronegative and reactive among all elements (ATSDR, 2010). Its well-known cariostatic effect led to the addition of fluoride to water, salt, and milk in some countries. Other sources of fluoride include dental products, such as toothpastes, mouth rinses, and varnishes, supplements, processed foods made with fluoridated water, fluoride-containing pesticides, teas, and fluorinated pharmaceuticals. Systemic ingestion of fluoride through water and water-based beverages is the main source of fluoride intake, accounting for approximately 75% of dietary fluoride intake among adults living in communities that fluoridate their water supply in the United States (U.S. Environmental Protection Agency, 2010; USDA (U.S. Department of Agriculture), 2005). However, in Mexico City, individuals are primarily exposed to fluoride through fluoridated salt (mean concentration of fluoride in salt is 250 ± 50 ppm), and to varying degrees of naturally-occurring fluoride in water, which have been reported to range from 0.15 to 1.38 mg/L (Juárez-López et al., 2007; Martinez-Mier et al., 2005). Public water supplies are not fluoridated in Mexico and the mean fluoride content of the water supply is not publicly available.

Long-term exposure to fluoride is regarded by the World Health Organization as being beneficial, including both prevention of dental caries and treating osteoporosis, though excess intake can also cause potential health hazards, including dental and skeletal fluorosis. Fluoride is also shown to readily cross the placenta (Shen and Taves, 1974) and accumulate in fetal brain tissues (Narayanaswamy and Piler, 2009), thereby inducing toxicity (Dong et al., 1993; Jiang et al., 2014). Several animal (Chen et al., 2003; Mcpherson et al., 2018; Mullenix et al., 1995) and human studies (Bashash et al., 2017; Choi et al., 2012) have explored associations between early-life exposure to fluoride and decrements in cognitive function and attention-related behaviors. An ecologic study reported an association between state level prevalence of community water fluoridation and prevalence of ADHD among youth living in the United States (Malin and Till, 2015). Given the increased vulnerability of the developing fetus to environmental exposures (Lanphear, 2015), as well as the widespread distribution of fluoride in society, the potential impact of prenatal exposure to fluoride warrants further study.

Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in school-aged children and adolescents, with a worldwide prevalence estimated at about 5% (Polanczyk et al., 2007). Symptoms of ADHD include difficulties with attention, impulsivity, and/or hyperactivity at a level that is severe enough to be associated with impairments in academic and social functioning (American Psychiatric et al., 2013). Although genetics have been shown to play an important role in an individual's susceptibility to ADHD, with estimates of heritability from twin studies in the range of 60–70% (Posthuma and Polderman, 2013), several environmental factors have also been implicated. Environmental risk factors for ADHD include prenatal tobacco and alcohol exposure, heavy metal and chemical exposures, including lead (Huang et al., 2016), mercury, organochlorines, air pollution (Fuertes et al., 2016; Perera et al., 2018; Sentís et al., 2017) and nutritional factors (Polańska et al., 2012).

The purpose of the current study was to prospectively assess the relationship between prenatal exposure to fluoride and parent-reported behaviors associated with ADHD among 6–12 year old children born to mothers living in Mexico City. We tested whether fluoride exposure associated with inattentive and/or hyperactive behaviors.

2. Methods

2.1. Study population

Participants included a subset of mother-child dyads enrolled in various longitudinal birth cohort studies of the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) project (Aafeiche et al., 2011; Bashash et al., 2017). We included mother-child pairs from two of the four ELEMENT cohorts (cohorts 2A and 3) for which maternal urinary samples during trimesters of pregnancy were available. Participants in cohort 2A (Bashash et al., 2017) were recruited between 1997 and 1999 whereas participants in cohort 3 were recruited between 2001 and 2003. We included participants if they had at least one archived urine sample from pregnancy, were ≤14 weeks of gestation at the time of recruitment, and their children underwent behavioral testing between the ages of 6 and 12, as described elsewhere (Bashash et al., 2017). Participants were excluded if they reported a history of psychiatric disorder(s), if there were medical complications (i.e. high-risk pregnancy, gestational diabetes, pre-eclampsia, renal disease, circulatory diseases, hypertension, continuous use of prescription drugs, or seizures during the index pregnancy), or if there was known maternal alcohol or illegal drug use during pregnancy. The study procedures were approved by the Institutional Review Boards of the National Institute of Public Health of Mexico, University of Michigan, Indiana University, University of Toronto, and Harvard School of Public Health, as well as participating clinics. Written informed consent was obtained from all participating families prior to study evaluation.

2.2. Fluoride measurements

Concentration of fluoride measured in maternal urinary samples was used as biomarker of prenatal fluoride exposure. Urine has been described as a suitable biomarker for fluoride since it serves as the main pathway through which fluoride is eliminated from the body and excretion is proportional to the total fluoride intake, but modified by factors like diet and various systemic conditions, such as recent fluoride exposure and urinary pH, as well as variation in creatinine excretion by muscle mass, age, sex, and other factors (Barr et al., 2005; Aylward et al., 2015). Ideally, overnight fasting or 24-hour urine samples are considered to be the optimal dosimeter for measuring chronic fluoride exposure in order to limit diurnal variations and the influence of diet associated with spot samples (Petersen et al., 2014). Because 24-hour urinary samples were not available in our sample, we used spot samples that were corrected for urinary dilution using urinary creatinine, as described elsewhere (Petersen et al., 2014). Each woman in the current sample provided at least one spot (second morning void) urine sample (Thomas et al., 2016) during pregnancy (range: 10 to 38 weeks). We then calculated the average of all available creatinine-adjusted maternal urinary fluoride (MUF) concentrations (Bashash et al., 2017). Further information regarding participant recruitment, data collection methods, as well as methods for fluoride sample shipping, storage, and analysis can be found elsewhere (Bashash et al., 2017).

2.3. Attention outcomes

Behaviors associated with ADHD were assessed using the Spanish version of the Conners' Rating Scales-Revised (CRS-R) (Conners, 1997), which has been validated for the evaluation of ADHD (Ortiz-Luna and Acle-Tomasini, 2006). The CRS-R contains three ADHD scales that correspond with the Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) criteria for ADHD: 1) DSM-IV Inattention Index, 2) DSM-IV Hyperactive-Impulsive Index, and 3) DSM-IV Total Index (inattentive and hyperactive-impulsive behaviors combined). It also examines seven types of behavior problems that were derived through factor analysis, including: Oppositional, Anxious-Shy, Cognitive Problem/Inattention, Hyperactivity, Perfectionism, Psychosomatic, and Social Problems. In addition, the CRS-R contains four index scores that were derived based on theory and prior research: Conners' ADHD Index; Conners' Global Index (CGI): Restless-Impulsive; CGI: Emotional Lability, and CGI. For the purpose of the current study, we examined the three DSM-IV ADHD scales as our primary outcomes because these scales are intended to screen for ADHD, and are commonly used to

study the association between diverse environmental contaminants and ADHD-behavior problems (Huang et al., 2016; Perera et al., 2018). We also examined outcomes from two behavior scales (Cognitive Problem/Inattention and Hyperactivity) and two index scores (Conners' ADHD Index and CGI: Restless-Impulsive), as done in our prior work with lead (Huang et al., 2016). The Conners' ADHD Index, in particular, has been shown to exhibit favorable specificity and sensitivity in ADHD assessment (Chang et al., 2016). In addition, we assessed sustained attention and inhibitory control using the Conners' Continuous Performance Test (CPT-II, 2nd Edition), a computer-administered signal detection paradigm (Conners, 2000). Using the CPT-II, we measured errors of omission and commission, and hit reaction time (response latency). Mothers completed the CRS-R at the same follow-up visits that the child completed the CPT-II. All measures were standardized for age- and sex. Higher T-scores (mean of 50, SD of 10) indicate poorer performance. All psychometric tests were applied under the supervision of an experienced psychologist (LS).

2.4. Measurement of covariates

Covariate data were individually obtained throughout the duration of the study. During the first pregnancy visit, questionnaires were used to collect information concerning maternal age, maternal education, history of smoking, and marital status. At delivery, information regarding birth weight, child sex, birth order, and gestational age (calculated by nurses) was obtained. Mothers also responded to a socioeconomic status questionnaire (Bashash et al., 2017) during the visit when the psychometric tests were administered. Individual items on this questionnaire assess the ability of households to meet the needs of its members in terms of housing, health, energy, technology, prevention and intellectual development; an overall score was derived by summing across each item. The Home Observation for Measurement of the Environment (HOME) Inventory, a semi-structured interview that measures quality and quantity of the caregiving environment, was administered in a subset of participants at approximately the same time as the visits for the neurobehavioral tests.

2.5. Data analysis

Univariate statistics, appropriate transformations, and graphical displays were obtained for all variables before bivariate analyses. Bivariate analysis of the data included Chi-square tests for categorical variables and analysis of variance (ANOVA) to compare the continuous outcomes or exposure within groups defined according to the distribution of each covariate. In initial fully adjusted linear regression models, the outcomes demonstrated highly skewed residuals (with the exception of CPT-II commission score and hit reaction time). Thus, to address the skewness of the residuals, gamma regression was used to examine the adjusted association between prenatal fluoride and each neurobehavioral outcome instead of log transformation, which may obscure model interpretation. In the gamma regression, we selected an identity link, so that the interpretation for the regression coefficients is the same as the linear regression (i.e., absolute difference in the mean of the outcome per unit change in predictor). All statistical analyses were performed in SAS software version 9.4. Covariates were selected a priori based on their theoretical relevance or observed associations with fluoride exposure, and/or the analyzed neurobehavioral outcomes. As such, models were adjusted for the following maternal characteristics: age at delivery (continuous, in years), years of education (continuous, in years), marital status (married vs. others), and smoking history (ever-smoker vs. non-smoker). Models were further adjusted for the following child characteristics: gestational age at birth (continuous, in weeks), age at neurobehavioral measurement (continuous, in years), sex (female vs. male), and birth order (first born vs. others), and socioeconomic status through a continuous measure based on reported possessions and household assets (Thomas et al., 2016). Lastly, models adjusted for potential cohort and Ca intervention effects through inclusion of a variable denoting from which study the participants originated (cohort 2 - A, an observational cohort), cohort 3 subjects who were randomized to the calcium supplement (cohort 3 - Ca^{+}), and cohort 3 subjects who were randomized to the placebo (cohort 3 - Placebo) (Bashash et al., 2017).

Other potential confounders that were examined in sensitivity analyses involving subsets of participants included the home environment (i.e. HOME score) (Thomas et al., 2016) assessed at the time of outcome measurement, child contemporaneous fluoride exposure measured by child urinary fluoride adjusted for specific gravity (CUF_{sg}) (Bashash et al., 2017), as well as maternal blood mercury and maternal bone lead levels (a proxy for prenatal lead exposure to the fetus) given that both are established neurodevelopmental toxicants (Bashash et al., 2017). This was done through identifying and including the subset of cases with data on each respective variable. In each subset, results were then compared between the model adjusting for that variable and the model not adjusting for that variable.

Model diagnostics were used to assess for violations of the model assumptions and for identification of remaining influential observations. Cook's D identified three exposure observations as potentially influential to the model results, and models were run with and without these observations (Supplementary Fig. S1). Generalized additive models (GAMs), estimated via cross validation in the R software, were used to visualize the adjusted association between fluoride exposure and measures of attention to examine potential non-linearity. Non-linearity of the fluoride-outcome association was tested through the inclusion of a quadratic term in the model, and found to be significant in four out of ten of the models (see Fig. 2 and Supplementary Fig. 1). We applied the Benjamini–Hochberg false discovery rate (FDR) procedure to address multiple testing corrections, using a false discovery rate of $Q = 0.05$ and $m = 10$ tests to determine significance (Benjamini and Hochberg, 1995).

3. Results

3.1. Population characteristics

Overall, 231 mothers with a minimum of one MUF_{cr} and a matching outcome (CRS-R or CPT-II) were identified for this project. However, complete demographic and outcome information were missing among 17 mother-child pairs, leaving 214 participants for our analyses, of whom 210 mother-child pairs had data for the CRS-R and CPT-II analyses (206 had data for both) (Fig. 1). Demographic information on participants including data on exposure, outcomes, and key covariates by cohort is shown in Table 1. Of the mothers included in our analysis, 154 (72%) were married at the time of recruitment, and 103 (48%) had reported a history of ever smoking. Among the children, 147 (69%) were not of firstborn status and 116 (54%) were female. Besides for younger age of participants in cohorts 3 relative to cohort 2-, there were no significant differences of maternal and children characteristics across cohorts.

3.2. Exposure and outcome assessment

Of the 214 participants included in the study, 175 participants had measurements of MUF_{cr} from trimester 1, 80 from trimester 2, and 62 from trimester 3; 14 (6.5%) participants had all three measures, 78 (36.4%) had two measures, and 122 (57.0%) had one. The overall mean level of MUF_{cr} averaged across all the trimesters was 0.85 mg/L, with an Interquartile Range (IQR) of 0.46 mg/L. There was no significant difference of MUF_{cr} across cohorts (Table 1A).

Overall, Mean $\pm$ SD scores across all of the CRS-R scales fell within the average range (i.e. mean $T = 50 \pm 10$) (Table 1B). Around 10% of participants fell in the clinically significant range (i.e. T-score ≥ 70 on the Index scores); specifically, clinically elevated scores were found

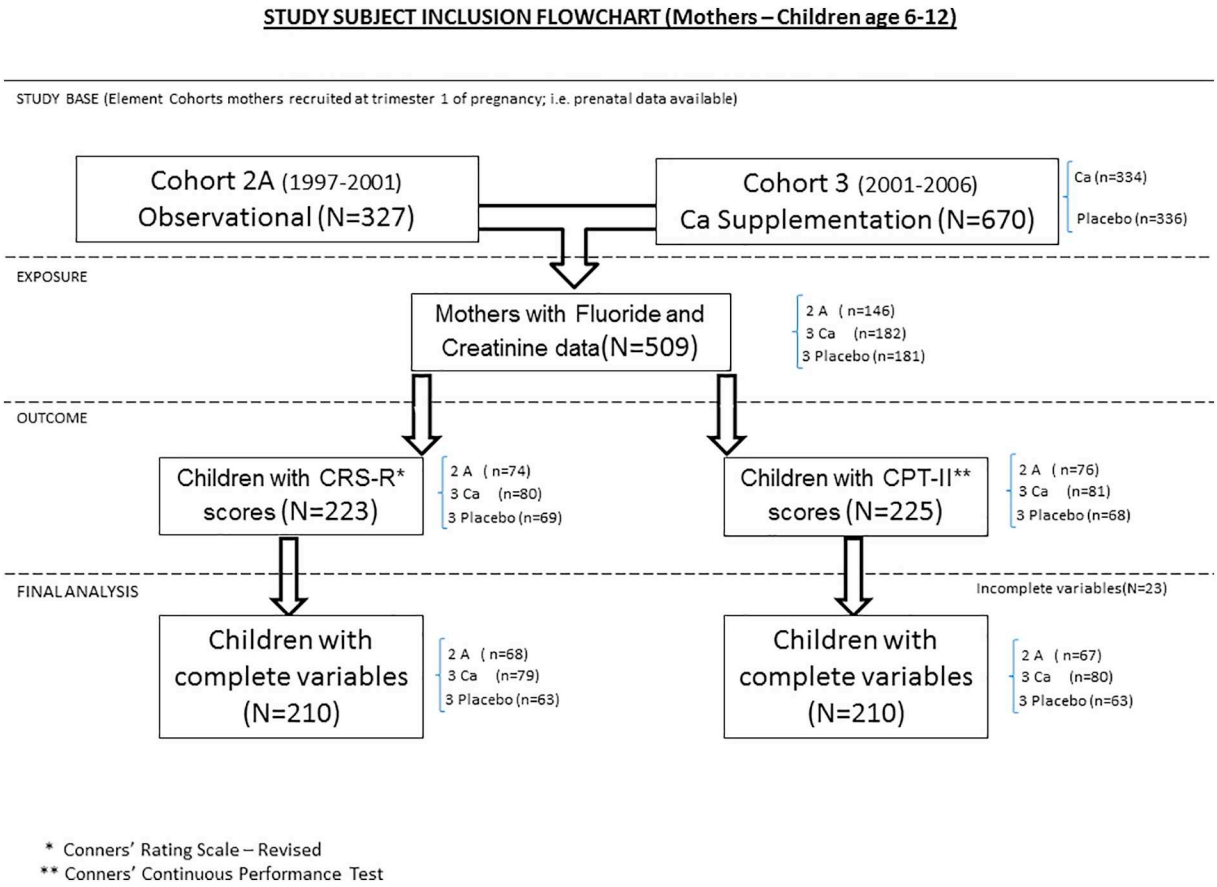

Fig. 1. Flowchart describing source of mother–offspring subject pairs, fluoride and cognition study. Cohort 2A was designed as an observational birth cohort from 1997 to 2001. Cohort 3 was designed as a randomized double-blind placebo-controlled trial of calcium supplements, with mothers recruited early during pregnancy from 2001 to 2006. "Ca" denotes subjects who were randomized to the calcium supplement; "placebo" denotes subjects who were randomized to the placebo. CRS-R denotes Conners' Rating Scale – Revised and CPTII is Conners' Continuous Performance Test.

among 22 (10.5%) children on the DSM-IV Hyperactivity-Impulsivity scale, 18 (8.6%) children on the DSM-IV ADHD Total scale, and 17 (8.1%) children on the DSM-IV Inattention scale.

Mean ± SD for CPT-II scores for Omission Errors (55.53 ± 13.67), Commission Errors (49.93 ± 9.22), and Hit Reaction Time (52.51 ± 10.53) also fell within the average range (Table 1B).

3.3. Models of neurobehavioral outcomes

MUF_{cr} was significantly associated with measures of the CRS-R in the adjusted model (Table 2). Higher concentrations of MUF_{cr} were associated with a higher likelihood of parent-endorsed symptoms on the following scales: DSM-IV Inattention, DSM-IV Total ADHD, Cognitive Problem/Inattention, and the ADHD Index. On average, a 0.5 mg/L higher MUF_{cr} corresponded with a 2.84 ($p < 0.01$) higher score on the DSM-IV Inattention Index; 2.38 ($p = 0.02$) higher score on the DSM-IV Total ADHD Index; a 2.54 ($p = 0.02$) higher score on the Cognitive Problem/Inattention Index; and 2.47 ($p = 0.02$) higher score on the ADHD index. The associations between MUF_{cr} and CRS-R scales remained significant after correction for the multiple testing. As shown in Fig. 2, a subset of the CRS-R outcomes exhibit a non-linear association with the relationship between MUF_{cr} and behavioral outcomes increasing at first, followed by a plateau. There were no significant associations between MUF_{cr} and any of the outcomes on the CPT-II (Table 2; and Supplementary Fig. S2).

3.4. Sensitivity analyses

Sensitivity analyses on adjusted models for the study population subset that also had HOME scores, CUF_{sg} (there was no correlation between MUF_{cr} and CUF_{sg}), maternal lead and mercury exposures did not appreciably change the results for the CRS-R scores (Supplementary Table 1). There was no significant interaction between sex and MUF_{cr} when we added an interaction term to the models.

4. Discussion

The current study aimed to characterize the longitudinal association between prenatal fluoride exposure and symptoms of ADHD in offspring as measured by parent-ratings on the CRS-R and a computerized test of sustained attention and inhibitory control (CPT-II). In our cohort, higher prenatal fluoride exposure, as measured by MUF_{cr}, corresponded to more ADHD-like symptoms on the CRS-R, particularly related to inattention as indicated by the strong association with the following two scales: Cognitive Problem/Inattention, and DSM-IV Inattention. In contrast, MUF_{cr} during pregnancy did not predict child performance on any of the hyperactivity measures (i.e. Restless-Impulsive; Hyperactivity; DSM-IV Hyperactivity-Impulsivity) nor the CPT-II outcomes.

In general, a 0.5 mg/L higher MUF_{cr} (approximately the IQR) corresponded to higher scores on the CRS-R for DSM-IV Inattention (2.84 points) and Cognitive Problems and Inattention (2.54 points). Consistency in these results across both of these outcome measures strengthens the conclusion that inattention appears to be associated with prenatal exposure to fluoride. These two scales contribute to the global ADHD Index and the DSM-IV Total scores, which were also associated with higher levels of prenatal fluoride exposure; a 0.5 mg/L increase in MUF_{cr} corresponded to a 2.38 higher point score on the DSM-IV ADHD Total Index and a 2.47 higher point score on the ADHD

Table 1
Cohort characteristics including key covariates, urinary fluoride levels, and outcome measurements. Statistical differences across the cohorts are reported upon in the final column.

	Cohort *	N	Mean (95% CI) %	p
A) PARTICIPANTS				
Child Sex (Girl)	2 A	37	52.90%	.831
	3 Ca	43	53.10%	
	3 Placebo	36	57.10%	
	Total	116	54.00%	
First Child	2 A	24	34.30%	.839
	3 Ca	25	30.90%	
	3 Placebo	18	28.60%	
	Total	67	31.00%	
Birth Weight (Kg)	2 A	70	3.05 (2.94, 3.16)	.103
	3 Ca	81	3.20 (3.10, 3.30)	
	3 Placebo	63	3.11 (3.01, 3.21)	
	Total	214	3.13 (3.07, 3.18)	
Gestational Age (Weeks)	2 A	70	38.60 (38.21, 38.99)	.647
	3 Ca	81	38.74 (38.46, 39.02)	
	3 Placebo	63	38.49 (38.01, 38.97)	
	Total	214	38.62 (38.41, 38.84)	
Age At Outcome Assessment (Year)	2 A	70	10.04 (9.89, 10.21)	*< .01*
	3 Ca	81	7.63 (7.52, 7.75)	
	3 Placebo	63	7.57 (7.44, 7.69)	
	Total	214	8.40 (8.23, 8.57)	
Marital Status (Married)	2 A	46	65.70%	.428
	3 Ca	60	74.10%	
	3 Placebo	48	76.20%	
	Total	154	72.00%	
Maternal Smoking (Ever Smoked)	2 A	32	46.40%	.726
	3 Ca	42	51.90%	
	3 Placebo	29	45.70%	
	Total	103	48.10%	
Maternal Education (Years)	2 A	70	10.73 (10.08, 11.37)	.580
	3 Ca	81	11.11 (10.47, 11.75)	
	3 Placebo	63	10.68 (10.03, 11.34)	
	Total	214	10.86 (10.49, 11.23)	
SES[1]	2 A	70	6.69 (6.10, 7.27)	.604
	3 Ca	81	6.32 (5.82, 6.82)	
	3 Placebo	63	6.33 (5.64, 7.02)	
	Total	214	6.44 (6.11, 6.78)	
B) EXPOSURE AND OUTCOMES				
MUF_{cr} [2]	2 A	70	0.87 (0.80, 0.95)	0.889
	3 Ca	81	0.85 (0.78, 0.92)	
	3 Placebo	63	0.85 (0.76, 0.95)	
	Total	214	0.85 (0.81, 0.90)	
CRS-R [3]				
Cognitive Problems + Inattention	2 A	68	55.16 (52.45, 57.87)	.884
	3 Ca	79	54.32 (51.85, 56.78)	
	3 Placebo	63	54.43 (51.78, 57.08)	
	Total	210	54.62 (53.14, 56.10)	
Restless-Impulsive	2 A	68	55.43 (52.56,58.30)	.490
	3 Ca	79	55.19 (52.32, 58.07)	
	3 Placebo	63	54.28 (52.11, 56.45)	
	Total	210	54.35 (52.94, 55.75)	
Hyperactivity	2 A	68	56.67 (53.62, 56.35)	.217
	3 Ca	79	54.52 (52.42, 56.62)	
	3 Placebo	63	53.70 (51.74, 55.66)	
	Total	210	54.97 (53.59, 56.35)	
ADHD [4] **Index**	2 A	68	54.53 (51.77, 56.29)	.865
	3 Ca	79	54.56 (52.29, 56.82)	
	3 Placebo	63	53.70 (51.25, 56.14)	
	Total	210	54.30 (52.88, 55.71)	
DSM-IV [5] **Inattention**	2 A	68	54.42 (51.60, 57.23)	.825
	3 Ca	79	53.92 (51.65, 56.22)	
	3 Placebo	63	53.29 (50.98, 55.60)	
	Total	210	53.89 (52.48, 55.30)	
DSM-IV Hyperactivity-Impulsivity	2 A	68	57.54 (54.77, 60.32)	.685
	3 Ca	79	56.80 (54.59, 59.01)	
	3 Placebo	63	56.00 (53.76, 58.24)	
	Total	210	56.80 (55.42, 58.18)	
DSM-IV ADHD Total	2 A	68	56.35 (53.72, 58.99)	.670
	3 Ca	79	55.63 (53.46, 57.81)	
	3 Placebo	63	54.79 (52.47, 57.12)	
	Total	210	55.61 (54.26, 56.97)	
CPT-II [6]				

(*continued on next page*)

Table 1 (*continued*)

	Cohort *	N	Mean (95% CI) %	p
Omission Errors	2 A	67	51.76 (48.49, 55.03)	*.024*
	3 Ca	80	57.56 (54.25, 60.87)	
	3 Placebo	63	56.80 (53.89, 59.70)	
	Total	210	55. 48 (53.62, 57.34)	
Commission Errors	2 A	67	46.99 (44.43, 49.55)	*.007*
	3 Ca	80	51.18 (49.17, 53.20)	
	3 Placebo	63	51.37 (49.59, 53.16)	
	Total	210	49.90 (48.65, 51.15)	
Hit Reaction Time	2 A	67	49.43 (47.00, 51.86)	*.016*
	3 Ca	80	53.77 (51.35, 56.18)	
	3 Placebo	63	54.05 (51.49, 56.60)	
	Total	210	52.46 (51.03, 53.90)	

*Cohort: 2 A; ELEMENT Cohort 2A, an observational birth cohort from 1997 to 2001. 3 Ca and 3 Placebo, ELEMENT Cohort 3, a randomized double-blind placebo-controlled trial of calcium supplements from 2001 to 2006. "Ca" denotes subjects who were randomized to the calcium supplement; "placebo" denotes subjects who were randomized to the placebo. 1) SES, socioeconomic status; 2) MUFcr, Creatinine adjusted maternal urinary fluoride; 3) CRS-R, Conners' Rating Scale – Revised; CPT-II; 4) ADHD, Attention Deficit Hyperactivity Disorder; 5) DSM-IV, Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition; 6) CPT-II, Conners' Continuous Performance Test – Second Edition.

Table 2
Multivariate[a] gamma regression models of differences across CRS-R and CPT-II scores per 0.5 mg/L higher maternal creatinine-adjusted urinary fluoride (MUF_{cr}).

	β	95% CI		p
CRS-R scores (N = 210)				
Cognitive Problems + Inattention	2.54	0.44	4.63	*.0178*
Restless-Impulsive	1.92	−0.07	3.91	0.0586
Hyperactivity	1.05	−0.91	3.00	0.2953
ADHD Index	2.47	0.43	4.50	*0.0175*
DSM-IV Inattention	2.84	0.84	4.84	*0.0054*
DSM-IV Hyperactivity-Impulsivity	1.69	−0.33	3.70	0.1016
DSM-IV ADHD Total	2.38	0.42	4.34	*0.0176*
CPT-II scores (N = 210)				
Omission Errors	0.22	−2.30	2.74	0.8643
Commission Errors	−0.43	−2.38	1.51	0.6641
Hit Reaction Time	1.07	−1.19	3.32	0.3546

[a] Adjusted for gestational age, birth weight, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. non-smoker), marital status (married vs. others), education, socioeconomic status and cohort (Cohort 3 - Ca, Cohort 3 - placebo and Cohort 2A).

Index. Our observed association of MUF_{cr} and CRS-R seems to demonstrate a ceiling effect, suggesting that higher levels of urinary fluoride concentration did not substantially increase risk of ADHD-like symptoms.

Overall, our results are consistent with the ecological study by Malin and Till (2015). Their cross-sectional study used national health surveys conducted by the Centers for Disease Control and Prevention to estimate the prevalence of ADHD and water fluoridation for each state. Their findings showed that, after controlling for household income, states in which a greater proportion of people received community water fluoridation in 1992 tended to have a greater proportion of children and adolescents who received an ADHD diagnosis in 2003, 2007, and 2011. The prevalence of ADHD increased from 7.8% in 2003 to 11% in 2011. A distinction between this U.S. study and the current study is that our study was a longitudinal birth cohort with individual biomarkers of fluoride exposure obtained during pregnancy when the developing brain is thought to be at the highest risk for fluoride neurotoxicity (Bashash et al., 2017). Moreover, the current study controlled for relevant confounders that may be associated with ADHD, including smoking, maternal education, child sex, HOME score, and exposure to other contaminants. Further, our measure for ADHD was not physician-diagnosed but rather approximated through validated questionnaires and performance-based tests. Both studies examined populations that are exposed to "optimal" levels of fluoride either through water or salt fluoridation schemes. The exposure level in the Mexico City cohort is generally lower than the populations living in endemic fluorosis areas studied in China (Choi et al., 2012) where natural levels of fluoride are often higher (> 2 mg/L) than recommended levels for North American (0.7 mg/L). The mean concentration of MUF in our study is in the range of the Canadian cohort (in review), and a New Zealand cohort of 59 pregnant women (median MUF = 0.82 mg/L) (Skeaff and Te Morenga, 2017).

Our finding of an association between MUF_{cr} and symptoms of inattention are consistent with the growing body of evidence showing dose-response relationships between early-life exposure to fluoride and attention outcomes. Animal studies (Mullenix et al., 1995) reported fewer behavioral initiations and less time exhibiting exploration behaviors among male and female rats exposed to 100 or 125 ppm fluoride as weanlings (21 days postnatal) and among male rats whose mothers were injected with 0.13 mg/L of sodium fluoride on gestational days 17–19. These particular behavioral effects are suggestive of hypoactivity. In human studies, high exposure to fluoride, as reflected by the presence of moderate to severe dental fluorosis in primary teeth of children living in southern Sichuan, China, was associated with poor working memory, but not with other cognitive domains that were assessed (Choi et al., 2015). Working memory is linked with the ability to control attention and it is common for youth with ADHD to have weaknesses in working memory (Kasper et al., 2012). A possible explanation for the specific effect on inattention (Dugbartey, 1998) is that fluoride exposure is contributing to thyroid hormone insufficiency. Recent studies demonstrate that even relatively subtle changes in circulating levels of TH in pregnancy (i.e. subclinical hypothyroidism) can have adverse outcomes, including preterm birth, lowered IQ (Hollowell et al., 1999; Murphy et al., 2015; Stagnaro-Green and Rovet, 2016; Thompson et al., 2018) (Yang et al., 2008) and increased risk for attention disorders (Modesto et al., 2015; Pakkila et al., 2014) (Rovet and Hepworth, 2001). Some (Swarup et al., 1998) (Swarup et al., 1998), but not all (Mcpherson et al., 2018), animal studies showed reductions in T3 and T4 levels from fluoride exposure, even at low doses. Several human studies have shown that elevated levels of fluoride in drinking water predict higher TSH and lower T3 levels (Bachinskii et al., 1985; Kheradpisheh et al., 2018; Singh et al., 2014), especially among children (Yasmin et al., 2013), as well as an increased likelihood for a diagnosis of hypothyroidism. However, further research is needed to examine how exposure to fluoride may affect thyroid function in pregnancy. Another potential mechanism through which fluoride may contribute to ADHD relates to the dopamine system. Animal studies have shown that fluoride exposure can alter the levels of dopamine (Pal and Sarkar, 2014). Dopamine is an important modulatory

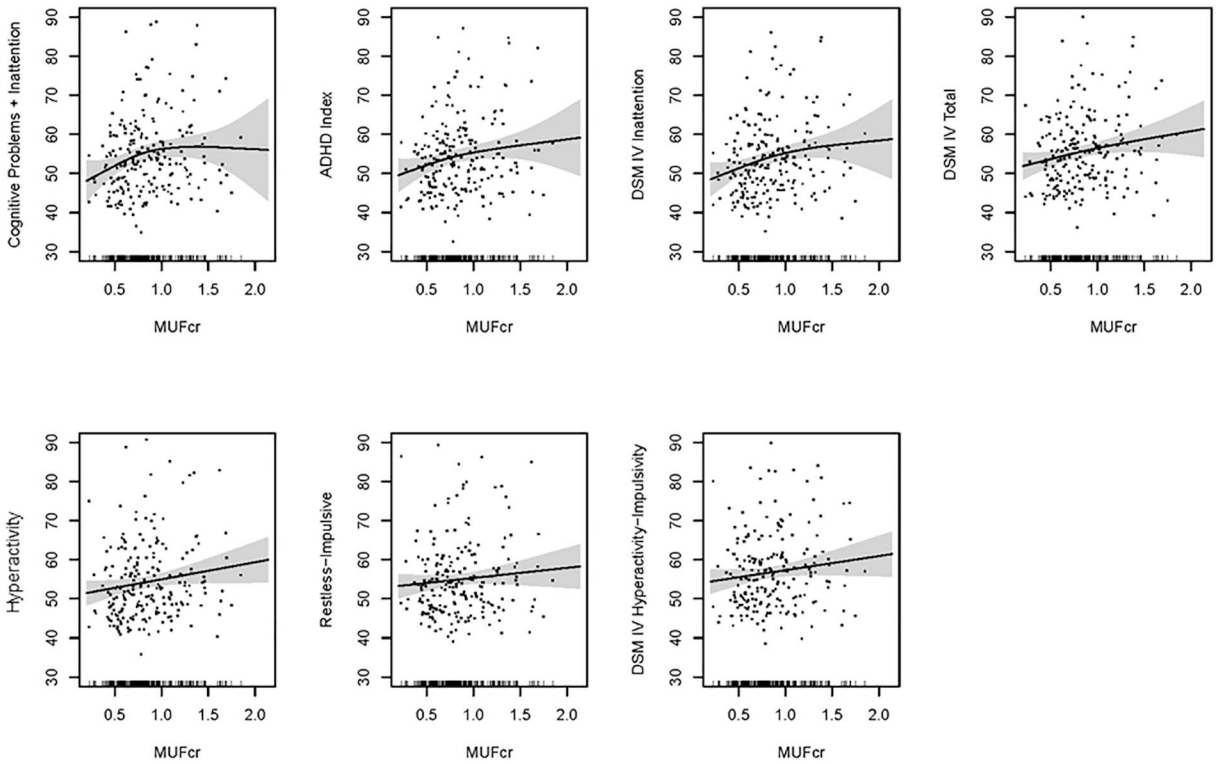

Fig. 2. Association of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and Conners' Parent Rating Scales-Revised (CRS-R) measures in children at age 6 to 12 years.

Outcome data are adjusted for gestational age, birth weight, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. non-smoker), marital status (married vs. others), education, socioeconomic status and cohort (Cohort 3 Ca, Cohort 3 placebo and Cohort 2A). Shaded area is the 95% confidence interval. The short vertical bars on the x-axis reflect the density of urinary fluoride measures. Individual data points are individual observations, n = 210.

neurotransmitter in planning and initiation of motor responses, activation, switching, reaction to novelty and processing of reward (Faraone et al., 2015).

The stronger association between prenatal fluoride exposure and parent-reports of attention problems may be explained by the CRS-R measuring distinct and more extensive constructs that rely on attention (e.g. new learning, ability to hold information and complete tasks, organizational skills, etc.) than those assessed by the CPT-II. Additionally, it has been shown that CPT-II performance and parent rating scales are moderately correlated at best (Gualtieri and Johnson, 2005), suggesting that these measures are assessing different constructs. Other studies examining prenatal Polychlorinated Biphenyis (PCBs) exposure and sustained attention (Vreugdenhil et al., 2004) that report using the computerized continuous performance test with children aged 4 and 11 years also fail to show an association with this measure, but do find an association using other psychometric tests of attention (e.g. digit cancellation task). Further investigation of cognitive performance on other domains, such as learning and memory, is warranted in our study cohort.

Key strengths of this study include the relatively large pregnancy cohort that has a biorepository with a capacity to capture high quality individual biomarker exposure across multiple developmental time points, longitudinal follow-up, detailed assessment of ADHD-like behaviors using both rating scales and performance based measures, as well as measurement of additional health outcomes and potential covariates using validated techniques (Thomas et al., 2016). Assessment of attention, hyperactivity, and impulsivity using multiple measures allowed us to examine different types of ADHD-like behaviors using continuous scales that are sensitive to both clinical and subclinical symptoms of ADHD. This approach minimizes the limitations of viewing ADHD as a categorical and conceptually distinct disorder.

Our study also has some limitations. The cohort was not initially designed to study fluoride exposure and so we are missing some aspects of fluoride exposure assessments (e.g., detailed assessments of diet, water, etc.) that are now underway. The urinary samples were not available for all trimesters of pregnancy for majority of the participants; in particular, for those with only one sample, we cannot rule out the possibility that some samples may reflect acute exposure. Differences in the proportion of fluoride that is excreted in the urine have been described for different age groups as well as for pregnant women. Data on the percentage of fluoride excreted for children and adults are available, which makes estimation of intake feasible. On the other hand, data for pregnant women are sparse, making estimates of intake from urinary concentration not feasible. Therefore, while urinary fluoride is a valid biomarker to identify differences in exposure levels in pregnant women, it is not possible, with the currently available data, to estimate how concentration levels relate to intake. With regards to our outcome measure, we did not have information on family history or genetic markers associated with ADHD, nor were children assessed clinically for a diagnosis of ADHD. Only parent reports were used for the CRS-R, and not teacher reports. This is a limitation to our study as previous studies have shown that there can be considerable variation between the two sources in terms of identifying ADHD-associated behaviors (Lavigne et al., 2012). Nevertheless, parents were unaware of their offspring's fluoride exposure status, removing reporting bias as a limitation. Although elevated scores on behavioral checklists like the CRS-R may be associated with a diagnosis of ADHD, the functional consequences of the symptoms must also be characterized for clinically diagnosing the disorder.

5. Conclusion

In summary, we observed a positive association between higher prenatal fluoride exposure and more behavioral symptoms of inattention, but not hyperactivity or impulse control, in a large Mexican cohort of children aged 6 to 12 years. The current findings provide further evidence suggesting neurotoxicity of early-life exposure to fluoride. Replication of these findings is warranted in other population-based studies employing biomarkers of prenatal and postnatal exposure to fluoride.

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All authors contributed to the final interpretation of the results and final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.09.017.

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