



# Long-term exposure to prenatal fluoride and social-emotional and behavioural outcomes in children in the New Hampshire Birth Cohort Study

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## ABSTRACT

**Background and objectives:** Prenatal fluoride exposure may pose risks for maladaptive social-emotional and behavioural development, but evidence using biomarkers that integrate long-term prenatal exposure is limited. This study examined associations between maternal toenail fluoride at multiple time points and water fluoride on preschool social-emotional and behavioural outcomes and evaluated potential differences by child sex and exposure window.

**Methods:** Participants included 358 mother-child dyads from the New Hampshire Birth Cohort Study using private, unregulated household water systems. Fluoride concentrations were measured in maternal toenails collected at ~28 weeks' gestation (reflecting early-pregnancy exposure) and 5 weeks postpartum (reflecting mid-to-late-pregnancy exposure), and in household tap water samples collected at ~24–28 weeks' gestation. Children's social-emotional and behavioural functioning was assessed at approximately 5 years old using the *Behavior Assessment System for Children–Second Edition, Parent Rating Scale–Preschool Form*. Primary composite scores were dichotomized as at-risk (T-score  $\geq 60$ ). Covariate-adjusted generalized estimating equations estimated associations between toenail fluoride and at-risk outcomes, and multiple logistic regressions estimated associations between water fluoride and at-risk outcomes, testing sex and exposure-window interactions.

**Results:** A 1- $\mu\text{g/g}$  increase in toenail fluoride concentration reflecting early pregnancy exposures, was associated with higher odds of at-risk Externalizing Problems (OR=1.39; 95% CI: 1.15–1.67). Toenail fluoride concentrations reflecting late-pregnancy exposures, showed a similar association (OR=1.30; 95% CI: 0.99–1.71). No associations were observed for other behavioural composites, or with water fluoride concentrations, with no apparent differences by sex or exposure window for the behavioural composites.

**Conclusions:** Higher maternal toenail fluoride concentrations, but not water fluoride concentrations, were associated with greater odds of at-risk externalizing problems in preschoolers in this U.S. cohort. Generalizability may be limited because participants were predominantly White, college-educated families from rural New England using private water systems. Further research incorporating both individual-level biomarkers and population-level exposure measures, together with information on major fluoride sources (e.g., drinking water), is needed to clarify the relationship between prenatal fluoride exposure and child neurobehavioural development.

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## 1. Introduction

Fluoride naturally occurs in certain rock formations and can accumulate in groundwater (Agency for Toxic Substances and Disease Registry (ATSDR), 2003). In rural New Hampshire (U.S.), many residents rely on private wells, which may contain naturally occurring fluoride (Private Wells, 2025). Community water fluoridation (CWF) programs adjust fluoride concentrations to 0.7 mg/L (U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation, 2015), whereas fluoride concentrations in private wells can vary widely depending on local geology (Moore, 2004). Wells drilled in regions with felsic igneous rock have particularly high fluoride levels; 13% exceed the secondary maximum contaminant level of 2.0 mg/L (McMahon et al., 2020). Drinking water is the primary source of fluoride exposure for adults (U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation, 2015) living in areas served by CWF, or where naturally occurring fluoride levels are comparable to or higher than those in fluoridated systems. Other sources of fluoride include food and beverages, such as seafood (Jáudenes-Marrero et al., 2024), green and black tea (Krishnankutty et al., 2021), and any beverage made with fluoridated water (e.g., juice, pop, etc.) (Alejandro-Vega et al., 2024). Further, fluoride is added to a range of dental-care products, including fluoridated toothpaste, mouth rinses, supplements, and professionally applied gels, foams, and varnishes, which can be unintentionally ingested (Petrović et al., 2023; Saad et al., 2022).

Fluoride readily crosses the placenta (Abduweli Uyghurturk et al., 2020) and penetrates the blood-brain barrier (Ghosh and Ghosh, 2020), thereby exposing the developing brain to fluoride. A growing body of epidemiological research has found associations between higher fluoride concentrations in drinking water and urine with lower intelligence scores in children (Taylor et al., 2025). Far fewer studies have examined associations with children's social-emotional and behavioural outcomes. Some prospective studies report that higher maternal urinary fluoride concentrations during pregnancy are associated with increased internalizing problems and ADHD symptoms in children (Bashash et al., 2018; Malin et al., 2024), while others have not observed these associations (Ibarluzea et al., 2025).

Most prior studies have relied on maternal urinary fluoride (Bashash et al., 2018; Ibarluzea et al., 2025; Malin et al., 2024), a short-term exposure biomarker, that reflects fluoride intake over approximately six hours. In contrast, toenails integrate exposure over several months and are associated with drinking water fluoride concentrations, total daily fluoride intake, and dental fluorosis (Lavallo-Carrasco et al., 2021, 2023, 2025). Furthermore, associations between prenatal fluoride exposure and child outcomes may vary by sex and timing of exposure (Bellinger et al., 2016; Farmus et al., 2021).

To address these research gaps, we analyzed maternal toenail fluoride concentrations measured at two time points, along with household water fluoride concentrations, to examine associations with children's social-emotional and behavioural outcomes and to test for sex- and exposure window-specific effects in a U.S. cohort reliant on unregulated private well water systems that frequently contain fluoride (McMahon et al., 2020). We hypothesized that higher levels of maternal toenail fluoride concentrations across pregnancy, and water fluoride, would be associated with symptoms of inattention, hyperactivity, and overall maladaptive behaviour. We further hypothesized that these associations would differ by sex.

## 2. Methods

### 2.1. Study sample

This study included mother-child pairs from the New Hampshire Birth Cohort Study (NHBCS), originally designed to examine the impact of environmental contaminants found in unregulated water systems on

the health of pregnant women and children living in rural New Hampshire (Gilbert-Diamond et al., 2011). Between 2009-2013, an unselected sample of pregnant women (18-45 years old) were recruited from prenatal clinics at approximately 28 weeks' gestation. Eligibility criteria included receiving prenatal care at one of the study clinics in New Hampshire, using a private household water system, English literacy, carrying a singleton pregnancy, and having resided at the same address since their last menstrual period and not planning to move. Participants provided written informed consent in accordance with the guidelines from the Committee for the Protection of Human Subjects at Dartmouth College. The analysis was restricted to mother-child pairs who had at least one maternal toenail fluoride measurement and/or a water fluoride measurement, a child behavioural assessment at age 5, and complete data on primary covariates described below (Figure 1).

### 2.2. Maternal toenail fluoride

Women provided toenail clippings at approximately 28 weeks' gestation and 5 weeks' postpartum (collection procedures are reported elsewhere (Karagas et al., 2000)). Given their slow growth rate, toenail fluoride generally represents exposure approximately 3-6 months prior (Buzalaf et al., 2006; Whitford et al., 1999). Thus, collected toenails represent fluoride exposures occurring in early and mid-to-late-pregnancy (hereafter referred to as early- and late-pregnancy fluoride). The current study analyzed clippings from the lesser toes (i.e., excluding the big toe) based on the samples available in this cohort.

Toenail samples analyzed for fluoride were selected from a subsample of participants whose children completed intelligence testing at age 5 which was a primary outcome of interest (Goodman et al. *In Preparation*). Samples with a minimum mass of 1 mg were shipped to Indiana University School of Dentistry's fluoride laboratory for analysis. Toenails were analyzed for inorganic fluoride using a modification of the hexamethyldisiloxane (HMDS; Sigma Chemical Co., St Louis, MO, USA) microdiffusion procedure, developed and validated for nails (Buzalaf et al., 2012; Whitford et al., 1999). The electrode's limit of detection (LoD) was 0.019 µg/g fluoride. Following this analysis, toenail mass was found to influence the reliability of the HMDS-facilitated diffusion method, where samples <2.5 mg were not found to yield reliable results (Tamayo-Cabeza et al., 2026a). Therefore, participants whose toenail sample weights were below 2.5 mg were excluded from the early-pregnancy (n = 81) and late-pregnancy (n = 51) analyses.

### 2.3. Water fluoride

At enrollment, women received detailed instructions and materials to collect tap-water samples from their kitchen faucet (Karagas et al., 2000). If water filters were used, then one filtered and one unfiltered sample was requested. Water samples were analyzed for fluoride using a fluoride ion-selective electrode (Martínez-Mier et al., 2011), with an LoD of 0.02 mg/L.

At enrollment, women were asked: "Overall, what percentage of the water you use for drinking and cooking comes from your home tap water?". Seventeen women reported "never," and were excluded from the water analyses. For quality control purposes, duplicate samples were analyzed (n = 64; r = 0.97) to ensure reliability; the average water fluoride concentration was used for these participants. When both filtered and unfiltered samples were available (n = 42), filtered values were used (assuming these values more likely reflected their actual intake); when two filtered samples were provided (n = 3), their values were averaged.

### 2.4. Outcomes

Children's social-emotional and behavioural functioning was assessed using the *Behavior Assessment System for Children, Second*

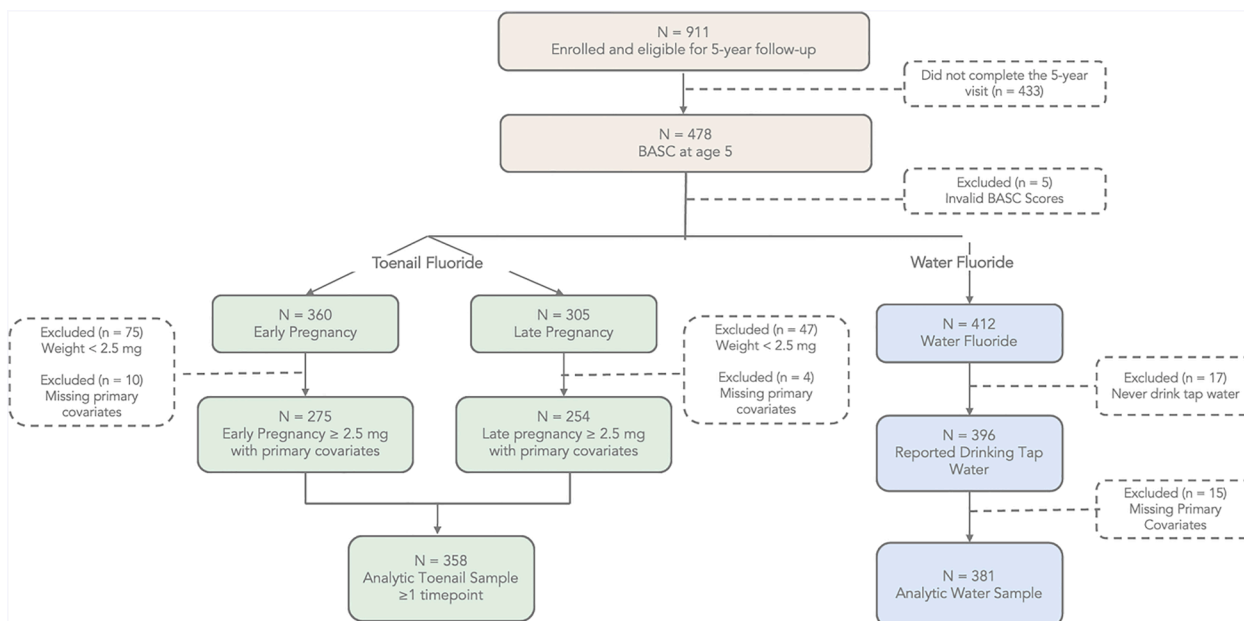


Fig. 1. Flow diagram of participant selection and analytic sample.

*Edition-Parent Rating Scale Preschool Form (BASC-2 PRS-P)* (Reynolds and Kamphaus, 2004). The BASC-2 includes eight clinical scales of maladaptive behaviours. These scales are used to generate composite behaviour measures (Reynolds and Kamphaus, 2004): the Behavioural Symptoms Index (derived from the Aggression, Attention Problems, Atypicality, Depression, Hyperactivity, Withdrawal scales), Externalizing Problems (derived from the Aggression and Hyperactivity scales), and Internalizing Problems (derived from the Anxiety, Depression, and Somatization scales). The scales and composites are age-standardized using T-scores, with a mean of 50 and a standard deviation of 10. Higher scores on the maladaptive scales and composites indicate more problematic behaviour, with T-scores  $\geq 60$  considered at-risk. Participants were excluded from the analyses if any of the BASC-2 validity indices were scored as “extreme caution” ( $n = 5$ ) (Reynolds and Kamphaus, 2004). The analyses focused on the age-5 assessment because ADHD-relevant behaviours, including those captured by the BASC Hyperactivity and Attention subscales, become more predictively valid for later clinical outcomes from approximately age 4 onward.

## 2.5. Potential covariates

A directed acyclic graph (DAG) was created to facilitate the selection of covariates (Supplemental Figure 1). We considered maternal age at enrollment, maternal education, child sex assigned at birth, recruitment clinic location, household income during pregnancy, maternal marital status, maternal smoking and alcohol consumption during pregnancy, prenatal dietary quality (alternate Healthy Eating Index [AHEI-2010]) (Chiuve et al., 2012), pre-pregnancy body mass index (BMI), parity, maternal depressive symptoms (Beck Depression Inventory, 2<sup>nd</sup> edition (Beck et al., 1996)), breastfeeding duration, maternal race/ethnicity, parenting quality (Parenting Relationship Questionnaire [PRQ], measuring attachment, discipline practices, involvement, parenting confidence, and relational frustration (Rubinic and Schwickrath, 2010)), maternal intelligence (Kaufman Brief Intelligence Test, Second Edition (Kaufman, 2004)), and home environment quality [Home Observation for Measurement of the Environment Short Form (HOME-SF) (Mott, 2004)].

Additional covariates considered include gestational age, birth weight, and concentrations of As, Pb, Cd, and Zn in toenails collected at 28 weeks’ gestation and 5 weeks’ postpartum and measured by

inductively coupled plasma mass spectrometry (Agilent 7900x; detection limits: As and Pb, 0.02  $\mu\text{g/g}$ ; Cd, 0.005  $\mu\text{g/g}$ ; Zn, 5.0  $\mu\text{g/g}$  (Doherty et al., 2020; White et al., 2018); values below the LoD imputed as  $\text{LoD}/\sqrt{2}$ ).

## 2.6. Statistical analyses

The preregistration is available at <https://osf.io/4reuh/>. Deviations from the analytic plan are detailed alongside the plan and in Appendix A. The overall modeling strategy was to use the composite BASC-2 scores as primary outcomes due to their better psychometric properties compared with clinical scales (Reynolds and Kamphaus, 2004) and the BASC-2 clinical (subscales) as secondary outcomes.

In primary analyses, generalized estimating equations (GEE) were applied with an independent correlation structure (Farmus et al., 2021) to estimate associations between maternal toenail fluoride concentrations reflecting early- and late-pregnancy exposures, and BASC-2 composite scores, modeled dichotomously ( $T \geq 60$ , at-risk). According to the DAG, the minimum sufficient set of covariates to avoid overadjustment bias (Schisterman et al., 2009) – the primary covariates – included maternal age at enrollment, maternal education, child sex assigned at birth, and study site. These covariates were selected a priori from the full set of covariates. Each model included a main effect for toenail fluoride (per 1- $\mu\text{g/g}$  increase), a two-way interaction between exposure window and fluoride concentration, a two-way interaction between sex and exposure window, a two-way interaction between sex and fluoride concentration, and a three-way interaction between sex, exposure window, and fluoride concentration. Interaction terms were included in the model regardless of their statistical significance to provide estimates by exposure window and sex in keeping with the study hypotheses. Multiple logistic regression were used to assess associations between water fluoride concentrations and BASC-2 composite outcomes, including effect modification by child sex.

Secondary analyses used GEE to estimate covariate-adjusted associations between maternal toenail fluoride concentrations reflecting early- and late-pregnancy exposures, and the individual BASC-2 clinical scores, modeled dichotomously ( $T \geq 60$ , at-risk). Secondary analyses also used multiple logistic regression to assess associations between water fluoride concentrations and individual BASC-2 clinical scores.

In sensitivity analyses, multiple logistic regression were used to

estimate unadjusted, primary covariate-adjusted, and secondary covariate-adjusted associations between toenail fluoride concentrations at each time point and social-emotional and behavioural outcomes. Secondary covariates were from the remaining covariates considered in the DAG and retained if  $p < .20$  or if inclusion altered the fluoride coefficient by  $> 10\%$ . Retained secondary covariates included parity, maternal depression, HOME-SF score, household income, and PRQ subscales (attachment, involvement, parenting confidence, relational frustration). Sensitivity analyses were also performed using multiple imputation by chained equations for missing toenail data ( $n = 45\%$  overall;  $n = 14\%$  due to sample weight  $< 2.5$ ) and covariates ( $n = 6\%$ ). The imputed datasets were analyzed with multiple logistic regression models adjusted for primary covariates. Furthermore, sensitivity analyses were run with logistic regression models adding, one-at-a-time, gestational age, birth weight, and toenail concentrations of As, Pb, Cd, and Zn to the minimum (primary) set of covariates. Further sensitivity analyses were conducted with the outcomes modelled as continuous.

Standard errors for all analyses were derived from the regression models using default model-based (maximum likelihood) estimators—logistic regression for dichotomous outcomes and linear regression for continuous outcomes. Across all models, regression diagnostics were assessed as appropriate for the type of model (normality of errors, variance inflation factors, residual plots, nonlinearity checks, and influential observations) and no violations of regression assumptions were observed. In additional sensitivity analyses, analyses were run removing any potential influential observations, defined as those exceeding an absolute DFBETAS threshold of 0.2 for the toenail fluoride coefficient (Harrell, 2015). Statistical significance for main effects was set at  $p < .05$ , and interaction terms were set at  $p < .10$ . Analyses were conducted in R (version 4.4.3) and Stata/SE 18.5.

### 3. Results

The sample included 358 mother-child pairs with maternal toenail data and 381 mother-child pairs with water fluoride data. A majority of mothers reported white race (97%), a college-education (71%), being married (89%), and incomes greater than the average U.S. household ( $\sim \$50,000$ ) (U.S. Census Bureau, 2010 and 2011, 2012) (68%). The mean (SD) maternal age was 31.6 (4.8) years. Most women were non-smokers, did not drink alcohol during pregnancy, and reported low depressive symptoms. Approximately half of the children were male (51%) and were breastfed for a mean (SD) of 9.9 (8.1) months (Table 1). Baseline characteristics were similar between participants with  $\geq 2.5$  mg early-pregnancy and late-pregnancy toenail samples and those excluded due to insufficient mass ( $< 2.5$  mg, Supplementary Tables 1–2). Among the eligible  $N = 911$  participants (Figure 1), we compared key demographic and neonatal characteristics according to whether the BASC-2 was completed at age 5. Mothers of children who completed the BASC-2 were, on average, slightly younger (30.6 vs. 31.6 years) and less educated (62% vs. 70% college graduates), and were less likely to be married (81% vs. 86%). The groups did not differ with respect to maternal race, BMI, smoking, birthweight, gestational age, or infant sex.

Most children scored near the normative mean across both composites and clinical scales; 6% to 28% scored in the “at-risk” range or higher ( $T \geq 60$ ), depending on the scale; 7% scored in the “at-risk” range for the Behaviour Symptoms Index, 6% for the Externalizing Index, and 16% for the Internalizing Index (Supplemental Table 3).

#### 3.1. Fluoride measurements

Toenails were collected at a mean (SD) 28 (4) weeks’ gestation and 5 (5) weeks postpartum. Median (IQR) toenail fluoride concentrations reflecting early- and late-pregnancy exposures as well as water fluoride levels were 2.78 (1.92)  $\mu\text{g/g}$ , 2.15 (1.41)  $\mu\text{g/g}$ , and 0.20 (0.40)  $\text{mg/L}$ , respectively. Spearman rank correlations showed significant positive associations among toenail and water measures, ranging between 0.26

**Table 1**

Demographic characteristics of study participants ( $N = 358$ ).

| Demographic Characteristi           | Toenail Fluoride Sample<br>N = 358 | Water Fluoride Sample<br>N = 381 |
|-------------------------------------|------------------------------------|----------------------------------|
| Continuous variables, mean $\pm$ SD |                                    |                                  |
| Maternal age, y                     | 31.6 $\pm$ 4.8                     | 31.8 $\pm$ 4.67                  |
| Maternal IQ                         | 104.5 $\pm$ 11.5                   | 104.6 $\pm$ 11.5                 |
| Pre-pregnancy BMI, $\text{kg/m}^2$  | 26.0 $\pm$ 5.5                     | 26.1 $\pm$ 5.7                   |
| AHEI diet quality score             | 55.6 $\pm$ 11.8                    | 55.5 $\pm$ 11.6                  |
| Beck Depression Inventory (BDI-II)  | 6.4 $\pm$ 6.7                      | 6.3 $\pm$ 6.5                    |
| HOME-SF total score                 | 14.9 $\pm$ 1.1                     | 15.0 $\pm$ 1.1                   |
| Child breastfeeding duration, mo    | 9.9 $\pm$ 8.1                      | 10.0 $\pm$ 8.2                   |
| PRQ subscales                       |                                    |                                  |
| Attachment                          | 55.0 $\pm$ 8.2                     | 55.4 $\pm$ 8.0                   |
| Discipline                          | 47.4 $\pm$ 11.1                    | 47.4 $\pm$ 10.8                  |
| Parenting confidence                | 56.9 $\pm$ 9.6                     | 53.4 $\pm$ 8.4                   |
| Involvement                         | 50.4 $\pm$ 8.8                     | 56.9 $\pm$ 9.4                   |
| Relational frustration              | 53.2 $\pm$ 8.6                     | 50.3 $\pm$ 8.8                   |
| Categorical variables, n (%)        |                                    |                                  |
| Maternal education                  |                                    |                                  |
| $\geq$ College graduate             | 253 (70.7)                         | 273 (71.7)                       |
| $<$ College graduate                | 105 (29.3)                         | 108 (28.4)                       |
| Study site                          |                                    |                                  |
| Lebanon, NH                         | 87 (24.3)                          | 96 (25.2)                        |
| Concord, NH                         | 271 (75.7)                         | 285 (74.8)                       |
| Child sex                           |                                    |                                  |
| Male                                | 183 (51.1)                         | 196 (51.4)                       |
| Female                              | 175 (48.9)                         | 185 (48.6)                       |
| Household income                    |                                    |                                  |
| $<$ \$75 000                        | 103 (32.1)                         | 106 (31.3)                       |
| $\geq$ \$75 000                     | 218 (67.9)                         | 233 (68.7)                       |
| Maternal race                       |                                    |                                  |
| White                               | 348 (97.2)                         | 369 (97.1)                       |
| Other                               | 10 (2.8)                           | 11 (2.9)                         |
| Parity                              |                                    |                                  |
| 0 births                            | 152 (42.5)                         | 157 (41.2)                       |
| 1 birth                             | 133 (37.2)                         | 149 (39.1)                       |
| $\geq 2$ births                     | 73 (20.4)                          | 75 (19.7)                        |
| Marital status                      |                                    |                                  |
| Married                             | 320 (89.4)                         | 339 (89.0)                       |
| Single                              | 29 (8.1)                           | 32 (8.4)                         |
| Separated/divorced                  | 9 (2.5)                            | 10 (2.6)                         |
| Smoked during pregnancy             |                                    |                                  |
| Yes                                 | 18 (5.0)                           | 16 (4.2)                         |
| No                                  | 340 (95.0)                         | 363 (95.8)                       |
| Alcohol use during pregnancy        |                                    |                                  |
| Yes                                 | 62 (17.3)                          | 64 (16.8)                        |
| No                                  | 296 (82.7)                         | 316 (83.2)                       |

Abbreviations: AHEI, Alternate Healthy Eating Index; BMI, body mass index; BDI-II, Beck Depression Inventory II; HOME-SF, Home Observation for Measurement of the Environment–Short Form; PRQ, Parenting Relationship Questionnaire. Sample sizes for some variables are reduced due to missing data.

and 0.33 (Supplemental Table 4).

#### 3.2. Fluoride and social-emotional and behavioural outcomes

Each 1- $\mu\text{g/g}$  increase in toenail fluoride concentrations reflecting early pregnancy exposure was associated with higher odds of scoring in the “at-risk” range for Externalizing Problems ( $\text{OR} = 1.39$ , 95% CI, 1.15–1.67,  $P = .001$ ). For late-pregnancy fluoride, the point estimate was similar, although the confidence interval was wider and included one ( $\text{OR} = 1.30$ , 95% CI, 0.99–1.71,  $P = .055$ ; Fig. 2). No statistically significant two- or three-way interactions involving sex, exposure window, and fluoride concentration were identified (Supplemental Table 5). Water fluoride concentration did not show statistically significant associations with the composite scales, and there were no significant interactions by sex (Table 2).

Regarding the individual clinical scales, each 1- $\mu\text{g/g}$  increase in toenail fluoride reflecting early pregnancy exposure was associated with

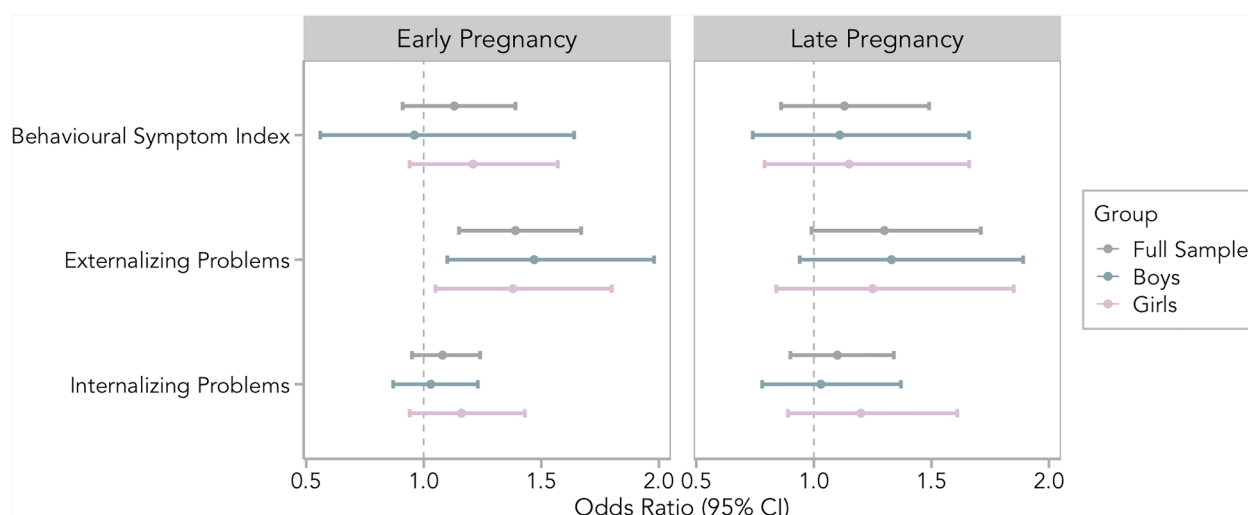


**Fig. 2.** Adjusted odds ratios (95% Confidence Intervals) from GEE models for BASC-2 composite scores per 1 µg/g increase in maternal toenail fluoride concentrations, by exposure window and child sex estimates from GEE models, adjusted for maternal age at enrollment, maternal education, child sex, and study site (N = 358). Outcomes are modeled dichotomously (T-score ≥ 60, at risk). Points represent odds ratios; horizontal lines indicate 95% confidence intervals. Dashed vertical line marks the null value (OR = 1).

**Table 2**

Adjusted odds ratios (95% CI) from multiple logistic regression models of BASC-2 composite scores per 1 mg/L increase in water fluoride concentration, by sex (N = 381).

| Outcome              | Full Sample                  | Boys                    | Girls                   | Sex <i>p</i> -int |
|----------------------|------------------------------|-------------------------|-------------------------|-------------------|
|                      | OR (95% CI), <i>p</i> -value |                         |                         |                   |
| <b>Composites</b>    |                              |                         |                         |                   |
| Behavioural Symptoms | 0.99 (0.69, 1.43), .975      | 1.08 (0.71, 1.64), .707 | 0.92 (0.54, 1.55), .739 | .620              |
| Externalizing        | 1.12 (0.84, 1.50), .447      | 1.24 (0.92, 1.67), .162 | 0.89 (0.47, 1.66), .705 | .345              |
| Internalizing        | 1.00 (0.78, 1.28), .997      | 1.03 (0.76, 1.41), .847 | 0.96 (0.65, 1.41), .831 | .773              |

Abbreviations: CI, confidence interval; *p*-int, *P* value for interaction. Model covariates: maternal age; maternal education; child sex; study site. Sex *p*-int for sex × fluoride interaction.

higher odds of scoring in the “at-risk” range for Hyperactivity (OR = 1.20, 95% CI, 1.01–1.43, *P* = .04). For late-pregnancy fluoride, estimates were imprecise but suggested elevated odds of Hyperactivity (OR = 1.24, 95% CI, 0.97–1.58, *P* = .09). There was also a statistically significant sex difference in the association of fluoride with Depression (sex *p*-interaction = .04): among girls, each 1 µg/g increase in toenail fluoride concentration reflecting early pregnancy exposure was associated with 1.37 higher odds of scoring in the “at-risk” range for Depression (95% CI 1.09–1.71, *P* = .006), whereas no association was observed in boys (OR = 0.99, 95% CI, 0.79–1.23, *p* = .90). Furthermore, there was a sex difference in the relation between late-pregnancy fluoride and both Anxiety and Withdrawal (*p*-interaction < .10), with increased but imprecise odds of being “at risk” in girls (respective OR = 1.24 and 1.35), but no association in boys (Supplemental Table 6).

No statistically significant differences in the association of toenail fluoride with outcomes by exposure window were found (Supplemental Tables 5 and 6). Water fluoride concentration did not show statistically significant associations with the clinical scales, and there were no significant interactions by sex (Supplemental Table 7).

### 3.3. Sensitivity analyses

As shown in Supplemental Fig. 2 and Supplemental Table 8, the results were similar across analysis strategies (using GEE or logistic

regression to assess dichotomous outcomes); covariate inclusion (unadjusted, adjusted for primary covariates or primary covariates plus birth weight, gestational age and metals); or when using multiple imputation of missing data. However, when the full set of secondary covariates was included, effect estimates for Externalizing Problems increased, although confidence intervals widened likely due to the decreased sample size. To evaluate whether these differences reflected sample restriction, post-hoc analyses controlling for primary covariates only were conducted among the subsample of participants with complete data on all secondary covariates. In these analyses, effect estimates for associations between toenail fluoride concentrations and behavioural composite scores were similar in magnitude to those from the primary models using the larger sample.

Across primary models, between 8 and 13 observations were identified as potentially influential. Sensitivity analyses excluding these observations preserved the direction and statistical significance of all primary findings (Supplemental Table 9).

When outcomes were modeled continuously, toenail fluoride concentrations reflecting early pregnancy exposure demonstrated positive associations with all the composite scores, not just Externalizing Problems, although only Internalizing Problems reached statistical significance (Supplemental Tables 10 and 11).

## 4. Discussion

This study examined the association between prenatal fluoride exposure and social-emotional and behavioural outcomes in preschool-aged children in the NHBCS. The results demonstrated that prenatal fluoride concentrations in maternal toenails, but not water fluoride concentrations, were associated with higher odds of scoring in the “at-risk” range for externalizing problems, primarily driven by hyperactivity. Associations were consistent for both early- and late-pregnancy, suggesting that there is not a specific vulnerable window in pregnancy. No significant associations were observed for other behavioural composites, or with water fluoride concentrations, with no apparent differences by sex or exposure window for the behavioural composites.

These findings should be understood in the context of previous prospective epidemiological studies, which have produced mixed results. In Mexico, higher maternal urinary fluoride across trimesters was associated with more ADHD-like symptoms in children aged 6–12 (Bashash et al., 2018). Similarly, in Los Angeles, higher maternal urinary fluoride in the third trimester roughly doubled the odds that 3-year-

olds would score in the borderline/clinical range for total problems (Malin et al., 2024). A cohort in Sweden also found that higher maternal urinary fluoride exposure in the third trimester was associated with increased externalizing problems and ADHD raw scores at age 4 (Kampouri et al., 2024). In contrast, in Spain, higher maternal urinary fluoride across pregnancy was unrelated to externalizing or internalizing behaviours in children aged 8 and 11 (Ibarluzea et al., 2025). Similarly, in an Australian cohort, percent-lifetime exposure to fluoridated water (categorized as 0%, between 0 and 100%, or 100% from birth to age 5) was not significantly related to behavioural outcomes at ages 5 to 14 (Do et al., 2023).

The observed associations between prenatal toenail fluoride and at-risk externalizing problems should also be interpreted within the broader context of the prenatal environmental exposome, as fluoride is one of many environmental factors hypothesized to influence early neurobehavioral development. Prenatal exposure to metals and endocrine-disrupting chemicals, have been associated with externalizing and attention-related outcomes in prospective cohorts (Tien et al., 2020), and these exposures may co-occur with fluoride. Although a subset of these co-exposures was addressed through sensitivity analyses adjusting for prenatal metals, which did not materially alter the primary toenail fluoride associations, comprehensive measurement and joint modeling of the prenatal exposome were beyond the scope of this study. Therefore, residual confounding from unmeasured environmental co-exposures cannot be excluded, underscoring the need for harmonized multi-cohort and exposome-wide approaches in future research.

The results also demonstrated an association between early-pregnancy fluoride exposure and scoring in the “at risk” range for depression in girls. This is consistent with findings from the Los Angeles cohort which found higher third-trimester maternal urinary fluoride was associated with greater odds of borderline or clinically significant internalizing scores in 3-year-olds (Malin et al., 2024). Although studies of prenatal fluoride exposure have reported stronger associations among boys for neurodevelopmental outcomes such as IQ, fewer studies have examined sex-specific patterns for internalizing symptoms. Future research should continue to explore potential sex-specific effects of prenatal fluoride exposure across a broader range of neurodevelopmental and mental health outcomes. Importantly, depressive symptoms and externalizing behaviours may arise from shared trans-diagnostic processes, including emotion dysregulation and overlapping developmental pathways. (Carbonneau et al., 2024).

Fluoride may disrupt the thyroid axis (Ferreira et al., 2024; Griebel-Thompson et al., 2023; Hall et al., 2023, 2024), a concern in pregnancy because the fetus depends entirely on maternal thyroid hormones during the first trimester and, to a lesser extent, thereafter (Morreale De Escobar et al., 2004; Zoeller and Rovet, 2004). Even mild maternal thyroid dysfunction has been linked to both internalizing and externalizing problems in children (Endendijk et al., 2017; Fetene et al., 2017; Kampouri et al., 2019; Modesto et al., 2015). Prenatal fluoride exposure has also been shown to induce oxidative stress in both animal and human studies (Bartos et al., 2018; Basha and Madhusudhan, 2010; Ferreira et al., 2021; Souza-Monteiro et al., 2022; Tuomivaara et al., 2024), a biologic pathway associated with social-emotional and behavioural problems in children (Pham et al., 2023; Rommel et al., 2020). Evidence suggests that low iodine, which is an essential nutrient for thyroid hormone synthesis and supporting normal thyroid functioning more broadly, may exacerbate effects of fluoride (Goodman et al., 2022). Emerging evidence further suggests that thyroid regulation and oxidative stress responses may differ by fetal sex (Baksi and Pradhan, 2021; Batista and Hensch, 2019; Faria et al., 2025; Minghetti et al., 2013), although it remains unclear whether these differences confer greater vulnerability in girls or boys. Such sex-specific biological responses to prenatal exposures could nonetheless contribute to the differing patterns of internalizing and externalizing outcomes observed across studies. The effects of fluoride on these biological pathways may help explain the pattern of associations observed across externalizing

and internalizing domains and highlight the importance of future investigation into mechanisms by which prenatal fluoride exposure might impact neurodevelopment.

Water fluoride concentrations were not associated with any social-emotional or behavioural outcomes. Toenail fluoride is an *integrative* biomarker capturing total intake from all sources, including diet, whereas water fluoride captures one (stable but partial) exposure pathway and, we did not evaluate individualized data on water consumption volume in this analysis. Although women who reported never drinking tap water were excluded, participants in this sample may have reduced their intake if they were notified during the course of the study that the arsenic levels in their water exceeded 10 µg/L (He et al., 2018). Since water fluoride does not capture total exposure from other sources (e.g., beverages, diet, and dental products), which vary across individuals, this may result in exposure misclassification that can bias associations toward the null.

While median household water fluoride concentration in the sample (0.19 mg/L) is similar to other communities in the U.S. with naturally occurring fluoride (McMahon et al., 2020), we did observe a large range (0.02–13.80 mg/L). Furthermore, analyses of first-trimester spot urines from participants in the NHBCS (Tamayo-Cabeza et al., 2026b) found a median (IQR) maternal urinary fluoride concentration of 0.39 (0.38) mg/L, which is lower than levels reported in previous studies examining fluoride and behaviour (0.55–0.85 mg/L) (Bashash et al., 2018; Ibarluzea et al., 2023; Kampouri et al., 2024; Malin et al., 2024). In the same analyses (Tamayo-Cabeza et al., 2026b), average maternal toenail fluoride concentrations were correlated with water fluoride concentrations. This finding is consistent with the observed correlations between water fluoride concentrations and both toenail fluoride concentrations, supporting the use of toenail fluoride as a biomarker of longer-term fluoride exposure.

Moreover, while dichotomous analyses revealed associations between toenail fluoride and at-risk Externalizing Problems, Hyperactivity, and Depression. In continuous models, only Internalizing Problems and the Depression subscale reached statistical significance. These differences may reflect different interpretive frames. Continuous models detect subtle shifts in mean symptom levels within the normative range, whereas dichotomous analyses isolate the probability of crossing the clinically relevant threshold ( $T \geq 60$ ). Because most BASC-2 scores fall below 60, small exposure-related shifts can meaningfully increase the proportion of children exceeding the clinical cut-point without substantially altering mean scores. Further, the BASC-2 was developed and validated with established at-risk ( $T \geq 60$ ) and clinically significant ( $T \geq 70$ ) cutoffs as the psychometrically intended reference points for identifying children with clinically meaningful elevations.

#### 4.1. Strengths and limitations

**Strengths of this study** include the use of maternal toenails, a biomarker reflecting cumulative exposure over the preceding 3–6-months of exposure), measured at two timepoints in pregnancy; a well-characterized cohort with rich covariate data; and extensive sensitivity analyses that yielded consistent results. Effect estimates were larger in models adjusted for secondary covariate than models adjusted for primary covariates suggesting that residual confounding is likely to have biased results toward the null, and that our primary estimates may underestimate the true associations.

Several limitations warrant consideration. First, variability in toenail growth rates could cause exposure misclassification. Second, we did not measure postnatal fluoride exposure from diet (e.g., drinking water, formula prepared with fluoridated water), or from ingestion of fluoridated toothpaste. If prenatal and postnatal exposures are correlated, residual confounding is possible, and we cannot exclude the contribution of postnatal exposure to the observed associations. Third, selection into the analytic sample may have introduced bias, as mothers of children who completed the BASC-2 differed modestly on some

demographic characteristics. We adjusted for maternal age, education, and infant sex in all analyses, though we cannot exclude residual bias from unmeasured factors associated with both exposure and outcome. Fourth, participants were rural New England residents who were predominantly White and college-educated and who relied on private water systems. Whether these findings extend to populations with optimally fluoridated water, or to populations differing in demographic compositions, or in sociocultural contexts that shape both exposure and child development, requires further investigation. Fifth, although we tested multiple hypotheses, all analyses were specified a priori, and associations observed concentrated in the domains and directions hypothesized in advance. Finally, social-emotional and behavioural outcomes were assessed at a single preschool timepoint, and the small proportion of children in the at-risk range (e.g., 6% for Externalizing Problems) limited statistical power. Nevertheless, associations were robust across sensitivity analyses.

## 5. Future directions

Future work should continue evaluating maternal toenail fluoride as an integrative biomarker of prenatal fluoride exposure, given its ability to capture longer-term exposure windows. However, several methodological considerations are important for its use in future studies, including ensuring adequate sample mass, standardized cleaning and preparation procedures to minimize external contamination, and adjustment for factors that may influence nail growth and fluoride incorporation, such as maternal age and other biological characteristics. Given the novelty of toenail fluoride as a biomarker, further validation work is also needed to establish standardized reference ranges in pregnant populations. Maternal and infant toenails may also provide complementary exposure windows, with infant toenails potentially reflecting late-gestational exposure. Furthermore, more research is needed examining prenatal and postnatal exposures and how they may relate to different exposure pathways. Future studies should additionally explore emerging biomarkers, such as deciduous teeth, which may provide temporally resolved exposure histories spanning prenatal and early-childhood periods. Moreover, future research should examine the persistence and emergence of behavioural effects across development, including longitudinal assessment of outcomes from early childhood through later ages. Studies incorporating exposome-wide and mixture-based approaches are also needed to evaluate potential interactions between fluoride and co-occurring environmental exposures.

## 6. Conclusion

In conclusion, this study found that higher prenatal fluoride exposure, as measured in maternal toenails but not in household water concentrations, was associated with greater odds of at-risk externalizing problems, particularly hyperactivity, as well as depressive symptoms in girls at preschool age in a U.S.-based cohort relying on unregulated water. Although the demographic composition of the cohort limits generalizability, these findings contribute to the growing body of evidence on prenatal fluoride exposure and behavioural outcomes. Further research incorporating both individual-level biomarkers and population-level exposure measures, together with information on major fluoride sources (e.g., drinking water), is needed to clarify the relationship between prenatal fluoride exposure and child neurobehavioural development.

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## CRedit authorship contribution statement

**Carly V. Goodman:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Margaret R. Karagas:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization. **Janet L. Peacock:** Writing – review & editing, Validation, Methodology, Conceptualization. **Susan Korrick:** Writing – review & editing, Methodology, Investigation, Conceptualization. **David Flora:** Writing – review & editing, Validation, Methodology, Funding acquisition, Conceptualization. **Bruce Lanphear:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **E. Angeles Martinez-Mier:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Guillermo Tamayo-Cabeza:** Writing – review & editing, Resources, Conceptualization. **Frank Lippert:** Writing – review & editing, Resources. **Christine Till:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: E. Angeles Martinez-Mier reports a relationship with Caries Advisory Board for the Colgate-Palmolive Company that includes: board membership. E. Angeles Martinez-Mier reports a relationship with U.S. Environmental Protection Agency, the U.S. Centers for Disease Control and Prevention, and the Colombian Department of Health that includes: consulting or advisory. Christine Till reports a relationship with Health Research Board, Dublin, Ireland that includes: consulting or advisory. Bruce Lanphear served as an expert witness for the plaintiffs in a federal trial challenging water fluoridation against the U.S. Environmental Protection Agency (Food & Water Watch et al. v. United States Environmental Protection Agency et al., United States District Court for the Northern District of California). He received no payment for his service. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Supplementary materials

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## Data availability

The authors do not have permission to share data.

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