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# Prenatal and Childhood Exposure to Fluoride and Cognitive Development: Findings from the Longitudinal MINIMat Cohort in Rural Bangladesh

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**BACKGROUND:** There are indications that fluoride exposure considered to be beneficial for dental health may not be safe from a neurodevelopmental perspective.

**OBJECTIVE:** We assessed the impact of prenatal and childhood fluoride exposure on cognitive abilities at 5 and 10 years of age.

**METHODS:** We studied 500 mother–child pairs from the MINIMat (Maternal and Infant Nutrition Interventions in Matlab) birth cohort in rural Bangladesh. Urinary fluoride concentrations were measured in the pregnant women at gestational week 8 and in their children at 5 and 10 years of age using an ion-selective electrode and adjusting for specific gravity. Cognitive abilities were assessed using the Wechsler Preschool and Primary Scale for Intelligence, Third Edition, and the Wechsler Intelligence Scale, Fourth Edition, at 5 and 10 years of age, respectively. Associations of urinary fluoride concentrations ($\log_2$-transformed) with cognitive abilities (raw scores) were assessed with multivariable-adjusted linear or spline regression models. Water fluoride concentrations at the time of the follow-up of the children at 10 years of age were also measured.

**RESULTS:** Maternal urinary fluoride concentrations (median: 0.63 mg/L, 5th–95th percentiles: 0.26–1.41 mg/L) were inversely associated with full-scale raw scores at 5 and 10 years [*B* (95% confidence interval): −2.8 (−5.1, −0.6) and −4.9 (−8.0, −1.8), respectively, by exposure doubling]. In cross-sectional analysis at 10 years, child urinary fluoride (overall median: 0.66 mg/L, 5th–95th percentiles: 0.34–1.26 mg/L) above −0.47 on the $\log_2$-scale (corresponding to 0.72 mg/L) was inversely associated with full-scale raw scores [*B* (95% confidence interval): −12.1 (−21.2, −3.0)]. The association at 5 years of age was also negative but nonsignificant. For both prenatal and childhood exposure, associations were most noticeable with perceptual reasoning, but also verbal scores. The estimate for the association between urinary fluoride at 10 years of age and perceptual reasoning became 18% lower after adjustment for prenatal exposure. Inconsistent sex-specific differences were observed.

**CONCLUSION:** Urinary fluoride concentrations measured prenatally and during childhood (child urinary fluoride concentrations above −0.47 on the $\log_2$ scale, corresponding to 0.72 mg/L) were associated with lower cognitive abilities, especially perceptual reasoning and verbal abilities, in Bangladeshi children. https://doi.org/10.1289/EHP14534

## Introduction

Decades of studies support the use of fluoride to protect tooth enamel against dental caries,[1] and therefore fluoride is added to dental care products and in several locations to drinking water, table salt, or milk.[2] Conversely, elevated exposure has been associated with dental and skeletal fluorosis due to accumulation of fluoride in calcified tissue.[1,2] Since natural fluoride concentrations in drinking water vary considerably, the World Health Organization (WHO) has recommended an upper limit of fluoride in drinking water of 1.5 mg/L.[2] Fluoride is easily absorbed in the gastrointestinal tract and then rapidly excreted in urine, resulting in a short half-life of fluoride in plasma of about 6 h.[3] Though it may be influenced by the accumulated fluoride content in the bone, the fluoride concentration in urine is considered a useful biomarker of the total current exposure.[2,3]

Fluoride is easily transferred across the placenta to the fetus.[4] Emerging evidence from a number of cross-sectional studies and a few prospective mother–child cohorts indicates that early life fluoride exposure is linked to adverse neurodevelopmental effects.[4] Studies in Mexico City (ELEMENT cohort), where fluoride exposure originates mainly from fluoridated table salt and naturally occurring fluoride in drinking water, showed that urinary fluoride concentrations during pregnancy were inversely associated with general cognitive ability at 4 years of age ($n = 287$; McCarthy Scales of Children's Abilities) and with intelligence at 6–12 years of age ($n = 211$; Wechsler Abbreviated Scale of Intelligence).[5] Also, the estimated fluoride intake from diet and beverages, based on a food frequency questionnaire administered in the second and third trimester ($n = 103$; Mexican PROGRESS cohort), was inversely associated with cognitive abilities in 1- to 2-year-old boys, particularly impacting nonverbal abilities, but not in girls (Bayley Scales of Infant and Toddler Development, Third Edition).[6] Similarly, in a prospective study in Canada (MIREC cohort), where some participants lived in cities with community water fluoridation, increasing gestational urinary fluoride concentrations across the three trimesters ($n = 512$) were associated with lower intelligence in boys at 3–4 years of age, but not in girls (Wechsler Preschool and Primary Scale of Intelligence, Third Edition).[7] In addition, higher maternal reported fluoride intake from tap water and other water-based beverages (tea and coffee) during the first and third trimesters was associated with lower intelligence in both boys and girls.[7] Other prospective studies conducted in Spain, Denmark, and Sweden found no inverse association between gestational fluoride exposure and child cognitive outcomes.[8–10]

The Canadian MIREC study also found inverse associations of estimated fluoride intake through infant formula with child intelligence.[11] In an attempt to compare the impact of prenatal

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and childhood exposure in the MIREC cohort ($n = 596$), it was concluded that fluoride exposure prenatally and during infancy resulted in the most pronounced inverse associations with child cognition, especially performance intelligence, while weaker associations with early childhood exposure were observed.[12] In a study conducted in New Zealand, there were no significant differences in intelligence at 7, 9, 11, or 13 years of age in children living in areas with community water fluoridation (range: 0.7 mg/L to 1.0 mg/L) at preschool age compared to those who did not.[13] Although several other studies have reported an inverse association of childhood fluoride exposure with cognitive abilities, their findings are limited by small sample size, insufficient adjustment for potential confounders, or evaluation of childhood exposure only.[14] Thus, there is a need to further explore the impact of fluoride exposure across different windows of exposure on child development.

Therefore, the objective of this study was to assess the impact of prenatal and childhood fluoride exposure, measured through urinary concentrations, on cognitive abilities in boys and girls at 5 and 10 years of age in a longitudinal cohort in rural Bangladesh. There is a lack of information on fluoride concentrations in drinking water in Bangladesh, but a study measuring fluoride in 304 water samples from different areas and sources in Bangladesh reported concentrations ranging from 0.01 to 2.3 mg/L.[15] Therefore, we also measured the fluoride concentrations in drinking water samples collected at the 10-year-old study visit in a subset of the cohort study participants.

## Materials and Methods

### *Study Population*

This study was based on a mother–child cohort[16–19] nested in a community-based randomized controlled trial [Maternal and Infant Nutrition Interventions in Matlab (MINIMat trial); registration number ISRCTN16581394]. The MINIMat trial was conducted in Matlab, a rural subdistrict in Bangladesh, about 57 km southeast of the capital Dhaka, with the overarching objective to assess effects of prenatal food and multiple micronutrient supplementation on gestational and child health.[20] The trial enrolled 4,436 pregnant women from November 2001 through October 2003, and this resulted in 3,625 live births. The pregnant women were randomly allocated to receive one of two food supplementations and one of three different multiple micronutrient supplementations.[20] The food supplementation was initiated either directly after recruitment (around gestational week 9) or during the usual care invitation at gestational week 20. The micronutrient supplementation was initiated at gestational week 14 and consisted of the following: *a*) 30 mg iron and 400 μg folic acid, *b*) 60 mg iron and 400 μg folic acid, or *c*) the United Nations Children's Fund (UNICEF)/WHO/ United Nations University (UNU) preparation with 15 micronutrients.[20]

The initial aim of the nested mother–child cohort was to assess the potential impact of elevated arsenic concentrations in drinking water[21] and, subsequently, the impact of other environmental toxicants and also nutrients on child health and development.[18,22] Singleton children born from May 2002 through December 2003 were invited to participate in the cognitive development assessment at 5 years of age ($n = 2{,}853$) and 2,260 children were assessed (Figure S1).[16] For the follow-up assessment of cognitive development at 10 years of age, we invited those who were born between October 2002 and December 2003 and were still registered as residents in the study area ($n = 1{,}607$), and 95% of them agreed to participate ($n = 1{,}530$).[18,22–24] For the present study on the association of urinary fluoride with child cognition at 5 and 10 years of age, we selected the first 500 tested children (born from October 2002 through May 2003) with urine samples collected both from the mothers during enrollment (median: gestational week 8) and from their children at 10 years of age (Figure S1). Since 423 of these 500 selected children also had urine samples collected at 5 years old, we decided to include urinary fluoride from the same children at 5 years of age. The prospective analyses of gestational urinary fluoride concentrations with outcomes at 10 years of age included all 500 children, and the models of outcomes at 5 years of age included 457 children [because of missing data in health observation for measurement of the environment (HOME) scores for 43 children]. Prospective models of child urinary fluoride concentrations at 5 years of age with outcomes at 10 years of age included 423 children (missing urine sample at 5 years of age for 77 children). Out of these, 388 were included in the cross-sectional analyses at 5 years of age (missing HOME scores for 35 children). The cross-sectional analyses at 10 years of age included all 500 children. Comparison of the included children ($n = 500$ and $n = 423$) with the remaining children born within the MINIMat trial ($n = 3{,}125$ and $n = 3{,}202$) suggested no major differences regarding maternal background characteristics, except for number of years of maternal education during pregnancy (4.1 vs. 5.2 years; $p < 0.001$) (Table S1).

The study has been approved by the research and ethical review committees at the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B) and the Regional Ethical Review Board in Stockholm, Sweden. The research has been conducted in accordance with the principles of the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki/). Both oral and written informed consent were obtained from the mother or other guardian at each follow-up, and participating families were informed that they could withdraw from the study at any time.

### *Exposure Assessment*

At the time of the routine monthly home visit by community health research workers, women with amenorrhea were invited to take a urinary pregnancy test, typically around gestational week 8. Upon confirmation of pregnancy, the women were asked to provide a spot urine sample (median: gestational week 8; range: 2.1–15 weeks) for measurements of arsenic,[21] which was later analyzed for other substances, including fluoride. Urine samples from the children were collected at the 5- and 10-year follow-up at the health clinics. In addition, drinking water samples were collected from all households at the 10-year follow up. To identify if drinking water could be a source of fluoride exposure, we randomly selected 100 out of the 500 studied children (20%) and measured the fluoride concentrations in their drinking water, which was almost exclusively from private wells. The drinking water samples were collected by trained community health workers in 20-mL trace element-free polyethylene containers from the source reported by the family during the home visit. Upon collection, the urine and water samples were immediately placed on ice in insulated boxes and transported within the same day to the Matlab hospital for storage at $-70°C$ until they were shipped on dry ice to Karolinska Institutet (KI), Sweden. At KI, the samples were stored at a minimum of $-40°C$ until analysis.

Urinary and water fluoride concentrations were measured using a fluoride-specific electrode (Orion 9609BNWP and Orion Star A214 pH/ISE meter; Thermo Fisher Scientific) according to the manufacturer's manual. An aliquot of 0.5 mL urine was diluted 1:1 with a total ionic strength adjustment buffer (TISAB II; Thermo Fisher Scientific) in 10-mL polypropene tubes (Sarstedt) and then vortexed. The external calibration curve was prepared daily through serial dilution from a 100-mg/L fluoride standard solution (Thermo Fisher Scientific) with adjustment buffer (50% TISAB II), and it ranged between 0.05 and 2 mg/L. The limit of detection (LOD) [mean blank value ($n = 13$) plus two times the standard deviation (SD)] of fluoride was 0.016–0.017 mg/L for maternal urine and child urine at 5 and 10 years and 0.012 mg/L for water at 10 years. No sample had a fluoride concentration below the respective LOD. As quality control, we measured the fluoride concentration in two commercial reference materials, fluoride in water (product number QC3162; Sigma-Aldrich; certified fluoride value: 0.420 mg/L) and Seronorm Trace Elements Urine L-2 (LOT 1706878; Sero AS; recommended analytical fluoride value: 4.0 mg/L), in the beginning, middle, and end of each run every day to assess reproducibility and accuracy (Table S2). In addition, following each run, the fluoride concentration in an in-house control urine sample was measured (mean ± SD fluoride concentration: $0.70 \pm 0.05$ mg/L), with an interday coefficient of variation (CV) of 7.1%.

To account for the variations in urinary dilution, the fluoride concentrations were adjusted to the median specific gravity (1.012 for both the mothers and their children), measured using a digital refractometer (EUROMEX RD712; Clinical Refractometer). The following formula was applied: adjusted urinary fluoride concentration = unadjusted urinary fluoride concentration × [(median specific gravity − 1)/(sample specific gravity − 1)].[25]

### Outcome Assessment

Child cognitive abilities at 5 years of age were measured using the Wechsler Preschool and Primary Scale for Intelligence, Third Edition (WPPSI-III), which provides full-scale, verbal, and performance scores.[26] Child cognitive abilities at 10 years of age were measured using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), which provides scores in full scale, verbal comprehension, perceptual reasoning, working memory, and processing speed.[27] Trained local psychologists (eight testers at the 5-year follow-up and five testers at the 10-year follow-up) tested the children in their native language at the health clinics. The procedures related to cognitive testing at 5 and 10 years of age have been described in detail elsewhere.[16,23,24] After a pilot study in 52 children from the study region, test materials were slightly modified to be culturally adapted to the population.[23] The modifications of the tests included replacement of images and questions that were unfamiliar to rural children, e.g., "Who was Columbus" to "Who was Rabindranath Tagore" as described in more detail elsewhere.[23] Raw scores represent the sum of correct responses to each test item and reflect performance without any adjustment to the norms of a general population. The raw scores were used to avoid potential biases that would arise from adjusting to scores obtained in western populations.[23]

### Potential Covariates

Information on maternal and family characteristics during the pregnancy period [maternal height (cm), weight (kg), age (years), parity (number of previously born children), level of education (years of formal schooling; continuous), and family's socioeconomic status (SES) (quintiles) were all collected at enrollment (median gestational week 8); food and micronutrient supplementation (two food groups and three micronutrient groups, resulting in a total of six groups), which the women were allocated to at gestational week 14] were collected within the MINIMat trial.[20,28] In cases of missing data or invalid data entry regarding basic characteristics such as maternal date of birth and education, data were collected from the health and demographic surveillance system (HDSS) in Matlab. The family SES was estimated via a wealth index, compiled from information on family asset ownership, e.g., consumer items, housing structure, and dwelling characteristics,[29] which was categorized into quintiles. Data on child and parental characteristics at the 5- and 10-year follow-up were either retrieved from the MINIMat database (child sex and age) or collected through various questionnaires [child education, type of school, maternal nonverbal reasoning (only at the 5-year follow-up), parental education, child HOME scores, and family SES (only at the 10-year follow-up using the same measurements as during pregnancy)] or clinical assessments (child weight and height). The information at 5 years included child sex (male/female), age (years), height (cm), weight (kg), level of education (number of months), school type (none, primary, Maktab, nonformal, kindergarten, or Madrasa), parental education (number of years of schooling), maternal nonverbal reasoning (scores; continuous), and HOME scores (health observation for measurement of the environment; continuous). Maternal nonverbal reasoning was evaluated using the combined Raven's Standard and Coloured Matrices (RSPM and RCPM).[16,30] The information at 10 years included child sex, age (years), height (cm), weight (kg), level of education (years), school type [public primary, Madrasa, English medium (private), or nongovernmental organization (NGO; nonprofit private)], parental education (number of years of schooling), family SES (quintiles), and HOME scores (continuous). The HOME instrument measures the quality and quantity of stimulation and support for the children at home.[31,32] We used a modified version of HOME at both 5 and 10 years of age.[16,22] We also considered season of maternal and child urine sampling [premonsoon (January–May), monsoon (June–September), and postmonsoon (October–December)].

Exposure to inorganic arsenic and cadmium and intake of iodine have previously been associated with child cognitive abilities in the MINIMat cohort[18,19,24] and were assessed by urinary concentrations adjusted for specific gravity for the mothers at gestational week 8 and for the children at 5 and 10 years of age. We also measured iodine concentrations in the water samples collected at the 10-year follow-up with inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7900; Agilent Technologies) as described in detail elsewhere.[33] The LOD (mean+3SD) was 0.6 μg/L, and no sample contained an iodine concentration below this LOD. Quality was ensured by inclusion of a reference material (Seronorm Trace Elements Urine L-2; LOT 1706878; Sero As) (Table S2). In addition, data on lead exposure, a well-known neurotoxicant, were available via measurements of maternal erythrocyte concentrations at gestational week 14, and child urinary concentrations at 5 and 10 years of age (adjusted for specific gravity).[34]

### Statistical Analysis

Statistical analyses were conducted using Stata/BE 17 (StataCorp LLC). $p$-Values below 0.05 were considered statistically significant for all tests, and we applied complete subject analysis (<10% missing data on children's urinary fluoride and HOME score at 5 years of age). Initially, we explored crude bivariate correlations of fluoride exposures (maternal and child urinary fluoride concentrations and water fluoride concentrations at visits with 10-year-old participants) with children's cognitive outcomes (5 years: full-scale, verbal comprehension, and performance raw scores; 10 years: full-scale, verbal comprehension, perceptual reasoning, working memory, and processing speed raw scores) or covariates, as well as the correlations of outcomes with covariates, using nonparametric tests (Spearman's rank correlation, Kruskal-Wallis, or Mann-Whitney $U$-test).

Univariate analyses indicated nonnormal distributions for the urinary fluoride concentrations of both mothers and children. To explore the linearity of our associations, we performed generalized additive models (GAMs) ($p$-gain <0.10 denotes statistical significance for nonlinearity) using both nontransformed and $\log_2$-transformed fluoride concentrations (Figures S2–S11). We chose to use $\log_2$ transformation to aid in the interpretation of the regression coefficients, i.e., mean change in outcome associated with a doubling of the exposure. The GAMs for the associations of nontransformed fluoride concentrations with the outcomes (Figures S2–S6) indicated both skewed urinary fluoride concentrations and nonlinearity for several associations. On the contrary, GAMs modeling associations of $\log_2$-transformed maternal urinary fluoride concentrations during early pregnancy and child urinary fluoride concentrations at 5 years with cognitive outcomes at 5 and 10 years of age had minimal influence of higher exposure levels and appeared linear (Figure S7–S10) ($p$-gain: 0.077–0.510). Similarly, the GAMs for the cross-sectional associations of $\log_2$-transformed child urinary fluoride concentrations with raw scores of working memory and processing speed at 10 years of age did not indicate nonlinearity (Figure S11). Thus, we took the decision to model these associations in linear regression models with $\log_2$-transformed fluoride concentrations. Conversely, nonlinear associations were still indicated for child urinary fluoride concentrations at 10 years with raw scores of full-scale, verbal comprehension, and perceptual reasoning at 10 years ($p$-gain <0.10) (Figure S11). Thus, spline regression models were applied with a spline knot at $-0.47$ on the $\log_2$ scale (corresponding to 0.72 mg/L). The spline knot was selected visually based on the inflection points where the associations of $\log_2$-transformed urinary fluoride with cognitive outcomes became inverse in the GAM plots.

To identify potential confounders, a directed acyclic graph (DAG) (Figure S7) was constructed based on previous knowledge and correlations of exposures and outcomes with covariates (Tables S3 and S4) using DAGitty version 3.0.[35] We present both unadjusted and adjusted models for all exposures and outcomes. In the adjusted model, we controlled for child sex (male, female), child age (years), testers of cognitive development (eight testers at the 5-year follow-up divided into three groups and five testers at the 10-year follow-up divided into four groups, due to the low number of children assessed by some of the testers), child height-for-age $z$-score (HAZ) (an important cognitive development predictor in populations with high stunting prevalence[36]) at 5 or 10 years (continuous), and HOME scores at 5 or 10 years (continuous), which were all selected *a priori*, as well as family SES at enrollment or 10 years (quintiles), maternal education at 5 or 10 years (years; continuous), maternal nonverbal reasoning at the time of the 5-year follow-up (raw scores; continuous), and parity at enrollment or 10-year follow-up (number of children; continuous), which were suggested to be in the minimally sufficient adjustment set established through the DAG. We did not observe any indication of multicollinearity in any of the models [variation inflation factor (VIF) <5]. Comprehensive post-estimation diagnostics (p and q norm plots, residual vs. fitted plots, heteroskedasticity, Akaike information criterion) demonstrated a good fit of the models. As previous studies have reported that associations of early life fluoride exposure with cognitive abilities may differ by child sex,[6,7,12] we assessed modifications by sex by including a multiplicative interaction term [sex × urinary fluoride concentration; ($\log_2$-transformed)] in the main adjusted models. We also stratified all models by child sex.

In sensitivity analyses, the adjusted models were additionally adjusted for exposure to several toxic pollutants, including concentrations of arsenic in urine (reflecting inorganic arsenic exposure) in early pregnancy or at 5 and 10 years, cadmium in maternal or child urine, and lead in maternal erythrocytes or child urine, all of which have previously been shown to lower children's cognitive abilities.[17,18,37] Also, previous studies have reported interactions between low iodine intake and fluoride exposure in relation to child cognition,[38] and therefore, we additionally adjusted the main models for urinary iodine concentrations at the time of the exposure (prenatally or at 5 and 10 years of age). As indicated in the DAG, the season of sampling was not a true confounder (Figure S7). Nevertheless, we adjusted both the prenatal and childhood exposure models for season of urine sampling (premonsoon, monsoon, and postmonsoon) to account for potential differences in fluoride exposure due to varying water intake by seasonal temperature variation. To investigate the effect of the MINIMat intervention for the women during pregnancy, the prenatal and childhood models were additionally adjusted for food and micronutrient supplementations (six groups). We also constructed a minimally adjusted model adjusting only for basic *a priori* selected factors (i.e., child sex and age and tester) and true confounders (correlated with exposure at any timepoint and outcome scores; i.e., parity, maternal education, and maternal nonverbal reasoning). Finally, to differentiate the impact of prenatal and childhood exposure, we adjusted the models of childhood urinary fluoride concentrations with cognitive abilities at 5 and 10 years of age for the maternal urinary fluoride concentrations in early pregnancy.

## Results

### *Participant Background Characteristics*

The background characteristics of the mothers and their children are presented in Table 1, and the distribution characteristics of the outcome are presented in Table 2. The mean age of mothers when they enrolled in the study was 26.6 years (range: 14.9–43.8 years). At the 5- and 10-year follow-up, 38% and 39%, respectively, of the women reported having more than 5 years of education. Fifty-four percent of the children were exclusively breastfed at 4 months. The mean child age at the time of the 5- and 10-year cognitive assessments were 5.35 years (range: 5.28–6.44) and 9.60 years (range: 9.43–10.11), respectively. Boys and girls made up similar proportions of the study sample (51% and 49%, respectively). At the 5-year follow-up, 80% of the children had attended school (range: 0–30 months), and at 10 years, the school attendance rate was 96%. Forty-one percent of the children were stunted at age 5 (according to WHO reference value of height-for-age $z$-score below $-2$), and 29% were stunted at age 10.

The median urinary fluoride concentration was similar in mothers and children [0.63 mg/L (range: 0.07–7.5) in mothers in early gestation, 0.62 mg/L (range: 0.11–3.6) in children at 5 years, and 0.66 mg/L (range: 0.08–2.8) in children at 10 years] (Table 3). Still, maternal and child urinary fluoride concentrations were only weakly correlated ($rho = 0.1$–$0.2$; $p < 0.01$) (Table S5). Maternal urinary fluoride concentrations in early gestation and child urinary fluoride concentrations at 5 and 10 years were moderately correlated ($rho = 0.30$–$0.55$; $p < 0.001$) with the fluoride concentrations in drinking water (median: 0.20 mg/L; range: 0.04–0.74 mg/L; $n = 100$) (Table S5), which was collected at the 10-year follow-up and came from wells for the majority of the participants (98%). Both maternal and child urinary fluoride concentrations were weakly positively correlated with their respective urinary iodine concentrations at gestational week 8, 5 years, and 10 years ($rho = 0.18$–$0.25$, $P < 0.001$) (Table S5). Maternal urinary fluoride concentrations showed a weak correlation with maternal urinary cadmium ($rho = 0.12$; $p = 0.003$) (Table S5), otherwise there were no significant correlations with urinary arsenic or cadmium. Child urinary fluoride concentrations were

**Table 1.** Main characteristics of the participating mother–child pairs of the MINIMat study, Matlab, Bangladesh.

| | $n$ or $n$ (%) | Mean ± SD[a] | Range |
|---|---|---|---|
| Maternal age at enrollment (y) | 500 | 26.6 ± 6.1 | 14.9–43.8 |
| Maternal BMI at GW 8 ($kg/m^2$) | 499[b] | 20.0 ± 2.4 | 14.4–29.6 |
| Parity at enrollment (no. of children) | 500 | 1.5 ± 1.4 | 0–7 |
| Parity at 10-year follow-up (no. of children) | 500 | 3.1 ± 1.1 | 1–7 |
| Family SES at enrollment [quintiles (%)] | 500 | — | — |
| Quintile 1 | 122 (24.4) | — | — |
| Quintile 2 | 120 (24) | — | — |
| Quintile 3 | 104 (20.8) | — | — |
| Quintile 4 | 87 (17.4) | — | — |
| Quintile 5 | 67 (13.4) | — | — |
| Family SES at 10-year follow-up [quintiles (%)] | 500 | — | — |
| Quintile 1 | 108 (21.6) | — | — |
| Quintile 2 | 116 (23.2) | — | — |
| Quintile 3 | 102 (20.4) | — | — |
| Quintile 4 | 80 (16) | — | — |
| Quintile 5 | 94 (18.8) | — | — |
| Maternal education at 5-year follow-up (y) | 500 | 4.2 ± 4.0 | 0–16 |
| Maternal education at 10-year follow-up (y) | 500 | 4.7 ± 3.7 | 0–16 |
| Maternal nonverbal reasoning (raw score) | 500 | 22.4 ± 10.9 | 0–65 |
| Food supplementation at gestation | 500 | — | — |
| Early food group (at around GW 9) | 252 (50.4) | — | — |
| Late food group (at around GW 20) | 248 (49.6) | — | — |
| Maternal micronutrients supplementation | 500 | — | — |
| Fe30F | 161 (32.2) | — | — |
| Fe60F | 178 (35.6) | — | — |
| Multiple micronutrients | 161 (32.2) | — | — |
| Exclusively breastfed at 4 months postpartum | 495[b] | — | — |
| No | 228 (46) | — | — |
| Yes | 267 (54) | — | — |
| Season of maternal urine sampling [categories (%)] | 500 | — | — |
| Premonsoon | 215 (43) | — | — |
| Monsoon | 258 (51.6) | — | — |
| Postmonsoon | 27 (5.4) | — | — |
| Child sex at 5-year follow-up (%) | 457 | — | — |
| Male | 229 (50.1) | — | — |
| Female | 228 (49.9) | — | — |
| Child age at 5-year follow-up (y) | 457 | 5.3 ± 0.1 | 5.3–6.4 |
| Child height at 5-year follow-up (cm) | 457 | 103.1 ± 4.6 | 90.4–120.6 |
| Child height-for-age at 5-year follow-up ($z$-score) | 457 | −1.6 ± 1.0 | −4.7–2.0 |
| Child weight at 5-year follow-up (kg) | 457 | 14.8 ± 1.7 | 10.1–23.1 |
| Child weight-for-age at 5-year follow-up ($z$-score) | 457 | −1.8 ± 0.9 | −4.7–1.5 |
| Child education at 5-year follow-up (months) | 366[b] | 5.8 ± 5.6 | 0–30 |
| School type at 5-year follow-up [categories (%)] | 457 | — | — |
| None | 91 (19.9) | — | — |
| Primary | 118 (25.8) | — | — |
| Maktab | 110 (24.1) | — | — |
| Nonformal | 91 (19.9) | — | — |
| Kindergarten | 26 (5.7) | — | — |
| Madrasa | 21 (4.6) | — | — |
| Season of urine sampling at 5 years [categories (%)] | 422[b] | — | — |
| Premonsoon | 318 (75.4) | — | — |
| Monsoon | 103 (24.4) | — | — |
| Postmonsoon | 1 (0.2) | — | — |
| HOME at 5 years (score) | 457 | 8.3 ± 4.9 | 0–25 |
| Child sex at 10-year follow-up (%) | 500 | — | — |
| Male | 255 (51) | — | — |
| Female | 245 (49) | — | — |
| Child age at 10-year follow-up (y) | 500 | 9.6 ± 0.1 | 9.4–10.1 |
| Child height at 10-year follow-up (cm) | 500 | 126.6 ± 6.2 | 108.1–149.6 |
| Child height-for-age at 10-year follow-up ($z$-score) | 500 | −1.5 ± 1.0 | −4.4–2.3 |
| Child weight at 10-year follow-up (kg) | 500 | 23.1 ± 3.6 | 15.1–40.4 |
| Child weight-for-age at 10-year follow-up ($z$-score) | 499[b] | −1.8 ± 1.0 | −4.7–1.7 |
| Child education at 10-year follow-up (y) | 500 | 3 ± 1 | 0–5 |
| School type at 10-year follow-up [categories (%)] | 497[b] | — | — |
| Public primary | 385 (77.5) | — | — |
| Madrasa | 55 (11.1) | — | — |
| English medium | 45 (9) | — | — |
| NGO | 12 (2.4) | — | — |
| Season of urine sampling at 10 years [categories (%)] | 500 | — | — |
| Premonsoon | 3 (0.6) | — | — |
| Monsoon | 384 (76.8) | — | — |
| Postmonsoon | 113 (22.6) | — | — |

Table 1. (*Continued.*)

| | *n* or *n* (%) | Mean ± SD[a] | Range |
|---|---|---|---|
| Main drinking water source at 10 years | 500 | — | — |
| Tubewell | 489 (97.8) | — | — |
| Other (i.e., surface water or rainwater) | 11 (2.2) | — | — |
| HOME at 10-year follow-up (scores) | 500 | 27 ± 5 | 14–44 |

Note: Maternal nonverbal reasoning (Raven's test; raw scores). —, not applicable; BMI, body mass index; Fe30F, 30 mg iron and 400 μg folic acid; Fe60F, 60 mg iron and 400 μg folic acid; GW, gestational week; HOME, quality of children's stimulation at home assessed through modified HOME Observation for Measurement of the Environment; MINIMat, Maternal and Infant Nutrition Interventions in Matlab; Multiple micronutrients, UNICEF/WHO/UNU preparation of 15 different micronutrients; NGO, nongovernmental organization; SD, standard deviation; SES, socioeconomic status assessed through a wealth index based on family ownership (quintiles).
[a]Mean ± SD is reported for continuous variables and % frequency for categorical variables, unless stated otherwise.
[b]Missing data: Maternal BMI at GW 8 ($kg/m^2$): $n = 1$; exclusively breastfed at 4 months postpartum: $n = 5$; child education at 5-year follow-up (months): $n = 91$ (maximum participants in analyses with outcome data at 5 years: $n = 457$); season of urine sampling at 5 years [categories (%)]: $n = 1$ (maximum participants with exposure data at 5 years: $n = 423$); HOME at 5 years (score): $n = 43$ (maximum participants with outcome data at 5 years: $n = 457$); child weight-for-age at 10-year follow-up (*z*-score): $n = 1$; school type at 10-year follow-up [categories (%)]: $n = 3$.

weakly correlated with their urinary lead concentrations ($rho = 0.20$ and 0.18, $p < 0.001$, at 5 and 10 years, respectively). The iodine concentrations in drinking water at age 10 (median: 52 μg/L) were moderately correlated with the fluoride concentration in drinking water at age 10 ($rho = 0.40$; $p < 0.001$) (Table S5).

### *Maternal Urinary Fluoride and Cognitive Abilities at 5 and 10 Years of Age*

In the adjusted analyses, the inverse associations of maternal urinary fluoride concentrations during pregnancy (median: 0.63 mg/L) with cognitive outcomes at 5 years of age were markedly strengthened compared to the unadjusted associations (Table 4). Maternal urinary fluoride concentrations were inversely associated with full-scale, verbal, and performance raw scores [*B* (95% confidence interval (CI): −2.8 (−5.1, −0.6), −1.4 (−2.6, −0.3), and −0.8 (−1.6, 0.1), respectively; per doubling of exposure]. The interaction between fluoride and child sex was not statistically significant ($p = 0.7$–$0.9$), and stratification by sex did not indicate any clear differences between boys and girls.

Associations of maternal urinary fluoride concentrations with cognitive abilities at 10 years of age were also markedly stronger in the adjusted than the unadjusted models (Table 4). Maternal urinary fluoride concentrations during pregnancy were inversely associated with full-scale raw scores [*B* (95% CI): −4.9 (−8.0, −1.8); per exposure doubling], mainly driven by lower perceptual reasoning raw scores [−2.4 (−3.5, −1.3); per doubling]. The interaction between fluoride and child sex was not significant in any of the models ($p = 0.2$–$0.7$), but after stratification by sex (Table 4), the inverse associations of maternal urinary fluoride concentrations with full-scale and perceptual reasoning raw scores appeared more pronounced in girls [*B* (95% CI): −7.3 (−12.2, −2.3) and −3.4 (−5.1, −1.7); per doubling of exposure] than in boys [−3.2 (−7.3, 0.9) and −1.4 (−2.9, 0.0); per doubling].

In sensitivity analysis, further adjustment for maternal urinary arsenic, cadmium, or iodine concentrations, season of urine sampling, or food and micronutrient supplementations resulted only in minor changes of the estimates (Tables S6 and S7). When additionally adjusting for maternal erythrocyte lead concentrations, the association of maternal fluoride with the full-scale raw scores at 5 years became moderately stronger (21%) (Table S6), while the association at 10 years was only marginally strengthened (Table S7). In sensitivity analyses with a simpler adjustment set, including only some basic *a priori* selected factors and true confounders, the estimates were slightly stronger at 5 and weaker at 10 years (Table S6 and S7).

Table 2. Distribution characteristics of children's cognitive abilities at 5 and 10 years of age in the MINIMat study, Matlab, Bangladesh.

| | *n* or *n* (%) | Mean ± SD | Range |
|---|---|---|---|
| WPPSI-III: full-scale raw score | 457 | 80 ± 25 | 5–180 |
| WPPSI-III: verbal scale raw score | 457 | 34 ± 12 | 0–74 |
| WPPSI-III: performance scale raw score | 457 | 34 ± 8 | 5–61 |
| Tester at 5-year follow-up [3 groups (%)][a] | 457 | — | — |
| 1 | 33 (7.2) | — | — |
| 2 | 265 (58.0) | — | — |
| 3 | 159 (34.8) | — | — |
| WISC-IV: full-scale raw score | 500 | 127 ± 35 | 9–267 |
| WISC-IV: verbal comprehension raw score | 500 | 35 ± 11 | 5–85 |
| WISC-IV: perceptual reasoning raw score | 500 | 30 ± 12 | 0–74 |
| WISC-IV: working memory raw score | 500 | 29 ± 6 | 4–43 |
| WISC-IV: processing speed raw score | 500 | 33 ± 12 | 0–70 |
| Tester at 10-year follow-up [4 groups (%)][a] | 500 | — | — |
| 1 | 144 (28.8) | — | — |
| 2 | 136 (27.2) | — | — |
| 3 | 132 (26.4) | — | — |
| 4 | 88 (17.6) | — | — |

Note: —, not applicable; MINIMat, Maternal and Infant Nutrition Interventions in Matlab; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.
[a]The 5-year testing was conducted by eight testers grouped in three groups, while the 10-year testing was conducted by five testers categorized in four groups, based both on the low number of children tested by some testers and on their scoring.

### *Children's Urinary Fluoride and Cognitive Abilities at 5 and 10 Years of Age*

In the cross-sectional analyses at 5 years, the children's urinary fluoride concentrations (median: 0.62 mg/L) were inversely associated with cognitive outcomes, but the associations were not statistically significant in the unadjusted or in the adjusted models (Table 5). The interaction with sex was not statistically significant in any of the models ($p = 0.4$–$0.9$). However, when models were stratified by sex, the inverse association with full-scale raw scores appeared more pronounced in girls [*B* (95% CI): −2.5 (−7.1, 2.0); per doubling] than in boys [−0.3 (−3.8, 3.2); per doubling], but none of the associations were statistically significant.

In the prospective analyses, associations of child urinary fluoride concentrations at 5 years with cognitive outcomes at 10 years were statistically nonsignificant in all models (Table 5). There was a significant interaction of fluoride with child sex for perceptual reasoning raw scores ($p = 0.009$), and the stratified analysis showed an inverse association for boys only [*B* (95% CI): −2.5 (−4.3, −0.6); per doubling]. Overall, when stratifying by sex, associations of urinary fluoride concentrations with all cognitive abilities were inverse in boys but positive in girls (Table 5), although not statistically significant.

In the cross-sectional analyses at 10 years, children's urinary fluoride concentrations ($log_2$-transformed) were nonlinearly associated

Table 3. Concentrations of fluoride and other toxicants in urine or blood (erythrocyte fraction) of women in early pregnancy and in their children at 5 ($n = 423$) and 10 ($n = 500$) years of age presented for all children and in boys and girls separately in the MINIMat study, Matlab, Bangladesh.

| Element concentrations | All children [median (5th–95th percentile)] | Boys [median (5th–95th percentile)] | Girls [median (5th–95th percentile)] |
|---|---|---|---|
| Urinary fluoride (mg/L)[a] | | | |
| Gestational week 8[a] | 0.63 (0.26–1.41) | 0.63 (0.29–1.51) | 0.62 (0.25–1.39) |
| Five years[a] | 0.62 (0.31–1.43) | 0.61 (0.31–1.44) | 0.63 (0.32–1.43) |
| Ten years[a] | 0.66 (0.34–1.26) | 0.67 (0.33–1.25) | 0.66 (0.34–1.26) |
| Urinary arsenic (μg/L)[a] | | | |
| Gestational week 8[a] | 100 (18–599) | 86 (18–611) | 107 (19–597) |
| Five years[a,b] | 51 (17–395) | 50 (18–403) | 54 (15–395) |
| Ten years[a] | 61 (19–429) | 64 (21–519) | 58 (17–400) |
| Urinary cadmium (μg/L)[a] | | | |
| Gestational week 8[a] | 0.6 (0.2–1.7) | 0.6 (0.2–1.7) | 0.6 (0.1–1.6) |
| Five years[a] | 0.2 (0.1–0.6) | 0.2 (0.1–0.6) | 0.2 (0.1–0.7) |
| Ten years[a] | 0.2 (0.1–0.6) | 0.2 (0.1–0.6) | 0.2 (0.1–0.7) |
| Erythrocyte or urinary lead | | | |
| Gestational week 14 [erythrocyte (μg/kg)][c] | 73.8 (40.6–153.4) | 72.7 (40.6–164.7) | 74.0 (40.7–144.6) |
| Five years [urinary (μg/L)][a,c] | 4.0 (1.6–11.2) | 3.8 (1.5–10.2) | 4.4 (1.6–12.0) |
| Ten years [urinary (μg/L)][a] | 1.5 (0.6–3.8) | 1.5 (0.6–3.6) | 1.5 (0.7–4.0) |
| Urinary iodine (μg/L) | | | |
| Gestational week 8[d] | 278 (37–1,473) | 258 (36–1,321) | 305 (38–1,497) |
| Gestational week 8, SG adjusted[a,d] | 318 (51–1,314) | 284 (48–1,304) | 334 (58–1,314) |
| Five years[d] | 383 (50–1,430) | 418 (53–1,520) | 348 (49–1,316) |
| Five years, SG adjusted[a,d] | 425 (109–1,139) | 420 (98–1,109) | 426 (121–1,176) |
| Ten years[d] | 340 (83–1,319) | 352 (94–1,380) | 327 (71–1,098) |
| Ten years, SG adjusted[a,d] | 332 (116–948) | 320 (126–904) | 340 (111–981) |

Note: Gestational week 8 (GW 8) (all children, $n = 500$; 255 boys and 245 girls), 5 years (all children, $n = 423$; 219 boys and 204 girls), 10 years (all children, $n = 500$; 255 boys and 245 girls). MINIMat, Maternal and Infant Nutrition Interventions in Matlab; SG, specific gravity.
[a]Adjusted for median specific gravity of 1.012.
[b]Total $n = 422$; 219 boys and 203 girls.
[c]GW 14 (total $n = 478$; 245 boys and 233 girls); 5 years (total $n = 494$; 252 boys and 242 girls).
[d]GW 8 (total $n = 496$; 252 boys and 244 girls); 5 years (total $n = 420$; 219 boys and 201 girls); 10 years (total $n = 499$; 255 boys and 244 girls).

with full-scale raw scores in both the unadjusted and adjusted models (Table 6). After covariate adjustment, the estimates became stronger and child urinary fluoride concentrations above −0.47 on the $\log_2$ scale (corresponding to 0.72 mg/L) were inversely associated with full-scale raw scores [$B$ (95% CI): −12.1 (−21.2, −3.0); per doubling], which was mainly driven by lower perceptual reasoning [−4.4 (−7.7, −1.1); per doubling] and verbal comprehension raw scores [−3.8 (−6.8, −0.8); per doubling], both of which were also evaluated nonlinearly. We did not observe any significant interaction with sex ($p = 0.3$–$0.9$) or differences between estimates for boys and girls in the stratified models (Table 6).

In sensitivity analysis, further adjustment for children's urinary arsenic, cadmium, or iodine concentrations, season of urine sampling, or food and micronutrient supplementation did not considerably change the estimates in the models mentioned above (Tables S8–S10). Further adjustment by child urinary lead concentrations, however, strengthened the cross sectional and prospective 5-year fluoride exposure estimates, but they were still not significant. Additional adjustment of the child fluoride exposure models (5 years) for the prenatal exposure changed the estimates to variable degrees, and all models remained nonsignificant (Table S11). In the cross-sectional models at 10 years, the additional adjustment for prenatal exposure resulted in <20% attenuation of the estimates (Table 7). After adjustment for prenatal exposure, child urinary fluoride concentrations had an inverse association with full-scale raw scores at 10 years of age [−10.5 (95% CI: −19.7, −1.4)], compared to the previously observed difference in raw scores [−12.1 (95% CI: −21.2, −3.0)]. When the associations were adjusted for the minimal adjustment set, including only some basic *a priori* selected factors and true confounders (Tables S8–S10), the estimates were weaker, but the associations observed in the main models remained robust.

## Discussion

In this longitudinal cohort study, urinary fluoride concentrations during both gestation and childhood were inversely associated with the measures of child cognition. Maternal urinary fluoride in early pregnancy was inversely associated with the children's cognitive scores both at 5 and 10 years of age, with no apparent threshold below which there was no effect. Similarly, the children's contemporary fluoride exposure at 10 years of age was inversely associated with cognition but only at urinary concentrations above −0.47 on the $\log_2$ scale (corresponding to 0.72 mg/L). Concerning the affected cognitive domains, both prenatal and childhood exposure appeared to predominantly affect perceptual reasoning and verbal comprehension. We did not observe any consistent sex differences.

The finding that maternal urinary fluoride concentrations in early pregnancy (median: 0.63 mg/L, range: 0.07–7.5 mg/L) were inversely associated with child cognition measured at 5 and 10 years of age is in accordance with results reported from other prospective cohort studies with similar exposure levels.[5,7,12,39] The ELEMENT study in Mexico reported that maternal urinary fluoride concentrations during pregnancy (median during pregnancy: 0.82–0.90 mg/L, range: 0.02–2.4 mg/L in two different evaluations; $n = 299$–$348$) were inversely associated with the children's intelligence scores at ages 4, 5, and 6–12 years.[5,39] In the Canadian MIREC study, maternal urinary fluoride concentrations (median across all trimesters: 0.41–0.44 mg/L, range: 0.06–2.5 mg/L; $n = 512$–$596$) were inversely associated with child intelligence at 3 to 4 years of age.[7,12] In line with the prospective studies from Canada and Mexico,[5,12] we also found that the prenatal fluoride exposure was associated primarily with perceptual reasoning, representing nonverbal reasoning, spatial processing, and visual motor skills at 10 years of age. Additionally, we found that the children's verbal skills (reasoning and comprehension) seemed to be impacted. This was also shown in the Mexican updated

**Table 4.** Linear regression of maternal urinary fluoride concentrations in early pregnancy (on average at gestational week 8) with their children's cognitive abilities at 5 and 10 years of age in the MINIMat study, Matlab, Bangladesh.

| | Maternal urinary fluoride in early pregnancy[a] [mg/L ($\log_2$-transformed)] | | | | | |
|---|---|---|---|---|---|---|
| | All children | | Boys | | Girls | |
| Outcomes | *B* (95% CI) | *p*-Value | *B* (95% CI) | *p*-Value | *B* (95% CI) | *p*-Value |
| Cognition at 5 years (WPPSI-III)[b] | *n* = 457 | — | *n* = 229 | — | *n* = 228 | — |
| Full-scale raw score | | | | | | |
| Unadjusted model | −0.2 (−3.1, 2.7) | 0.870 | 0.2 (−3.4, 3.8) | 0.906 | −0.8 (−5.5, 3.9) | 0.734 |
| Adjusted model | −2.8 (−5.1, −0.6) | 0.014 | −2.5 (−5.4, 0.3) | 0.083 | −2.8 (−6.5, 0.9) | 0.134 |
| *p*-Interaction[c] | — | 0.996 | — | — | — | — |
| Verbal-scale raw score | | | | | | |
| Unadjusted model | −0.3 (−1.7, 1.1) | 0.681 | −0.3 (−2.1, 1.4) | 0.718 | −0.2 (−2.4, 1.9) | 0.830 |
| Adjusted model | −1.4 (−2.6, −0.3) | 0.015 | −1.7 (−3.2, −0.2) | 0.029 | −1.1 (−3.0, 0.7) | 0.231 |
| *p*-Interaction[c] | — | 0.683 | — | — | — | — |
| Performance-scale raw score | | | | | | |
| Unadjusted model | −0.2 (−1.1, 0.8) | 0.728 | 0.0 (−1.2, 1.3) | 0.946 | −0.4 (−1.9, 1.1) | 0.568 |
| Adjusted model | −0.8 (−1.6, 0.1) | 0.076 | −0.6 (−1.7, 0.5) | 0.314 | −0.9 (−2.2, 0.4) | 0.190 |
| *p*-Interaction[c] | — | 0.768 | — | — | — | — |
| Cognition at 10 years (WISC-IV)[d] | *n* = 500 | — | *n* = 255 | — | *n* = 245 | — |
| Full-scale raw score | | | | | | |
| Unadjusted model | −2.8 (−6.7, 1.1) | 0.160 | −1.8 (−6.9, 3.3) | 0.492 | −4.1 (−10.1, 1.9) | 0.177 |
| Adjusted model | −4.9 (−8.0, −1.8) | 0.002 | −3.2 (−7.3, 0.9) | 0.121 | −7.3 (−12.2, −2.3) | 0.004 |
| *p*-Interaction[c] | — | 0.328 | — | — | — | — |
| Verbal comprehension raw score | | | | | | |
| Unadjusted model | −0.3 (−1.6, 1.0) | 0.635 | −0.2 (−1.9, 1.5) | 0.790 | −0.4 (−2.3, 1.5) | 0.670 |
| Adjusted model | −1.0 (−2.0, 0.0) | 0.059 | −0.9 (−2.2, 0.5) | 0.203 | −1.3 (−2.8, 0.3) | 0.119 |
| *p*-Interaction[c] | — | 0.577 | — | — | — | — |
| Perceptual reasoning raw score | | | | | | |
| Unadjusted model | −1.8 (−3.1, −0.5) | 0.006 | −1.3 (−3.0, 0.4) | 0.122 | −2.5 (−4.4, −0.5) | 0.014 |
| Adjusted model | −2.4 (−3.5, −1.3) | <0.001 | −1.4 (−2.9, 0.0) | 0.058 | −3.4 (−5.1, −1.7) | <0.001 |
| *p*-Interaction[c] | — | 0.187 | — | — | — | — |
| Working memory raw score | | | | | | |
| Unadjusted model | −0.2 (−0.9, 0.5) | 0.519 | −0.1 (−1.0, 0.8) | 0.841 | −0.4 (−1.5, 0.6) | 0.421 |
| Adjusted model | −0.5 (−1.1, 0.1) | 0.120 | −0.3 (−1.1, 0.5) | 0.433 | −0.9 (−1.8, 0.1) | 0.082 |
| *p*-Interaction[c] | — | 0.430 | — | — | — | — |
| Processing speed raw score | | | | | | |
| Unadjusted model | −0.4 (−1.8, 0.9) | 0.523 | −0.1 (−1.9, 1.6) | 0.882 | −0.8 (−2.9, 1.3) | 0.463 |
| Adjusted model | −1.1 (−2.3, 0.2) | 0.087 | −0.6 (−2.1, 1.0) | 0.477 | −1.7 (−3.7, 0.2) | 0.082 |
| *p*-Interaction[c] | — | 0.672 | — | — | — | — |

Note: —, not applicable; CI, confidence interval; HOME, health observation for measurement of the environment; MINIMat, Maternal and Infant Nutrition Interventions in Matlab; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.
[a]Urinary fluoride concentrations are adjusted to the median specific gravity of 1.012.
[b]Analyses of outcomes at 5 years (all children, *n* = 457; 229 boys and 228 girls); adjusted model for variables of child sex (male/female), child age (years), tester (three groups), family socioeconomic status at enrollment (quintiles), HOME scores at 5 years (continuous), parity at enrollment (continuous), maternal education at 5 years (continuous; years), maternal nonverbal reasoning at 5 years (continuous; raw score), and height-for-age *z*-score at 5 years (continuous).
[c]Addition of multiplicative interaction term, urinary fluoride ($\log_2$) × sex (boy = 1/girl = 2)] in the adjusted model.
[d]Analyses of outcomes at 10 years (all children, *n* = 500; 255 boys and 245 girls); adjusted model for variables for child sex (male/female), child age (years), tester (four groups), family socioeconomic status at enrollment (quintiles), HOME scores at 10 years (continuous), parity at 10 years (continuous), maternal education at 10 years (continuous; years), and maternal nonverbal reasoning at 5 years (continuous; raw score), and height-for-age *z*-score at 10 years (continuous).

ELEMENT study[39] but not in the Canadian MIREC study.[11] Also, a small ecological Chinese study (*n* = 99) observed lower verbal skills in children 8–12 years of age with dental fluorosis in comparison to a control group without dental fluorosis.[40] It can be speculated that the domain-specific neurotoxicity of fluoride varies across populations.

We also found that the children's contemporary fluoride exposure was inversely associated with their cognitive abilities at 10 years of age, although at higher exposure levels. Like with prenatal fluoride exposure, the association was mainly driven by lower scores of perceptual reasoning and verbal comprehension. A doubling of the exposure above 0.72 mg/L was associated with a decrease in full-scale raw score by 12, which corresponds to 0.35 standard deviation. Adjusting for the prenatal exposure decreased the full-scale estimate by about 13% only, suggesting a contribution of childhood exposure to the overall impact on child cognition. In our study, the correlation between maternal and child urinary fluoride was weak. To our knowledge, there is only one previous longitudinal study, based on the MIREC cohort, investigating the association with child cognition of both prenatal and childhood fluoride exposure. They found significant inverse associations of urinary fluoride concentrations during pregnancy, estimated infants' intake of fluoride, and children's urinary concentrations (median: 0.39 mg/L at 1.9–4.4 years) with performance intelligence quotient (IQ) at 3–4 years of age.[12] In a cross-sectional study of 2,886 Chinese children aged 7–13 years, like in our study, there was evidence of a threshold for the association of child urinary fluoride with intelligence at a concentration of 1.6 mg/L.[41] Another cross-sectional Chinese study reported that children (6–13 years of age, *n* = 709) in the fourth quartile of urinary fluoride had about 20% increased odds of developing dental fluorosis or having an IQ below 120 compared to children in the first quartile (overall range in urinary fluoride: 0.02–5.4 mg/L).[42]

Notably, we found no clear association of urinary fluoride at 5 years of age (median: 0.62 mg/L, range: 0.11–3.6 mg/L) with cognition, neither cross-sectionally nor at 10 years. Possibly, the shorter childhood exposure time at 5 years resulted in a milder impact on cognition than that at 10 years. Also, the fluoride concentration in a single spot urine sample at 5 years of age may be less reliable as an exposure biomarker than that in later childhood

**Table 5.** Linear regression of child urinary fluoride concentrations at 5 years with their cognitive abilities at 5 and 10 years of age in the MINIMat study, Matlab, Bangladesh.

| | Child urinary fluoride exposure at 5 years[a] [mg/L ($\log_2$-transformed)] | | | | | |
|---|---|---|---|---|---|---|
| | All children | | Boys | | Girls | |
| Outcomes | *B* (95% CI) | *p*-Value | *B* (95% CI) | *p*-Value | *B* (95% CI) | *p*-Value |
| Cognition at 5 years (WPPSI-III)[b] | $n=388$ | — | $n=200$ | — | $n=188$ | — |
| Full-scale raw score | | | | | | |
| Unadjusted model | −0.4 (−4.0, 3.2) | 0.829 | 0.2 (−4.4, 4.8) | 0.928 | −1.4 (−7.1, 4.3) | 0.636 |
| Adjusted model | −1.3 (−4.1, 1.4) | 0.338 | −0.3 (−3.8, 3.2) | 0.868 | −2.5 (−7.1, 2.0) | 0.273 |
| *p*-Interaction[c] | — | 0.487 | — | — | — | — |
| Verbal-scale raw score | | | | | | |
| Unadjusted model | −0.5 (−2.2, 1.2) | 0.541 | −0.5 (−2.7, 1.7) | 0.677 | −0.6 (−3.2, 2.0) | 0.655 |
| Adjusted model | −1.0 (−2.4, 0.4) | 0.143 | −0.8 (−2.7, 1.0) | 0.371 | −1.3 (−3.6, 1.0) | 0.266 |
| *p*-Interaction[c] | — | 0.858 | — | — | — | — |
| Performance-scale raw score | | | | | | |
| Unadjusted model | 0.3 (−0.9, 1.4) | 0.672 | 0.5 (−1.1, 2.1) | 0.533 | −0.1 (−2.0, 1.7) | 0.891 |
| Adjusted model | −0.1 (−1.1, 0.9) | 0.849 | 0.3 (−1.1, 1.7) | 0.655 | −0.6 (−2.2, 1.0) | 0.488 |
| *p*-Interaction[c] | — | 0.371 | — | — | — | — |
| Cognition at 10 years (WISC-IV)[d] | $n=423$ | — | $n=219$ | — | $n=204$ | — |
| Full-scale raw score | | | | | | |
| Unadjusted model | −0.4 (−5.3, 4.4) | 0.855 | −4.0 (−10.5, 2.6) | 0.231 | 4.1 (−3.1, 11.2) | 0.264 |
| Adjusted model | −0.6 (−4.4, 3.2) | 0.759 | −4.4 (−9.4, 0.7) | 0.090 | 3.1 (−3.0, 9.1) | 0.318 |
| *p*-Interaction[c] | — | 0.082 | — | — | — | — |
| Verbal comprehension raw score | | | | | | |
| Unadjusted model | 0.1 (−1.4, 1.7) | 0.868 | −0.4 (−2.6, 1.8) | 0.711 | 0.9 (−1.4, 3.2) | 0.442 |
| Adjusted model | 0.2 (−1.0, 1.5) | 0.708 | −0.6 (−2.3, 1.1) | 0.514 | 1.0 (−1.0, 2.9) | 0.316 |
| *p*-Interaction[c] | — | 0.373 | — | — | — | — |
| Perceptual reasoning raw score | | | | | | |
| Unadjusted model | −0.6 (−2.3, 1.0) | 0.427 | −2.5 (−4.6, −0.3) | 0.023 | 1.8 (−0.6, 4.2) | 0.140 |
| Adjusted model | −0.6 (−1.9, 0.8) | 0.415 | −2.5 (−4.3, −0.6) | 0.010 | 1.3 (−0.8, 3.4) | 0.229 |
| *p*-Interaction[c] | — | 0.009 | — | — | — | — |
| Working memory raw score | | | | | | |
| Unadjusted model | −0.1 (−1.0, 0.8) | 0.816 | −0.7 (−1.8, 0.4) | 0.234 | 0.8 (−0.6, 2.1) | 0.259 |
| Adjusted model | −0.0 (−0.8, 0.7) | 0.917 | −0.7 (−1.7, 0.3) | 0.153 | 0.7 (−0.5, 2.0) | 0.227 |
| *p*-Interaction[c] | — | 0.101 | — | — | — | — |
| Processing speed raw score | | | | | | |
| Unadjusted model | 0.2 (−1.5, 1.8) | 0.838 | −0.4 (−2.6, 1.8) | 0.716 | 0.6 (−1.8, 3.1) | 0.623 |
| Adjusted model | −0.2 (−1.7, 1.2) | 0.764 | −0.6 (−2.5, 1.3) | 0.530 | 0.0 (−2.3, 2.3) | 0.980 |
| *p*-Interaction[c] | — | 0.641 | — | — | — | — |

Note: —, not applicable; CI, confidence interval; HOME, health observation for measurement of the environment; MINIMat, Maternal and Infant Nutrition Interventions in Matlab; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.

[a]Urinary fluoride concentrations are adjusted to the median specific gravity of 1.012.

[b]Analyses of outcomes at 5 years (all children, $n=338$; 200 boys and 188 girls); adjusted model for variables of child sex (categorical; male/female), child age (years), tester (three groups), family socioeconomic status at enrollment (quintiles), HOME scores at 5 years (continuous), parity at enrollment (continuous), maternal education at 5 years (continuous; years), maternal nonverbal reasoning at 5 years (continuous; raw score), and height-for-age $z$-score at 5 years (continuous).

[c]Addition of multiplicative interaction term [urinary fluoride ($\log_2$) × sex (boy = 1/girl = 2)] in the adjusted model.

[d]Analyses of outcomes at 10 years (all children, $n=423$; 219 boys and 204 girls); adjusted model for variables of child sex (categorical; male/female), child age (years), tester (four groups), family socioeconomic status at 10 years (quintiles), HOME scores at 10 years (continuous), parity at 10 years (continuous), maternal education at 10 years (continuous; years), maternal nonverbal reasoning at 5 years (continuous; raw score), and height-for-age $z$-score at 10 years (continuous).

due to the rapid linear growth.[43] In young children, more than half of the ingested amount of fluoride may be retained in the skeleton.[3] Obviously, such retention differs between individuals, resulting in varying urinary excretion in relation to the ingested amount. This was supported by the weak correlation of urinary fluoride at 5 years with water fluoride (samples collected at 10-year follow-up) compared to urinary fluoride at early gestation and at 10 years of age.

The overall findings regarding sex differences in cognitive abilities in relation to fluoride exposure are inconsistent. In the present study, the impact of prenatal exposure on cognition seemed somewhat more pronounced in girls than in boys, though the difference was not significant and was observed mainly at 10 years of age. Similarly, a study in Calgary, Canada, found that women who used fluoridated drinking water (at 0.7 mg/L) during pregnancy gave birth to children with poorer cognitive flexibility, particularly in girls, compared to those using nonfluoridated water.[44] Also, a Chinese study involving 512 children 8–13 years of age reported lower cognition scores in girls compared to boys in an endemic fluorosis region but not in a similar region with low water fluoride concentrations.[45] In the Canadian MIREC study, however, maternal urinary fluoride concentrations were inversely associated with child intelligence mainly in boys.[7] In contrast, no sex differences were observed in the Mexican ELEMENT cohort.[5,39] As to childhood exposure, we found no sex-related difference in the associations of the children's contemporary fluoride exposure at 10 years of age with cognitive abilities. Similarly, the MIREC study found no sex-related difference in the association of childhood fluoride exposure and performance IQ.[12] The diverse findings in relation to child sex and critical windows of exposure highlight the need for more and larger prospective studies.

During fetal development, fluoride ingested by the mother crosses the placenta and thereafter the undeveloped fetal blood–brain barrier.[4,14] For example, passage of fluoride across the fetal blood–brain barrier is indicated by brain tissue analysis of aborted human fetuses.[46] There are also experimental studies in rodents with long-term oral fluoride exposure in adult life indicating that fluoride crosses the mature blood–brain barrier.[47] However, despite increasing evidence that fluoride has neurotoxic properties,[14] there is no consensus on the underlying mechanisms of action.

**Table 6.** Spline regression of child urinary fluoride concentrations [spline knot at −0.47 on the $\log_2$ scale (corresponding to 0.72 mg/L)] with their cognitive abilities at 10 years of age in the MINIMat study, Matlab, Bangladesh.

| | Child urinary fluoride exposure at 10 years[a] [mg/L ($\log_2$-transformed)] | | | | | |
|---|---|---|---|---|---|---|
| | All children | | Boys | | Girls | |
| Outcomes | *B* (95% CI) | *p*-Value | *B* (95% CI) | *p*-Value | *B* (95% CI) | *p*-Value |
| Cognition at 10 years (WISC-IV)[b] | *n* = 500 | — | *n* = 255 | — | *n* = 245 | — |
| Full-scale raw score | | | | | | |
| Unadjusted model | | | | | | |
| ≤ −0.47 on the $\log_2$ scale | 1.6 (−6.6, 9.8) | 0.701 | 0.6 (−9.9, 11.2) | 0.907 | 3.0 (−9.9, 16.0) | 0.647 |
| > −0.47 on the $\log_2$ scale | −9.8 (−21.4, 1.9) | 0.100 | −12.8 (−28.8, 3.3) | 0.118 | −7.0 (−24.1, 10.0) | 0.417 |
| Adjusted model | | | | | | |
| ≤ −0.47 on the $\log_2$ scale | 5.3 (−1.0, 11.7) | 0.101 | 3.3 (−4.8, 11.4) | 0.422 | 8.1 (−2.6, 18.8) | 0.137 |
| > −0.47 on the $\log_2$ scale | −12.1 (−21.2, −3.0) | 0.009 | −13.1 (−25.8, −0.4) | 0.044 | −12.6 (−26.5, 1.3) | 0.075 |
| *p*-Interaction[c] | — | 0.959 | — | — | — | — |
| Verbal comprehension raw score | | | | | | |
| Unadjusted model | | | | | | |
| ≤ −0.47 on the $\log_2$ scale | 1.2 (−1.4, 3.9) | 0.359 | 1.1 (−2.4, 4.6) | 0.548 | 1.5 (−2.6, 5.6) | 0.478 |
| > −0.47 on the $\log_2$ scale | −3.5 (−7.2, 0.3) | 0.072 | −3.8 (−9.2, 1.5) | 0.160 | −3.1 (−8.5, 2.2) | 0.253 |
| Adjusted model | | | | | | |
| ≤ −0.47 on the $\log_2$ scale | 2.4 (0.3, 4.5) | 0.026 | 1.9 (−0.8, 4.6) | 0.171 | 3.1 (−0.3, 6.5) | 0.072 |
| > −0.47 on the $\log_2$ scale | −3.8 (−6.8, −0.8) | 0.013 | −3.5 (−7.8, 0.7) | 0.105 | −5.0 (−9.4, −0.5) | 0.028 |
| *p*-Interaction[c] | — | 0.501 | — | — | — | — |
| Perceptual reasoning raw score | | | | | | |
| Unadjusted model | | | | | | |
| ≤ −0.47 on the $\log_2$ scale | 0.2 (−2.5, 2.9) | 0.885 | −0.1 (−3.6, 3.4) | 0.937 | 0.7 (−3.6, 5.0) | 0.752 |
| > −0.47 on the $\log_2$ scale | −3.9 (−7.8, −0.0) | 0.048 | −4.8 (−10.1, 0.5) | 0.078 | −3.2 (−8.8, 2.4) | 0.265 |
| Adjusted model | | | | | | |
| ≤ −0.47 on the $\log_2$ scale | 1.0 (−1.3, 3.3) | 0.383 | 0.4 (−2.6, 3.4) | 0.768 | 1.7 (−2.1, 5.4) | 0.380 |
| > −0.47 on the $\log_2$ scale | −4.4 (−7.7, −1.1) | 0.008 | −4.0 (−8.7, 0.7) | 0.099 | −4.6 (−9.5, 0.3) | 0.064 |
| *p*-Interaction[c] | — | 0.857 | — | — | — | — |
| Working memory raw scores[d] | | | | | | |
| Unadjusted model | −0.6 (−1.5, 0.4) | 0.224 | −0.8 (−2.1, 0.4) | 0.188 | −0.3 (−1.8, 1.1) | 0.652 |
| Adjusted model | −0.3 (−1.1, 0.5) | 0.448 | −0.7 (−1.8, 0.4) | 0.225 | −0.0 (−1.3, 1.2) | 0.942 |
| *p*-Interaction[c] | — | 0.589 | — | — | — | — |
| Processing speed raw score[d] | | | | | | |
| Unadjusted model | −0.2 (−2.0, 1.6) | 0.812 | −0.8 (−3.2, 1.6) | 0.494 | 0.5 (−2.2, 3.3) | 0.700 |
| Adjusted model | 0.1 (−1.5, 1.7) | 0.905 | −0.6 (−2.7, 1.5) | 0.579 | 0.8 (−1.8, 3.4) | 0.567 |
| *p*-Interaction[c] | — | 0.345 | — | — | — | — |

Note: —, not applicable; CI, confidence interval; HOME, health observation for measurement of the environment; MINIMat, Maternal and Infant Nutrition Interventions in Matlab; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition.
[a]Urinary fluoride concentrations are adjusted to the median specific gravity of 1.012.
[b]Analyses of outcomes at 10 years (all children = 500; 255 boys and 245 girls); child urinary fluoride above and below spline knot at $\log_2 - 0.47 = 0.72$ mg/L, number of individuals < and >0.72 mg/L: 297 and 203. Adjusted splined regression model for variables of child sex (categorical; male/female), child age (years), tester (four groups), family socioeconomic status at 10 years (quintiles), HOME scores at 10 years (continuous), parity at 10 years (continuous), maternal education at 10 years (continuous; years), maternal nonverbal reasoning at 5 years (continuous; raw score), and height-for-age *z*-score at 10 years (continuous).
[c]Addition of multiplicative interaction term [urinary fluoride ($\log_2$) × sex (boy = 1/girl = 2)] in the adjusted model.
[d]Linear regression analysis (all children = 500; 255 boys and 245 girls); adjusted linear regression model for variables of child sex (categorical; male/female), child age (years), tester (four groups), family socioeconomic status at 10 years (quintiles), HOME scores at 10 years (continuous), parity at 10 years (continuous), maternal education at 10 years (continuous; years), maternal nonverbal reasoning at 5 years (continuous; raw score), and height-for-age *z*-score at 10 years (continuous).

Several possible mechanisms have been suggested, including oxidative stress and mitochondrial dysfunction,[47–49] neuroinflammation, neuronal apoptosis, and neurotransmitter imbalance.[47] Besides a possible direct toxic effect on the central nervous system, fluoride has also been postulated to function as an endocrine disruptor.[14] In the Canadian MIREC cohort, a 0.5-mg/L increase in water fluoride concentrations in pregnant women was associated with a 65% increased odds of primary hypothyroidism.[50] Also, boys born to women with primary hypothyroidism had lower full-scale intelligence scores than children of euthyroid women.[50] In a Chinese study, including 571 children 7–13 years of age, fluoride exposure altered thyroid hormones and thyroid stimulating hormone (TSH) levels, which modified the association between fluoride and intelligence.[51]

Drinking water is an important source of fluoride exposure in many parts of the world.[2] The drinking water fluoride concentrations measured at the 10-year-old follow-up visit (median: 0.20 mg/L, range: 0.04–0.74 mg/L) were comparable to those in the Canadian MIREC study (fluoridated area median: 0.56 mg/L, range: 0.41–0.87 mg/L; nonfluoridated area median = 0.13, range: 0.04–0.20 mg/L).[52] We believe that drinking water was an important source of fluoride in the present study, as people drink several liters per day due to the hot climate.[53] Also, the children's urinary fluoride concentrations at 10 years of age were moderately correlated with their drinking water concentrations (*rho* = 0.44). A stronger correlation was found between the mothers' urinary fluoride in early gestation and the water fluoride concentrations at the children's 10-year-old visit (*rho* = 0.55), providing potential support for fairly stable exposure through drinking water over time. However, we did not measure water fluoride concentrations during early gestation or during the 5-year-old visit, and several of the wells (mainly private wells) were renewed or abandoned due to the elevated arsenic concentrations found in 2002–2003.[54] There is a paucity of data on exposure from other dietary and nondietary sources, though exposure to fluoride from black tea may be considerable.[55] However, tea consumption is low in rural Bangladesh.[56] A recent study reported that the fluoride concentrations in two commercial toothpastes for children in Bangladesh contained 803 and 1,042 mg/kg,[57] which is within the concentration range recommended by WHO (1,000–1,500 mg/kg).[1] Still,

**Table 7.** Multivariable-adjusted spline regression of child urinary fluoride concentrations [spline knot at −0.47 on the $\log_2$ scale (corresponding to 0.72 mg/L)] with their cognitive abilities at 10 years additionally adjusted for the mother's urinary fluoride concentrations during early pregnancy (gestational week 8) in the MINIMat study, Matlab, Bangladesh.

| | Child urinary fluoride at 10 years[a] [mg/L ($\log_2$-transformed)] | | | | | |
|---|---|---|---|---|---|---|
| | All children | | Boys | | Girls | |
| Outcomes | *B* (95% CI) | *p*-Value | *B* (95% CI) | *p*-Value | *B* (95% CI) | *p*-Value |
| Cognition at 10 years (WISC-IV)[b] | $n = 500$ | — | $n = 255$ | — | $n = 245$ | — |
| Full-scale raw score | | | | | | |
| Adjusted model | | | | | | |
| $\leq -0.47$ on the $\log_2$ scale | 5.3 (−1.0, 11.7) | 0.101 | 3.3 (−4.8, 11.4) | 0.422 | 8.1 (−2.6, 18.8) | 0.137 |
| $> -0.47$ on the $\log_2$ scale | −12.1 (−21.2, −3.0) | 0.009 | −13.1 (−25.8, −0.4) | 0.044 | −12.6 (−26.5, 1.3) | 0.075 |
| +Urinary fluoride GW8 [μg/L ($\log_2$)] | | | | | | |
| $\leq -0.47$ on the $\log_2$ scale | 5.3 (−1.1, 11.6) | 0.102 | 3.2 (−4.9, 11.3) | 0.435 | 8.4 (−2.0, 19.0) | 0.115 |
| $> -0.47$ on the $\log_2$ scale | −10.5 (−19.7, −1.4) | 0.024 | −11.9 (−24.8, 1.0) | 0.071 | −11.6 (−25.3, 2.1) | 0.096 |
| Verbal comprehension raw score | | | | | | |
| Adjusted model | | | | | | |
| $\leq -0.47$ on the $\log_2$ scale | 2.4 (0.3, 4.5) | 0.026 | 1.9 (−0.9, 4.6) | 0.171 | 3.1 (−0.3, 6.5) | 0.072 |
| $> -0.47$ on the $\log_2$ scale | −3.8 (−6.8, −0.8) | 0.013 | −3.5 (−7.8, 0.7) | 0.105 | −5.0 (−9.4, −0.5) | 0.028 |
| +Urinary fluoride GW8 [μg/L ($\log_2$)] | | | | | | |
| $\leq -0.47$ on the $\log_2$ scale | 2.4 (0.3, 4.4) | 0.027 | 1.9 (−0.8, 4.6) | 0.176 | 3.2 (−0.2, 6.6) | 0.065 |
| $> -0.47$ on the $\log_2$ scale | −3.5 (−6.5, −0.5) | 0.022 | −3.3 (−7.6, 1.1) | 0.138 | −4.8 (−9.2, −0.4) | 0.034 |
| Perceptual reasoning raw score | | | | | | |
| Adjusted model | | | | | | |
| $\leq -0.47$ on the $\log_2$ scale | 1.0 (−1.3, 3.3) | 0.383 | 0.4 (−2.6, 3.4) | 0.768 | 1.7 (−2.1, 5.4) | 0.380 |
| $> -0.47$ on the $\log_2$ scale | −4.4 (−7.7, −1.1) | 0.008 | −4.0 (−8.7, 0.7) | 0.099 | −4.6 (−9.5, 0.3) | 0.064 |
| +Urinary fluoride GW8 [μg/L ($\log_2$)] | | | | | | |
| $\leq -0.47$ on the $\log_2$ scale | 1.0 (−1.3, 3.3) | 0.389 | 0.4 (−2.6, 3.4) | 0.793 | 1.8 (−1.8, 5.5) | 0.320 |
| $> -0.47$ on the $\log_2$ scale | −3.6 (−6.9, −0.4) | 0.030 | −3.3 (−8.1, 1.5) | 0.172 | −4.1 (−8.8, 0.6) | 0.085 |
| Working memory raw score[c] | | | | | | |
| Adjusted model on the $\log_2$ scale | −0.3 (−1.1, 0.5) | 0.448 | −0.7 (−1.8, 0.4) | 0.225 | −0.0 (−1.3, 1.2) | 0.942 |
| +Urinary fluoride GW8 [μg/L ($\log_2$)] | −0.3 (−1.1, 0.6) | 0.538 | −0.6 (−1.7, 0.5) | 0.259 | 0.0 (−1.3, 1.3) | 0.969 |
| Processing speed raw score[c] | | | | | | |
| Adjusted model | 0.1 (−1.5, 1.7) | 0.905 | −0.6 (−2.7, 1.5) | 0.579 | 0.8 (−1.8, 3.4) | 0.567 |
| +Urinary fluoride GW8 [μg/L ($\log_2$)] | 0.2 (−1.4, 1.9) | 0.784 | −0.5 (−2.6, 1.6) | 0.632 | 0.9 (−1.7, 3.5) | 0.491 |

Note: —, not applicable; CI, confidence interval; GW8, gestational week 8; HOME, health observation for measurement of the environment; MINIMat, Maternal and Infant Nutrition Interventions in Matlab; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition.

[a]Urinary fluoride concentrations are adjusted to the median specific gravity of 0.012.

[b]Analyses of outcomes at 10 years (all children = 500; 255 boys and 245 girls): $\log_2 >$ and $< -0.47$; child urinary fluoride above and below spline knot at $\log_2 -0.47 = 0.72$ mg/L, number of individuals < and >0.72 mg/L: 297 and 203. Adjusted splined regression for the variables of child gender (categorical; male/female), child age (years), tester (four groups), family socioeconomic status at 10 years (quintiles), HOME scores at 10 years (continuous), parity at 10 years (continuous), maternal education at 10 years (continuous; years), maternal nonverbal reasoning at 5 years (continuous; raw score), and height-for-age *z*-score at 10 years (continuous).

[c]Linear regression analysis instead of spline regression (all children = 500; 255 boys and 245 girls); adjusted linear regression for the variable of child gender (categorical; male/female), child age (years), tester (four groups), family socioeconomic status at 10 years (quintiles), HOME scores at 10 years (continuous), parity at 10 years (continuous), maternal education at 10 years (continuous; years), maternal nonverbal reasoning at 5 years (continuous; raw score), and height-for-age *z*-score at 10 years (continuous).

dental care products could contribute to the total daily intake, especially for small children who are likely to swallow some toothpaste during brushing.[58]

The main strengths of the study include the prospective population-based design and a broad range of individual urinary fluoride concentrations measured during gestation and at 5 and 10 years of age. Child cognition was comprehensively and repeatedly measured at 5 and 10 years with reliable and widely used psychometric tools, and we were able to adjust the models for multiple potential confounders, including SES, HOME, maternal nonverbal reasoning, and maternal and child education, which have been found to influence child cognition. A limitation is that we used a single spot urine sample at each exposure assessment time point, which may have introduced exposure misclassification, given the short half-life of fluoride in plasma, ∼6 h.[3] Such exposure misclassification is expected to bias the observed results toward null.[59] As earlier studies have indicated that urinary fluoride concentrations increase slightly as pregnancy progresses,[12,52,60] it is possible that we may have underestimated the prenatal fluoride exposure since we measured the urinary fluoride concentrations in the first trimester. Conversely, urinary fluoride is probably more stable in early pregnancy than in late pregnancy, when increased bone resorption is more prominent due to the prioritized transport of calcium to the fetus,[61] leading to increased release of fluoride from bone. Because the WPPSI-III and WISC-IV were not standardized in the Bangladeshi population, we used raw intelligence scores, which limits the comparability of the effect sizes of the identified associations with other studies and between the various studied cognitive outcomes. We did not adjust for methylmercury exposure, as we have previously found it not to be associated with the children's cognitive abilities at 10 years in the present cohort.[62] Finally, although our associations are adjusted for multiple potential confounders, unmeasured residual confounding may exist.

To conclude, this study adds to the growing evidence that even low-level fluoride exposure early in life may adversely impact child cognition. Prenatal exposure was associated with lower cognitive abilities with no indication of a threshold. Also, childhood fluoride exposure was inversely associated with child cognition, although at higher exposure levels. Both perceptual reasoning and verbal ability appeared to be affected. Because even minor changes in cognition at a population level have important implications for public health, the overall results raise concerns about the existing guidelines and standards for fluoride in drinking water.


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