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Dose dependence of prenatal fluoride exposure associations with cognitive performance at school age in three prospective studies

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Background: Fluoride may be a developmental neurotoxicant at elevated exposures. We merged new data from a prospective Odense Child Cohort (OCC) with results from two previous birth cohort studies from Mexico and Canada to characterize the dose–effect relationship in greater detail. **Methods:** The OCC contributed 837 mother–child pairs to the total of >1500. We measured creatinine-adjusted urine-fluoride concentrations in maternal urine samples obtained during late pregnancy. Child IQ was determined at age 7 years using an abbreviated version of the Wechsler Intelligence Scales for Children. Findings from the three cohorts were used to calculate the joint benchmark concentration (BMC) and the lower confidence limit (BMCL) after adjustment for covariables. **Results:** In the OCC, urine-fluoride concentrations varied between 0.08 and 3.04 mg/l (median 0.52 mg/l) but were not significantly associated with full-scale IQ at age 7 years ($\beta = 0.08$; 95% confidence interval −1.14 to 1.30 for a doubling in exposure). No difference was apparent between boys and girls. In the OCC, the BMC was 0.92 mg/l, with a BMCL of 0.30 mg/l. The joint analysis of all three cohorts showed a statistically significant association between urine-fluoride and IQ, with a BMC of 0.45 mg/l (BMCL, 0.28 mg/l), slightly higher than the BMC previously reported for the two North American cohorts alone. **Conclusions:** As the BMCL reflects an approximate threshold for developmental neurotoxicity, the results suggest that pregnant women and children may need protection against fluoride toxicity.

Introduction

Fluoride has beneficial effects on the dental enamel in preventing caries, while systemic exposure may lead to toxic effects.[1,2] Although fluoride has been added to drinking water in certain parts of the world since the 1940s and toothpaste since the 1960s, little attention has been paid to the possible adverse effects of fluoride intake in pregnancy until fairly recently.[1] A substantial number of studies have shown cognitive deficits in children with elevated exposure to fluoride in drinking water, although mainly cross-sectionally.[1,3,4] However, prospective studies have now become available with individual data on prenatal fluoride exposure, as indicated by maternal urine-fluoride (U-F) excretion levels during pregnancy.[5,6]

Regulatory agencies often use benchmark concentration (BMC) calculations to identify safe or tolerable exposure levels.[7,8] In a prior study, we combined data from two prospective North American studies. A benchmark response of a one-point decrement in IQ was predicted by a BMC of 0.33 mg/l (lower confidence limit, BMCL, 0.20 mg/l) expressed in terms of maternal pregnancy U-F.[9] However, the relatively small number of data points at U-F levels at or below 0.2 mg/l may have introduced uncertainty in the observed monotonic associations. Accordingly, renewed calculations would be desirable with a better representation of low exposures. In addition, an update of the BMC calculation also appears warranted by the recently expanded results from the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) cohort that included additional exposure data.[10]

We now present findings from the prospective Odense Child Cohort (OCC),[11,12] from a Danish municipality with fluoride concentrations in drinking water that are low by international standards.[13] We examine the possible association between prenatal fluoride exposure, as represented by maternal pregnancy U-F, and IQ at school age and conduct a joint BMC analysis that includes data from the two previous prospective studies.

Methods

OCC study cohort

All new pregnant women residing in Odense municipality were contacted between 2010 and 2012; 2874 of the 4017 women agreed to be enrolled in the OCC, while 374 dropped out before and after giving birth.[12] The present study population included 837 singleton mother–child pairs with results on child IQ, a maternal urine sample analyzed for fluoride, and information about parental education, child sex and preterm birth.

Fluoride exposure

While the addition of fluoride to drinking water is not legal in Denmark, elevated fluoride concentrations up to 1.5 mg/l naturally occur in groundwater in parts of the country,[13] and some types of tea, especially black tea, constitute an additional source of exposure.[14] In Odense municipality, the fluoride concentration in drinking water is rather low, i.e. 0.2–0.3 mg/l.[13] Given the retention in and

continuous mobilization from calcified tissues, the maternal U-F concentration reflects the level in the blood that is available for passage through the placenta to reach the fetus.[1] We analyzed maternal urine samples collected at 28 weeks' gestation to assess individual fluoride exposure. Some women ($N = 384$; 45.9%) provided a 24-h urine sample, while a spot fasting urine sample was otherwise obtained in the morning ($N = 453$; 54.1%).

The fluoride concentrations were measured with an Orion™ Ion Selective Electrode (ISE 9609 BNWP) (Thermo Fisher Scientific, Waltham, MA, USA) coupled to a Model 15 pH-metre from Denver Instruments (Sartorius, Göttingen, Germany) as previously described.[14,15] All samples were diluted prior to the analysis (1:1) with total ionic-strength-adjusted buffer (TISAB II) solution, as recommended by the manufacturer. The accuracy of the method was controlled in each batch of samples by analyzing the fluoride Certified Reference Material (CRM) at 0.52 ± 0.02 mg/l (Merck, Darmstadt, Germany). The limit of determination was 0.02 mg/l, and the average imprecision of the method was <5.1% (see Supplementary Material).

All U-F concentrations were adjusted for the creatinine concentration (U-Cr) using the following equation: $U\text{-}F_{CR} = (U\text{-}F/U\text{-}Cr) \times U\text{-}Cr_m$, where $U\text{-}F_{CR}$ is the creatinine-adjusted fluoride concentration (in mg/l), U-F is the measured fluoride concentration (mg/l) and $U\text{-}Cr_m$ is the median creatinine concentration of the samples.[5] In the two previous cohorts, the creatinine-adjusted U-F was assessed by comparable analytical protocols.[6,10,16]

Cognitive assessment

At age 7, the OCC children were invited to participate in the Danish version of the abbreviated Wechsler Intelligence Scales for Children to obtain a full-scale IQ (FSIQ), and 1570 completed the test.[11] Similarly, in the ELEMENT study,[5,17] a Spanish version of the Wechsler Abbreviated Scale of Intelligence was administered to 259 children at age 6–12 to derive an age-adjusted FSIQ. In addition, the Spanish version of the McCarthy Scales of Children's Abilities was administered to 287 children at age 4 to derive a General Cognitive Index (GCI) as a standardized composite score highly correlated with the FSIQ. In the Maternal-Infant Research on Environmental Chemicals (MIREC) study,[6] the 407 children's FSIQ were assessed at age 3–4 years in either English or French. These different measures of intellectual ability are considered equally valid and highly correlated,[18] thus justifying pooling the scaled (age-adjusted) IQ scores across the cohorts. Examiners were blinded to fluoride exposure status in the OCC, ELEMENT and MIREC studies.

Covariables

In the OCC, we considered maternal, child and socioeconomic variables correlated with child FSIQ for inclusion in the statistical analyses along with sex and preterm birth (gestational age <37 weeks).[11] As a key socioeconomic variable in the Danish population, parents reported their highest achieved education, which was categorized into short (high school or less, $N = 229$), intermediate (1–4 years post high school, $N = 446$) and long (>4 years post high school, $N = 162$), as based on the highest achieved education by either parent.[11] Dichotomized maternal smoking (yes, $n = 23$) and alcohol intake (yes, $n = 209$) during pregnancy, duration of breastfeeding (dichotomized as ≤3 and >3 months), school type (public or private), school grade (preschool or first) and psychologist examiner were also considered as covariables possibly associated with the FSIQ.

In the ELEMENT cohort,[5] covariables included gestational age in weeks, birth weight, sex, age at outcome measurement, maternal parity, maternal smoking history, marital status, age at delivery, maternal IQ, education and the specific sub-cohort identity. The MIREC study[6] selected similar covariables, including sex, city of residence, HOME score, maternal education and maternal race/ethnicity.

Statistical analysis

In the OCC, we first used covariable-adjusted linear regressions to model differences in child FSIQ score by the maternal U-F concentration. Because the U-F concentrations were positively skewed, a $\log_2$ transformation was applied. Thus, the regression coefficient (beta) therefore shows the difference in FSIQ for a doubling of the maternal U-F concentration.

A simple model accounted for sex, parental education and preterm birth. In a more comprehensive model involving a subset of mother–child pairs with additional information available, we added breastfeeding duration, maternal smoking and alcohol intake during pregnancy, age of children at the time of testing, examiner, school grade and school type. In both models, sex was introduced as a potential interaction term. In addition, the creatinine-adjusted U-F was stratified for the type of urine sample available (i.e. 24 h and spot), and a joint analysis was also conducted with a fixed effect for the type of urine sample. For descriptive purposes, a cubic spline model was also developed.

BMC calculations were carried out to assess the maternal U-F concentration associated with a benchmark response of a one-point reduction in child FSIQ score, as compared with an unexposed mother and the same profile of covariates. Then the results from the OCC study were compared and merged with the results previously obtained from the studies in Mexico[5] and Canada.[6] We used a similar statistical approach as in our previous benchmark calculations using results from the North American studies,[9] but we now included the updated ELEMENT cohort data with an increased sample size.[10]

In the benchmark analysis, we applied a linear dose–response function to approximate the effect of fluoride exposure (i.e. without a log scale for U-F). To better allow for different exposure distributions across studies, we derived two piecewise linear models, with breakpoints at 0.5 and 0.75 mg/l.[9] All models were fitted separately, including sex interaction, and adjusted for parity, maternal education, smoking, gestational age and the type of urine sample.

The regression coefficients in the linear model were used for the calculation of the BMC for each cohort, and joint BMCs were obtained by combining results from the three cohorts using a weighting approach.[9] The main result of the BMC analysis is the BMCL, i.e. the lower one-sided 95% confidence limit of the BMC.[19]

Differences between the regression coefficients in the three cohorts were tested using a Wald test, and we calculated the Akaike Information Criterion (AIC) to compare the fit of the different regression models. As the linear model is nested in the piecewise linear model, the fit of these two models can be directly compared. Thus, we calculated the *P* values for the hypothesis that the concentration response is linear in a test where the alternative is the piecewise linear model; a low *P* value indicates that the linear model has a poorer fit.

Results

Table 1 shows the main characteristics of the 837 OCC children included in the present study, as compared with the characteristics of all cohort children originally recruited. Of the 837 children in the present study, 435 (52%) were boys, and their average age was 7 years (6.5–8.3 years). Most (75.9%) of the children were breastfed for more than 3 months, and only 27 (3.2%) were born preterm. The maternal U-F concentrations averaged 0.58 mg/l (SD, 0.32; range, 0.08–3.04) (with a median of 0.52 mg/l) and did not differ between the sampling conditions (Supplementary table S1) nor with season. The creatinine-adjusted U-F results from the OCC and for the two other prospective cohorts are shown in figure 1.

After adjustment for covariables, the log2-converted maternal U-F was not significantly associated with the child's FSIQ score (table 2). A doubling in maternal fluoride concentration led to a slight decrease of 0.04 FSIQ points in girls and a small increase of 0.20 points

Table 1 Characteristics of 837 children from the OCC and included in the present study, as compared with the total cohort

Variable	Present cohort sample (*N* = 837) Mean (SD)/count (%)	Total cohort (*N* = 2448) Mean (SD)/count (%)
Sex		
Girl	402 (48.03)	1155 (47.18)
Boy	435 (51.97)	1293 (52.82)
Weight at birth (g)		
Mean (SD)	3.54 (0.52)	3.53 (0.53)
Missing	0	6
Breastfeeding duration		
<3 months	165 (24.05)	429 (25.09)
>3 months	521 (75.95)	1281 (74.91)
Missing	151	738
Maternal parity		
Primiparidae	457 (54.60)	1351 (55.21)
Multiparidae	380 (45.40)	1096 (44.79)
Missing	0	1
Gestational age <37 weeks		
No	810 (96.77)	2344 (96.10)
Yes	27 (3.24)	95 (3.90)
Missing	0	9
School type		
Public school	492 (80.00)	768 (78.77)
Private school	123 (20.00)	207 (21.23)
Missing	222	1473
School grade		
1st grade	431 (58.64)	742 (59.31)
Preschool	304 (41.36)	508 (40.61)
Missing	0	6
Age at test (years)		
Mean (SD)	7.15 (0.19)	7.18 (0.21)
Missing	0	938
FSIQ score		
Mean (SD)	99.44 (12.34)	99.43 (12.04)

Note: FSIQ, Full-Scale IQ.

in boys, but the interaction between sex and fluoride exposure was marginal (figure 2). Among important covariables, a higher parental education level predicted a higher FSIQ score[11] but was of marginal importance in the fluoride–IQ analysis. The type of maternal urine sample (fixed effect in the model) had no clear effect on FSIQ scores (−0.83; 95% confidence interval −2.52 to 0.86), with no difference in a likelihood ratio test for sample interaction.

When additional covariables were included, 377 observations in the OCC were disregarded due to missing information, and the comprehensive model included complete cases of 460 children (table 2). Again, only a weak association between the U-F and child FSIQ score was observed in the OCC, with no clear interaction between sex and fluoride exposure (table 2). Stratifying regression models by urine sample type did not reveal any significant associations between the maternal fluoride excretion variables and FSIQ score, and no significant interactions by sex were observed (table 2). A cubic spline for the log-transformed fluoride concentration again showed no association with FSIQ (Supplementary figure S1).

Relative to the OCC study, stronger associations between fluoride and IQ were observed among the MIREC boys and in the full sample of the ELEMENT cohort; regression coefficients for the girls in the MIREC cohort were fairly similar to the OCC study.[5,6] Nevertheless, the adjusted linear associations between maternal U-F and cognitive function in each of the three studies did not differ statistically ($P = 0.28$), and the combined data showed that an increase in maternal pregnancy U-F by 1 mg/l significantly predicted an IQ decrease by 2.06 points (Supplementary table S2).

Detailed results of the benchmark analysis are shown in Supplementary table S3. The joint BMC based on the linear model is 0.47 mg/l in maternal U-F, with a BMCL of 0.28 mg/l. The study-specific BMC and BMCL results show only minor variability. The BMCL values are generally larger in the OCC cohort compared with the two North American cohorts. In the OCC and MIREC studies, the joint linear results for both sexes were closer to the ones obtained for boys alone, while the results for girls seemed to differ. For the linear model, the joint BMCL for the three studies (0.28 mg/l) is similar to the one obtained from the piecewise model with a breakpoint at 0.75 (0.23 mg/l), while the piecewise model with a lower breakpoint at 0.5 showed a higher BMCL of 0.42 mg/l. This tendency was apparent in the combined analysis as well as in the sex-specific BMCL calculations.

Although the piecewise model is more flexible than the linear model, the AIC results did not reveal any important differences between the model fits. The same conclusion was reached based on likelihood testing where the linear model was not rejected, i.e., with $P = 0.46$ and 0.11 when the linear model was tested against piecewise linear models with breakpoints at 0.5 and 0.75, respectively.

Discussion

Experimental and cross-sectional studies have provided evidence of fluoride neurotoxicity, especially during early brain development.[1,20] Jointly with two prospective epidemiology studies on populations exposed to fluoridated water or fluoridated salt and other sources,[5,6] both of them rated as low risk of bias,[1] the present study adds new, comparable evidence from a population exposed to low water-fluoride levels. In the absence of other important fluoride sources, U-F concentrations will often be similar to the concentration in drinking water,[21,22] but substantial elevations can occur from tea drinking.[4] The two studies from North America showed creatinine-adjusted U-F concentrations averaging 0.89 mg/l (Mexico City) and 0.85 and 0.44 mg/l in fluoridated and non-fluoridated cities (Canada), respectively. Ranges of U-F levels from these two prior studies overlapped with the exposures encountered in the OCC study that reflected the low fluoride concentrations of 0.2–0.3 mg/l in the local drinking water,[13] as likely increased by tea drinking and other sources of exposure (figure 1). We calculated regression values for linear and, for comparison, piecewise linear dose–response functions for the new, low-exposure study so that it could be compared and merged with the previous findings.[9]

In the OCC study, we did not find evidence of fluoride neurotoxicity at low maternal U-F concentrations in the third trimester. This finding is consistent with the trimester-specific MIREC results,[23] as possibly affected by the imprecision of U-F measured in a single spot sample. Given the overlapping ranges of exposure, the fluoride–IQ relationships in the three studies were similar. Although the fluoride association was not statistically significant in the OCC cohort by itself, the joint association was significant when combined with information from the other two cohorts. This result can be explained by a relatively high variability in the OCC result, whereas the combined result is based on a larger sample size.

The joint BMC was found to be 0.45 mg/l (BMCL, 0.28 mg/l), i.e. slightly higher than previously found (BMC, 0.33 mg/l; BMCL, 0.20 mg/l) for the two North American cohorts alone.[9] Also, if instead relying on the GCI as a marker of child intelligence with the slightly larger Mexican sample, the results are similar (Supplementary table S3), as also seen previously.[9] Given the combined observations on more than 1500 mother–child pairs, the overall BMC results likely reflect a threshold for adverse cognitive effects of prenatal fluoride exposure that occur at levels prevalent in many countries.[21]

Due to the brain's continued vulnerability across early development,[24] infancy may also be a vulnerable period of exposure, especially among bottle-fed infants who receive formula reconstituted with fluoridated water.[23,25] However, in the OCC, exposure to fluoride in infancy is expected to be low because the majority of children were breastfed for at least 3 months (more than three out of four

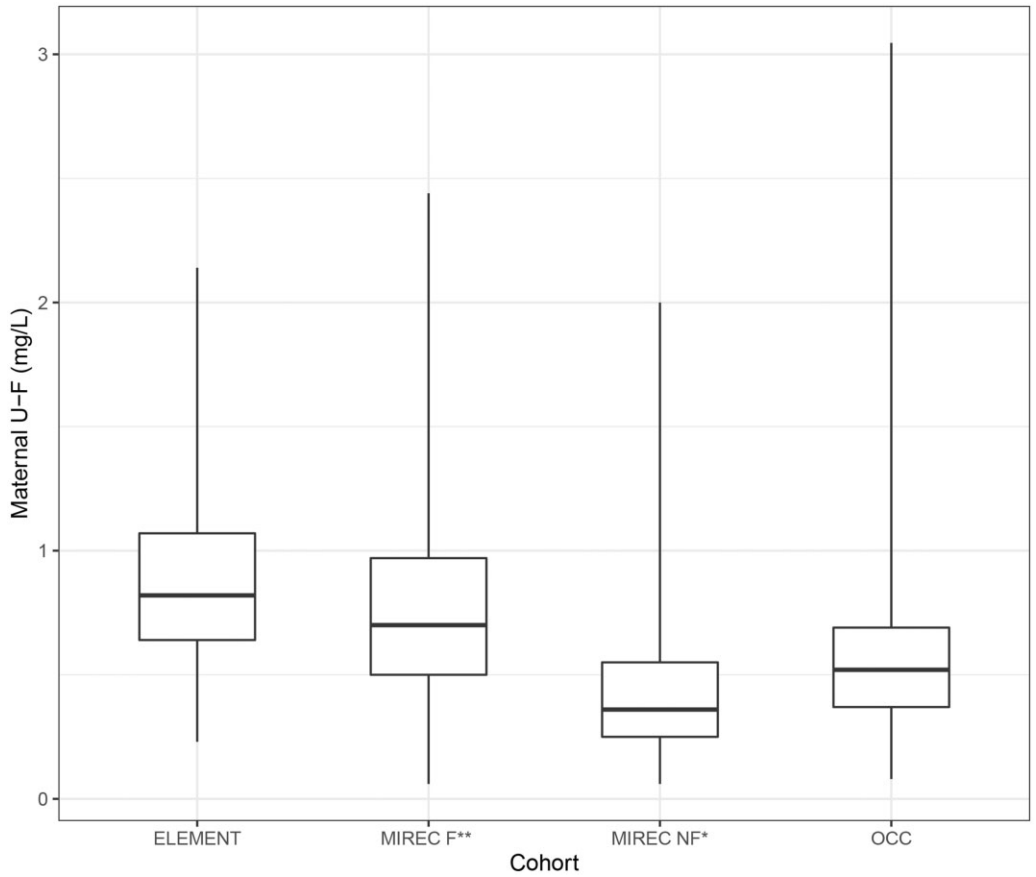

Figure 1 Maternal creatinine-adjusted urine-fluoride concentrations (U-F) in the three cohorts, where MIREC has been split into fluoridated (F) and non-fluoridated (NF) communities. Medians, quartiles, and 95% ranges are shown

Table 2 Predicted difference in FSIQ score for a doubling in the creatinine-adjusted fluoride concentration in mother's urine during pregnancy

	All samples (mg/l)		Spot samples (mg/l)		24-h samples (mg/l)	
	N	**β ^ (95% CI)**	***N***	**β ^ (95% CI)**	***N***	**β ^ (95% CI)**
Simple model[a]						
All	837	0.08 (−1.14 to 1.30)	453	−0.05 (−1.55 to 1.45)	384	0.36 (−1.73 to 2.45)
Girls	402	−0.05 (−1.80 to 1.70)	216	−0.83 (−2.98 to 1.32)	186	0.67 (−2.35 to 3.70)
Boys	435	0.20 (−1.47 to 1.87)	237	0.68 (−1.40 to 2.77)	198	0.09 (−2.75 to 2.93)
Comprehensive model[b]						
All	460	0.18 (−1.39 to 1.76)	223	0.58 (−1.53 to 2.69)	237	−0.72 (−3.24 to 1.80)
Girls	221	−0.40 (−2.52 to 1.71)	101	−0.78 (−3.64 to 2.08)	120	−0.91 (−4.27 to 2.45)
Boys	239	0.87 (−1.41 to 3.15)	122	2.14 (−0.92 to 5.20)	117	−0.50 (−4.13 to 3.13)

Notes: Results are shown for the total material with urine sample type as a fixed effect and for stratified analyses of the urine sample types by linear regression with sex as interaction. The simple model is adjusted for parental education and preterm birth. The comprehensive model accounts also for age at the time of testing, examiner, breastfeeding duration, school grade, school type and smoking and alcohol habits of the mother during pregnancy.
P values for sex interaction: a: 0.84 and b: 0.41.

children)[11] and because of the low fluoride concentration in the local drinking water.[13] As expected, the effects of fetal exposure (i.e. as represented by the U-F in pregnancy) remained significant in the MIREC study when adjusting for breastfeeding.[6] Likewise, in the ELEMENT study, the association of IQ with maternal U-F was only marginally reduced after controlling for child U-F. Further, fluoride exposure in preschool-age[23] and at school age[5] showed a weaker and non-statistically significant association with child IQ. These findings support that fetal brain development is highly vulnerable to fluoride exposure.

The IQ losses seen at elevated fluoride exposures are in accordance with findings in cross-sectional studies where the children examined had likely been exposed to chronic water-fluoride concentrations throughout development.[3,4] Similar results have been found in more recent studies that included areas with elevated water-fluoride levels.[26,27] These findings support that fluoride is a developmental neurotoxicant (i.e., causing adverse effects on brain development in early life) when exposures exceed a low background level. Given the ubiquity of elevated fluoride exposure, a recent study estimated that the population impact of adverse effects from fluoride

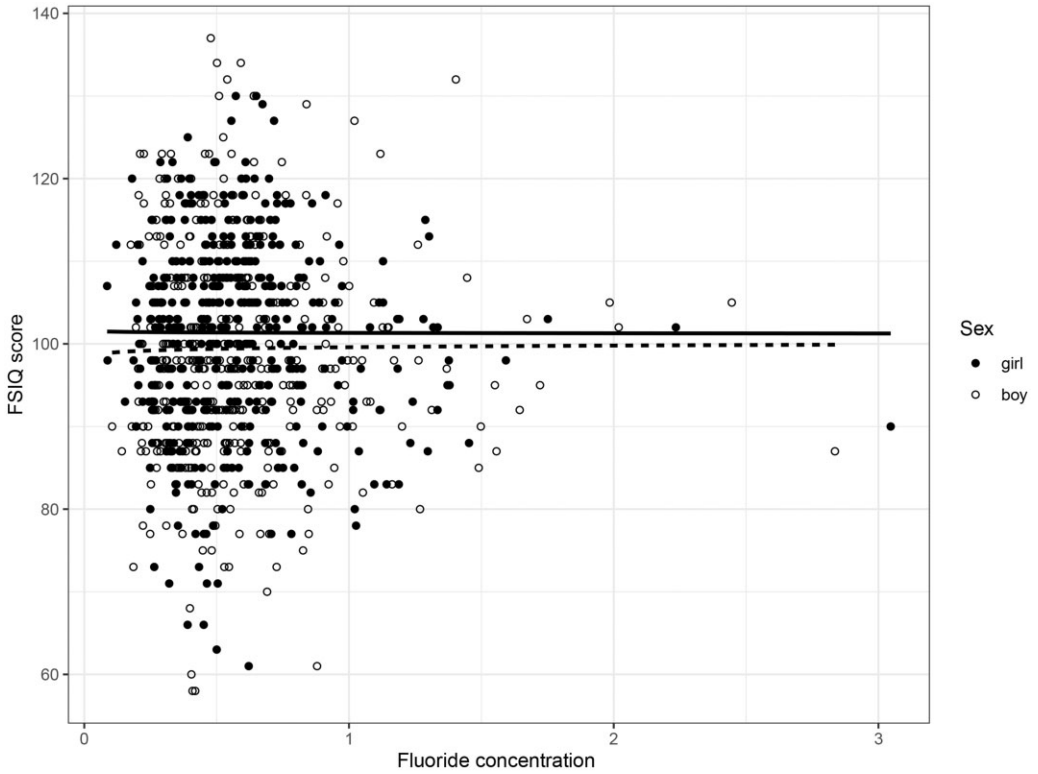

Figure 2 Creatinine-adjusted maternal U-F concentration during pregnancy as a predictor of Full-Scale IQ (FSIQ) in OCC children at age 7 with interaction by sex. The linear regression is adjusted for parental education and preterm birth (simple model). The type of urine sample is considered as a fixed effect. The filled circles and the full regression line are for girls, and the open circles and the dotted line refer to the boys

may exceed the one associated with other toxic elements like lead, mercury, and arsenic,[28] as also concluded in another modelling study.[29] Adverse effects of the latter trace elements are associated with blood concentrations substantially lower than the serum-fluoride concentration corresponding to the BMC.[24]

The OCC study focused on the FSIQ as a cognitive function indicator. Although fluoride neurotoxicity may not affect all cognitive domains equally,[10,23] the abbreviated WISC-V used in the OCC was not separated into subdomains. In addition to FSIQ as a main outcome, the ELEMENT cohort found that elevated maternal U-F concentrations were also associated with higher parent ratings of inattention on the Conners' Rating Scale, a common symptom of Attention-Deficit/Hyperactivity Disorder (ADHD).[16] Other studies on attention outcomes found an association between water fluoridation and diagnosis of ADHD in Canada, although cross-sectional data on child U-F did not replicate this association,[30] perhaps reflecting water-fluoride as a more stable proxy of early-life exposure compared with U-F measured in a later spot sample.

Individual vulnerability, including genetic predisposition,[31,32] may play a role in fluoride neurotoxicity. In the original MIREC study, boys were more vulnerable to prenatal fluoride neurotoxicity than girls,[6] perhaps suggesting sex-dependent endocrine disruption.[33] However, this tendency was not replicated in the present study. Other predisposing factors, such as iodine deficiency in pregnancy,[34] may also affect the outcome, though not likely in Denmark, where table salt is iodized. Overall, variability in such factors may result in difficulties documenting adverse cognitive effects at minor elevations of fluoride exposure.

Both the North American studies adjusted for a substantial number of covariables, including other neurotoxicants. Prenatal and early postnatal exposure to lead did not influence the fluoride-associated IQ deficits in the ELEMENT study.[5] Likewise, adjustment for arsenic, lead, perfluorooctanoic acid and mercury exposure did not appreciably change the estimates in the MIREC study.[6] The OCC cohort data were not adjusted for these other neurotoxicants, though the environmental exposures are low in the Odense area. Parental education was a key covariable in the Danish community,[11] while other socioeconomic factors were also considered important in the more diverse MIREC and ELEMENT populations.

The availability of 24-h urine samples might provide more precise fluoride exposure information, compared with morning spot urines, but the creatinine-adjusted results in the present study failed to show any important difference between the two exposure measures in association with the IQ outcome. Although maternal U-F seems to correlate with fluoride concentrations in serum that may pass the placenta,[1,21] the amount of fluoride that reaches the brain during early development is unknown. In addition, the OCC study collected urine on only one occasion during the third trimester, likely increasing imprecision, as suggested by previous studies that included multiple urine samples throughout pregnancy.[6,35] Thus, the maternal U-F averaged over three trimesters is a stronger predictor of child IQ than trimester-specific U-F.[23] Further, the creatinine-adjusted U-F is known to be the highest in the third trimester,[36] suggesting possible overestimation of fluoride exposure in the OCC cohort compared with the two other studies that relied on averages across trimesters. When occurring at random, such imprecision will tend to underestimate the fluoride association with the neurotoxicity outcome.[37]

The pooling of results from three prospective cohorts conducted in areas with wide ranges of overlapping exposure levels offers strong evidence of prenatal neurotoxicity, and these findings should inspire a revision of water-fluoride recommendations aimed at protecting pregnant women and young children. For example, the World Health Organization's recommendation of 1.5 mg/l as an upper limit for fluoride in drinking water[21] does not consider developmental neurotoxicity. While fluoride has dental health benefits,[38] the recent report on oral health from the National Institutes of Health (NIH)[39] emphasized improvements in preventing caries due to the increased topical use of new dental dentifrices, fluoride sealants and varnishes

in children above 2 years of age, i.e. after the teeth have erupted.[2,40] Although the NIH report stated that water fluoridation benefits the entire population (page I-39),[39] fluoridated toothpaste and other topical treatment are favoured as primary means of caries prevention.[2]

The present study contributes new information on the weak association between fairly low levels of prenatal fluoride exposure and cognitive function at school age in a Danish birth cohort. A possible negative association could not be confirmed within the exposures measured in the OCC. When merged with data from two previous prospective studies at higher exposures, a revised BMCL fluoride concentration of about 0.3 mg/l in maternal pregnancy urine suggests that elevated fluoride intakes, whether from drinking water, black tea, or other sources, during pregnancy may require public health attention.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Author contributions

P.G. and E.B.J. supervised this study and are the guarantors. P.G., A.M. and E.B.J. designed the study. P.G., F.N., I.H.B., N.B., C.G., C.T. and H.H. contributed to data collection. I.B.H., N.B., C.G., C.T. and H.H. contributed to data analysis and interpretation. All authors provided advice regarding critically important intellectual content and helped to draft the manuscript and approved submission of this manuscript.

Conflicts of interest: P.G. has served as an expert on the hazards of environmental chemicals on behalf of the plaintiffs in Food & Water Watch v. U.S. EPA, where H.H. served as a fact witness regarding ELEMENT research on fluoride. All other authors have no interest to declare regarding this research.

Data availability

The dataset analyzed in this study is not publicly available due to national data security legislation on sensitive personal data.

Key points

- In the OCC birth cohort, prenatal fluoride exposure was estimated using creatinine-adjusted maternal urine-fluoride concentrations, and child IQ was determined at age 7 years. No clear association was found at the relatively low levels of exposure.
- Merging these results with data from two more highly exposed cohorts strengthened the dose–response assessment and allowed calculation of more accurate benchmark concentrations for developmental fluoride neurotoxicity.
- Because fluoride excretion may vary over time and sources of fluoride intake were not assessed, the exposure assessment in the three cohorts may involve some degree of imprecision that could dilute the findings.
- While analyses were controlled for child sex, parental education, and prematurity, population differences may not have been fully captured by adjustment for covariables.
- The joint benchmark concentration results reflect an approximate threshold for fluoride neurotoxicity at about 0.3 mg/l in urine, which is more reliable than previous results, as now based on more than 1500 mother–child pairs from prospective studies.

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