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Correlation of fluoride intake with haemoglobin level and intelligence quotient in 8–12 year aged children: an observational study from India

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Abstract

Background Fluorosis caused by excess intake of fluoride can affects various soft tissues of the body, such as the gastrointestinal tract, blood, brain tissues and thyroid gland apart from dental fluorosis and skeletal fluorosis. Nonskeletal fluorosis is considered reversible if diagnosed early and treated promptly. Therefore, diagnostic methods that can be easily performed even by primary health care workers and depict any ongoing health problems, should be validated. Dental fluorosis, assessment of fluoride in urine and water are tests that fulfill these requirements. To date, no study has correlated haemoglobin (Hb) with dental fluorosis; moreover, studies focusing on intelligence quotient (IQ) had conflicting results and need further research. Hence, study was conducted to determine any relationship among different fluoride assessment parameters (severity of dental fluorosis, fluoride level in urine and drinking water) with IQ status and hemoglobin level of children aged 8–12 years, affected with or without dental fluorosis.

Methods A total of 300 children aged 8–12 years were evaluated for dental fluorosis via Dean's index, IQ level via Raven's coloured progressive matrices test, Hb level, and fluoride content in water and urine.

Results Water fluoride, age and gender were significantly associated with Hb. Intelligence was significantly related to urinary fluoride levels. Presence or absence of dental fluorosis and its severity were not significantly related to IQ or Hb.

Conclusions Excess fluoride intake has adverse effects on hematological parameters and children's cognitive neurodevelopment, which were evaluated by current fluoride exposure markers, i.e., water and urinary fluoride. However, dental fluorosis cannot be used as a definitive assessment marker for these conditions, as it is not significantly correlated with these conditions.

Keywords IQ, Hb, Fluoride, Fluorine, RCPM, Cognitive, Developmental neurotoxicity, Epidemiological studies, Risk assessment

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Background

Fluorosis is a public health problem caused by excess intake of fluoride through drinking water, food products and industrial pollutants over a long period [1–4]. In India, endemic fluorosis is a major concern; about 20 states are affected, with more than 66 million people drinking water with more than the optimal required concentration of fluoride [4–6]. The most seriously affected states are Andhra Pradesh, Punjab, Haryana, Rajasthan, Gujarat, Uttar Pradesh, Tamil Nadu, Karnataka and Maharashtra.

Once fluoride enters the body, it reaches various organs and tissues, and excessive amounts can lead to various health problems, such as dental fluorosis, skeletal fluorosis and nonskeletal fluorosis [1, 7, 8]. The literature suggests that nonskeletal fluorosis affects various soft tissues of the body, such as the gastrointestinal tract, blood, brain tissues and thyroid gland [9–16]. In RBCs, the erythrocyte membrane, due to the influx of F^- loose calcium ions, leads to the formation of echinocytes, which are structurally and functionally deranged RBCs with short life span and are phagocytosed and eliminated from the bloodstream, leading to anaemia. Some researchers have also reported a correlation between high fluoride exposure and low intelligence quotient (IQ) in children [17–22].

The increase in the number of cases of nonskeletal fluorosis, which can lead to anaemia and mental disabilities, has long been recognized. Nonskeletal fluorosis can be reversible if diagnosed in initial stages; mitigation can be performed through the provision of safe drinking water, promotion of nutrition and avoidance of foods with high fluoride content [23]. However, to diagnose these conditions, invasive blood tests and specialized psychiatric assessments at higher health centers are needed. These facilities are not easily accessible in rural and remote areas. Therefore, there is need for some diagnostic methods that can be easily performed clinically even by rural health care workers.

Assessment of dental fluorosis, fluoride level in urine and drinking water are simple, easy and non-invasive diagnostic tests that can act as an important tool in suspecting any underlying systemic problem caused due to excessive fluoride intake. To date, no study has correlated the haemoglobin (Hb) with dental fluorosis; moreover, studies focusing on intelligence quotient (IQ) had conflicting results and need further research. Moreover, there is a need for more research on school-going children to curb the rise of fluorosis and linked disorders in developing countries. To address these issues, a study was conducted to determine any relationship among different fluoride assessment parameters (severity of dental fluorosis, fluoride level in urine and drinking water) with IQ status and hemoglobin level of children aged 8–12 years, affected with or without dental fluorosis.

Methods

Study design and setting

An observational cross-sectional study was conducted between January 2023 and July 2024. The study was conducted in accordance with the Declaration of Helsinki of 1975, revised in 2013, and the protocol was approved by the Biomedical and Health Research Committee, PGIDS, Rohtak vide letter no PGIDS/BHRC/21/4. Written informed assent from the participants and consent from their parents/guardians for inclusion were obtained.

Both high- and low-fluoride areas (optimum drinking water fluoride level $<= 1$ ppm) in Rohtak district, Haryana, India, were included in the study according to fluoride mapping survey [24]. The areas selected were rural areas with similar climatic conditions, with the majority of the population having a lower socioeconomic status with similar standards of living, quality of education, medical facilities, and cultural status and participants having comparable physical health and nutritional status. The children aged 8–12 years attending the schools in the study areas (high- and low-fluoride areas) were selected via random sampling method.

Inclusion criteria

a. Healthy cooperative children aged between 8 and 12 years were included.
b. Children whose parents provided informed written consent for participation were included.
c. The residents of the study area have continuously lived since birth and drinking water from the same source.
d. Similar socioeconomic status (as assessed by Revised Kuppuswamy’s socioeconomic status scale) [25].
e. Normal birth history.
f. There was no history of chronic illness or trauma to the head, and the patient was not on any medication.
g. Children who had average or above average birth weight (> 2.5 kg) and were breastfed for the initial six months of life were included [26].

Exclusion criteria

a. History of trauma to the head or other neurological disorders.
b. Any congenital or acquired disease affecting intelligence or the blood profile.
c. History of any genetic disease or systemic disorders.
d. Children who had a change in the source of drinking water since birth.

e. Severe extrinsic stains on teeth due to which assessment of the dental fluorosis status was not possible.
f. Parents and patients unwilling to participate in the study.

The patients who fulfilled the abovementioned inclusion criteria, along with parental written informed consent and assent from the participants, were selected for the study. A detailed questionnaire was completed, including information about the child's demographic status, parent's education, family income, source of drinking water and duration of use of the present source of drinking water, oral hygiene practices and toothpaste used (fluoridated or nonfluoridated) and dietary regime. (Supplementary file-1)

Study tools

Data were collected by clinical examination for assessment of dental fluorosis via Dean's fluorosis index, and the IQ levels were tested via Raven's Coloured Progressive Matrices (1998 edition) [27, 28]. The clinical examination was followed by three laboratory tests: (i) haemoglobin estimation, (ii) estimation of fluoride content in drinking water, and (iii) estimation of fluoride content in urine samples.

Sample size calculation

The sample size was calculated on the basis of the mean difference in IQ scores in high- and low-fluoride areas (91.37 ± 16.63 and 97.80 ± 15.95, respectively) [29]. Considering the power to be 80% at the 95% confidence interval, the formula used for the calculation was based on 2 independent samples with continuous outcomes, i.e., means ± SDs.

$$\mathrm{Sp} = \surd\,(\mathrm{n1}-1)\mathrm{s1}^2 + (\mathrm{n2}-1)\mathrm{s2}^2$$

$$(n_1 + n_2 - 2)$$

Where n_1 = Mean of the low fluoride area, n_2 = Mean of the high fluoride area, s_1 = Standard deviation (SD) of the low fluoride area, s_2= (SD) of the high fluoride area, and Sp = Pooled (SD) of the 2 groups.

The pooled (SD) value of the 2 groups was 15.8. With all the values in the equation, the sample size was 95 per group, which was verified with an online sample size calculator (Statulator). To increase the power of the study and compensate for nonresponses, a total of 300 subjects, 150 per group, were recruited for the study.

Project implementation

All the participants were screened for assessment of dental fluorosis via Dean's fluorosis index [27]. The participants were divided into 2 groups on the basis of the presence or absence of dental fluorosis. To avoid selection bias, a comparable sample population from each grade of dental fluorosis was included. Considering that 5 grades of fluorosis ranging from questionable to severe (0.5-4) exist, 30 children were included per group.

Clinical examination for the assessment of dental fluorosis

The severity and grading of dental fluorosis were done in accordance with Dean's fluorosis index which is a six-point scale [27]. Two most affected teeth were evaluated, however, if the two teeth were not equally affected, the score for the less affected tooth was recorded. Scoring was done starting from the higher end of the index "severe", and each score was eliminated until the final condition was reached. In case of doubt, the lower score was recorded. The categorization was as follows: normal/unaffected (score 0) - the enamel is translucent. The surface of the tooth is smooth, glossy, and usually has a pale creamy white color. Questionable (score 0.5) - enamel shows slight changes ranging from a few white flecks to occasional white spots. Very mild (score 1) -small opaque paper-white areas are scattered over the tooth surface but do not involve as much as 25% of the surface. Mild (score 2) - white opaque areas on the surface are more extensive but do not involve as much as 50% of the surface. Moderate (score 3) - white opaque areas affecting more than 50% of the enamel surface and severe (score 4) - enamel surfaces are affected. The major feature of this class is the presence of discrete or confluent pitting on the enamel surface.

Standardization of the recording procedure The examination and recording of the scores for all the subjects were carried out by a single examiner. The examiner was calibrated before the study as well as during the study.

Assessment of IQ status

Assessment of IQ status was performed by a clinical psychologist using Raven's coloured progressive matrices 1998 edition (RCPM) [28]. This is a nonverbal validated test for basic cognitive abilities and is widely used to evaluate normal brain functions for young children and old people, for anthropological studies, and for clinical work. It consists of twelve problems each in three sets: A, Ab and B; totaling 36 problems that include a matrix of geometrical design, with a part removed. The child must select the missing cell from six given alternatives. The maximum time allotted is 30 min according to the specifications of the test manual. The original scores from the tests were converted into percentile ranks according to the age norms of the children. The children's percentile ranks were subsequently categorized, according to the classification of the test manual, into the following five

IQ grade groups: Grade I—intellectually superior (at or above the 95th percentile); Grade II—definitely above the average intellectual capacity (at or above the 75th percentile); Grade III—intellectually average (between the 25th and 75th percentiles); Grade IV—definitely below average intellectual capacity (at or below the 25th percentile); and Grade V—intellectually impaired (at or below the 5th percentile). For the data analysis, these five IQ grades were further combined into two groups: intellectually average or above (grades I, II and III) and intellectually below average (grades IV and V).

Haemoglobin estimation

Sahli haemoglobinometer was used to determine the haemoglobin content of the blood {Haemometer Sahli-plano parallel, typesquare (TopTechBiomedicals, Vasai East, Palghar, Thane, Maharashtra)}.The haemoglobin level was expressed as g/dl. For data analysis, Hb content in blood was categorized according to the Indian Council of Medical Research categories of anaemia: participants with low Hb (anaemic) - less than 11 g/dl and participants with normal Hb- equal to or greater than 11 g/dl[30]

Fluoride estimation in urine

Each child was provided a plastic, wide-mouth bottle, with the name of the child, age and date written on a label of adhesive plaster. The collected samples were placed in an icebox immediately and brought to the laboratory. Urine fluoride testing was performed with an ion-selective fluoride meter with a fluoride-ion-selective electrode (Orion Versa Star prometer, Thermo Fisher Scientific water and lab products, Chelmsford, MA). In brief, fluoride standard solutions of 0.1, 1.0 and 10.0 mg/L were prepared by diluting a 100 mg/L fluoride standard solution in distilled water. The urine samples and standards were allowed to stand at room temperature and TISAB II solution (Total Ionic Strength Adjustment Buffer II) was then added to the test tubes at a ratio of 1:1 and shaken until stabilized. The direct readings of fluoride concentration (expressed in mg/L or ppm) were obtained according to the manufacturer's instructions. The results of fluoride content in urine were divided into 2 groups as follows: less than 1 mg/L or ppm and equal to or greater than 1 mg/L or ppm.

Fluoride estimation in drinking water

The participants were asked to obtain water (approximately 50 ml) in a plastic bottle directly from their domestic source of water and not from collected or stored water. The bottles were provided with the name of the child and the age and date of collection. The fluoride in the water sample was analyzed by an ion-selective fluoride meter (the results are expressed as mg fluoride/L) as described previously. The content of fluoride in the water was divided into less than 1 mg/L or ppm and equal to or greater than 1 mg/L or ppm.

Statistical analysis

The statistical analysis was performed via IBM SPSS version 21 (Statistical Package for Social Sciences) and Jamovi Statistics Software. Appropriate descriptive and inferential statistics were applied to analyze the data. Haemoglobin (Hb) levels were categorized into two groups: Normal and Anaemic. IQ scores were dichotomized, with grades I-III placed in the first group and grades IV and V in the second group. Urinary and water fluoride levels equal to or greater than 1 ppm was classified as high. The normality of the data was assessed by Shapiro−Wilk and Kolmogorov−Smirnov tests, which revealed a nonnormal distribution of variables. Associations between the variables were determined depending upon the number of groups (two or more than two) and the type of variable (categorical or quantitative). Mann-Whitney U test was utilized to compare variables between dental fluorosis and non- dental fluorosis groups. Kruskal-Wallis test was applied to compare variables among different grades of dental fluorosis. Additionally, Chi-square test was used to assess the significance of categorized haemoglobin levels, urinary fluoride levels, water fluoride levels, and IQ scores. Correlations were assessed by Spearman's rank correlation coefficient. A linear regression analysis was performed to predict Haemoglobin levels based on the predictor variables. Furthermore, a binary logistic regression was used to predict the dichotomized IQ categories. All statistical tests were conducted with a significance level set at $p < 0.05$.

Results

A total of 300 participants, 150 without dental fluorosis and 150 affected with different grades of dental fluorosis, ranging from questionable to severe (0.5-4), with 30 participants per group were included in the study. These children were using tap water or ground water for drinking and household purposes. Most of the parents were either illiterate (24%) or had schooling to the primary level (51%) and belonged to the lower or upper lower socioeconomic class according to the socioeconomic status scale [18]. The outliers were excluded from the study results on the basis of urine and water fluoride assessment using box and whisker plots and data of total 294 children was analysed. Table 1 presents the descriptive characteristics of the participants in terms of the presence or absence of dental fluorosis. Intergroup comparisons via the Mann−Whitney U test revealed significant differences in age (p-0.008), whereas nonsignificant differences were present in the hemoglobin level and the

Table 1 Descriptive statistics of participants with or without dental fluorosis

	Group	Number	Mean	SD (±)	SE	Median	*p*-value
Age	NF	149	9.49	1.445	0.1184	9	0.008**
	F	145	9.93	1.461	0.1213	10	
Hb	NF	149	9.50	1.785	0.1462	9.000	0.308
	F	145	9.63	1.455	0.1208	9.800	
Water F	NF	149	1.20	0.948	0.0777	0.989	0.979
	F	145	1.20	1.142	0.0949	1.016	
Urine F	NF	149	2.32	1.867	0.1530	1.689	0.807
	F	145	2.30	1.810	0.1503	1.670	

{NF-Non dental fluorosis, F- Dental fluorosis, SD- Standard deviation, SE- Standard error, Hb- Haemoglobin, Water F- Water fluoride level present in parts per million (ppm), Urine F- Urine fluoride level present in parts per million (ppm), IQ-Intelligence Quotient}

**- Highly significant ($p < 0.001$), *- significant ($p < 0.05$) (Mann-Whitney U test applied for intergroup comparison)

Table 2 Descriptive statistics of participants with different grades of dental fluorosis

	Dental Fluorosis Scale	Number	Age		Hb	Urine F	Water F
Mean	0.5	28	9.036	Alignment of table needs to be corrected	8.971	1.990	1.091
	1.0	30	9.633		9.620	1.866	1.229
	2.0	29	10.276		10.255	2.307	0.988
	3.0	28	10.036		9.507	2.792	1.264
	4.0	30	10.633		9.773	2.561	1.425
SE	0.5	28	0.2088		0.2809	0.3428	0.2299
	1.0	30	0.2603		0.2270	0.2884	0.2694
	2.0	29	0.2759		0.2332	0.2973	0.1216
	3.0	28	0.2439		0.2567	0.3957	0.1755
	4.0	30	0.2733		0.3068	0.3446	0.2306
Median	0.5	28	9.000		8.600	1.307	0.994
	1.0	30	9.000		9.400	1.470	0.988
	2.0	29	10		10.400	1.755	1.061
	3.0	28	10.000		9.200	2.263	1.075
	4.0	30	11.000		10.000	1.696	1.050
SD (±)	0.5	28	1.105		1.486	1.814	1.216
	1.0	30	1.426		1.243	1.580	1.475
	2.0	29	1.486		1.256	1.601	0.655
	3.0	28	1.290		1.358	2.094	0.929
	4.0	30	1.497		1.681	1.887	1.263
p-value			0.001**		0.014**	0.187	0.598

{NF-Non dental fluorosis, F- Dental fluorosis, SD- Standard deviation, SE- Standard error, Hb- Haemoglobin, Water F- Water fluoride level present in parts per million (ppm), Urine F- Urine fluoride level present in parts per million (ppm), IQ-Intelligence Quotient}

**- Highly significant ($p < 0.001$), *- significant ($p < 0.05$) (Kruskal Wallis test applied for intergroup comparison)

levels of fluoride in the water and urine. Table 2 depicts the stratification of the participants with dental fluorosis into 5 categories. Intergroup comparisons via the Kruskal‒Wallis test revealed that age and haemoglobin level were significantly related to different grades of fluorosis (< 0.001), whereas nonsignificant differences were present for levels of fluoride in water and urine. The frequency of different IQ grades was not significantly different among different grades of fluorosis (Table 3).

Associations between dental fluorosis, water fluoride, and urinary fluoride with iq and hemoglobin

The content of fluoride in the water was < 1 ppm and ≥ 1 ppm in equal numbers of participants i.e., 147 each (50%).The content of fluoride in the urine was < 1 ppm in 63 participants (21.4%) and ≥ 1 ppm in 231 participants (78.6%). In the present study, 218 participants (74.1%) were anaemic (haemoglobin < 11 g/dl), and 76 participants (25.9%) had normal Hb levels (≥ 11 g/dl) on the basis of the ICMR criteria for anaemia. A total of 185 participants (62.9%) were intellectually average or above (grades I, II and III), and 109 participants (37.1%) were intellectually below average (grade IV, no participant had Grade V IQ). No significant differences were observed regarding the presence or absence of dental fluorosis and different grades of fluorosis with IQ status. Similar findings were noted for haemoglobin, showing no significant differences associated with fluorosis (Tables 4

Table 3 Analysis comparing different grades of Dental Fluorosis with IQ scores

Dental Fluorosis Scale	**IQ Grades**					
	I	**II**	**III**	**IV**	**Total**	***p*-value**
0.0	13 (8.7%)	15(10.1%)	61(40.9%)	60(40.3%)	149	0.446
0.5	0(0%)	5(17.9%)	11(39.3%)	12(42.9%)	28	
1.0	2(6.7%)	7(23.3%)	11(36.7%)	10(33.3%)	30	
2.0	5(17.2%)	4(13.8%)	12(41.4%)	8(27.6%)	29	
3.0	5(17.9%)	6(21.4%)	8(28.6%)	9(32.1%)	28	
4.0	3(10%)	6(20%)	11(36.7%)	10(33.3%)	30	
Total	28(9.5%)	43(14.6%)	114(38.8%)	109(37.1%)	294	

(IQ- Intelligence quotient)

Table 4 Analysis comparing Dental Fluorosis with IQ and Haemoglobin

Dental Fluorosis	**IQ**		**Hb**	
	Scores I-III	**Score IV-V**	**Anaemic**	**Normal**
NF	89(59.7%)	60(40.3%)	107(71.8%)	42(28.2%)
F	96(66.2%)	49(33.8%)	111(76.6%)	34(23.4%)
TOTAL	185(62.9%)	109(37.1%)	218(74.1%)	76(25.9%)
p-value	0.250		0.353	
Odd's ratio	0.757(0.471,1.22)		0.78(0.462,1.32)	

{NF-Non dental fluorosis, F- Dental fluorosis, IQ-Intelligence Quotient, Hb- Haemoglobin}

Table 5 Analysis comparing different grades of Dental Fluorosis with IQ and Haemoglobin

Dental Fluorosis Scale	**IQ**		**Hb**	
	Scores I-III	**Score IV-V**	**Anaemic**	**Normal**
0	89(59.7%)	60(40.3%)	107(71.8%)	42(28.2%)
0.5	16(57.1%)	12(42.9%)	23(82.1%)	5(17.9%)
1	20(66.7%)	10(33.3%)	24(80%)	6(20.0%)
2	21(72.4%)	8(27.6%)	19(65.5%)	10(34.5%)
3	19(67.9%)	9(32.1%)	23(82.1%)	5(17.9%)
4	20(66.7%)	10(33.3%)	22(73.3%)	8(26.7%)
TOTAL	185(62.9%)	109(37.1%)	218(74.1%)	76(25.9%)
p-value	0.727		0.554	

(IQ- Intelligence quotient, Hb- Haemoglobin)

Table 6 Analysis comparing Water Fluoride with IQ and Haemoglobin

Water F	**IQ Transform**		**Hb Transform**	
	Scores I-III	**Score IV-V**	**Anaemic**	**Normal**
< 1ppm	92(62.5%)	55(37.5%)	98(66.7%)	49(33.3%)
≥ 1ppm	93(63.3%)	54(36.7%)	120(81.6%)	27(18.4%)
TOTAL	185(62.9%)	109(37.1%)	218(74.1%)	76(25.9%)
p-VALUE	0.904		0.003**	
Odd's ratio	0.971(0.605,1.56)		0.450(0.262,0.772)	

{Water F- Water fluoride level present in parts per million (ppm), IQ-Intelligence Quotient, Hb- Haemoglobin}

**- Highly significant ($p < 0.001$), *- significant ($p < 0.05$)

and 5). The fluoride content in water was inversely correlated with the haemoglobin level at highly significant level {p-0.003, OR: 0.450(0.262, 0.772)}, i.e., as water F level increases, Hb value decreases; but no correlation was observed with the IQ (Table 6). However, the fluoride content in urine was positively correlated with IQ {p-0.011,OR: 0.484(0.275,0.852)}, i.e., as urine F level increases, IQ grading increases or in other terms, intelligence decreases but no correlation was observed with the haemoglobin level (Table 7). The correlation matrix depicted a weak negative correlation of haemoglobin with water fluoride level and positive correlation with age and gender (Table 8). However, the inverse association of IQ with the fluorosis scale cannot be corroborated with previous contingency tables.

Table 7 Analysis comparing urine fluoride levels with IQ and Haemoglobin

Urine F	**IQ**		**Hb**	
	Scores I-III	**Score IV-V**	**Anaemic**	**Normal**
< 1ppm	31(49.2%)	32(50.8%)	48(76.2%)	15(23.8%)
≥ 1ppm	154(66.7%)	77(33.3%)	170(73.6%)	61(26.4%)
TOTAL	185(62.9%)	109(37.1%)	218(74.1%)	76(25.9%)
p-VALUE	0.011*		0.676	
Odd's ratio	0.484(0.275,0.852)		1.15(0.60,2.20)	

{Urine F- Urine fluoride level present in parts per million (ppm), IQ-Intelligence Quotient, Hb- Haemoglobin}

**- Highly significant ($p < 0.001$), *- significant ($p < 0.05$)

Table 8 Correlation Matrix

Hb	**Hb**	**Water F**	**Urine F**	**IQ**	**Dental Fluorosis scale**	**Age**	**Sex**
Water F	-0.215**	-					
Urine F	0.068	0.024	-				
IQ	0.048	0.010	0.078	-			
Dental Fluorosis scale	0.089	0.029	0.036	-0.121*	-		
Age	0.239**	0.016	-0.129*	-0.074	0.230**		
Sex	0.327**	-0.044	0.019	0.010	-0.12*	0.057	
Dental fluorosis (NF/F)	0.060	-0.002	-0.014	-0.102	0.032	0.154**	-0.129*

Spearman's rho correlation coefficient

{NF-Non dental fluorosis, F- Dental fluorosis, Hb- Haemoglobin, Water F- Water fluoride level present in parts per million (ppm), Urine F- Urine fluoride level present in parts per million (ppm), IQ-Intelligence Quotient}

**- Highly significant ($p < 0.001$), *- significant ($p < 0.05$)

Table 9 Linear regression to predict haemoglobin levels

Predictor	**Estimate**	**SE**	**95% Confidence Interval**		**t**	***p***
			Lower	**Upper**		
Intercept	5.9493	0.7077	4.55638	7.3421	8.41	< 0.001
Age	0.2712	0.0604	0.15229	0.3901	4.49	< 0.001
IQ	0.1706	0.0913	-0.00910	0.3504	1.87	0.063
Group	0.1805	0.1755	-0.16495	0.5260	1.03	0.305
Sex	1.0339	0.1734	0.69255	1.3753	5.96	< 0.001
Water F	-0.2338	0.0821	-0.39541	-0.0722	-2.85	0.005
Urine F	0.0542	0.0475	-0.03926	0.1476	1.14	0.255

{Hb- Haemoglobin, Water F- Water fluoride level present in parts per million (ppm), Urine F- Urine fluoride level present in parts per million (ppm), IQ-Intelligence Quotient}

Regression models predicting Haemoglobin & IQ

The multiple linear regression equation was calculated for predicting haemoglobin levels based on age, IQ, presence or absence of dental fluorosis (group), sex, water and urine fluoride. A significant regression equation was found ($p < 0.001$) with R [2] of 0.206. Participant predicted haemoglobin is equal to 5.9493 + 0.2712(Age) + 0.1706(IQ) + 0.1805(Group) + 1.0339(Sex) -0.2338(Water F) + 0.0542(Urine F) where age was measured in years, urine and water fluoride in ppm, IQ in 5 categories and groups as fluorosis and non-fluorosis. Each additional year of age increases haemoglobin levels by 0.2712 units. Each unit increase in IQ is associated with a 0.1706 unit increase in haemoglobin levels. The dental fluorosis group had 0.1805 units higher Hb as compared to the non-fluoride group and males had 1.0339 units higher Hb as compared to females. Each unit increase in urine fluoride levels is associated with a 0.0542 unit increase in haemoglobin levels whereas each unit increase in water fluoride levels is associated with a 0.2338 unit decrease in haemoglobin levels. Water fluoride, age and gender were significantly associated with haemoglobin (less than 11 g/dl vs. equal to or greater than 11 g/dl) (Table 9).

Binomial logistic regression analysis was done to predict IQ and non significant regression equation was found ($p = 0.551$) with R [2] of 0.04. Intelligence (below average vs. intellectually average or above average) was significantly related to urinary fluoride levels, with decrease in 0.7999 units IQ with increasing urinary fluoride level (Table 10).

Table 10 Binomial Logistic Regression for IQ scores

Predictor	Estimate	95% Confidence Interval		SE	Z	*p*	Odds ratio
		Lower	Upper				
Intercept	-0.6087	-2.6079	1.391	1.0200	-0.597	0.551	0.544
Age	-0.0321	-0.2051	0.141	0.0883	-0.364	0.716	0.968
Hb	0.1343	-0.0333	0.302	0.0855	1.571	0.116	1.144
Group	-0.3531	-0.8484	0.142	0.2527	-1.397	0.162	0.703
Water F	0.0316	-0.4619	0.525	0.2518	0.126	0.900	1.032
Urine F	-0.7999	-1.3752	-0.225	0.2936	-2.725	0.006	0.449
Sex	-0.2399	-0.7590	0.279	0.2648	-0.906	0.365	0.787

{Hb- Haemoglobin, Water F- Water fluoride level present in parts per million (ppm), Urine F- Urine fluoride level present in parts per million (ppm), IQ-Intelligence Quotient}

Discussion

Community water fluoridation is a public health program designed to supplement children and adults with fluoride, generally at concentrations ranging from 0.7 to 1.2 mg/L. However, in 2015, the Centers for Disease Control and Prevention updated its water fluoridation guidelines, setting it at 0.7 mg/L in the U.S [2]. The World Health Organization and Bureau of Indian Standards suggest that 1.0 ppm of fluoride in water is optimal for dental health and that 1.5 ppm is considered the maximum upper limit for overall health [31, 32]. The levels in surface water are generally less than 0.5 mg/L, whereas much wider ranges (0.1- 6 mg/L) have been reported in groundwater [33]. The adequate daily intake (ADI) of 1 mg/day, i.e., 0.05 mg/kg,[34] generally aims to achieve a balanced effect in precluding dental caries without increasing the risk of dental fluorosis; however, the results of few meta-analyses indicated that such an ADI may not be deemed safe from a cognitive development perspective, as children and babies retain advanced proportions of absorbed fluoride compared with adults [35].

Assessment of only water fluoride concentration cannot provide reliable insight into the total daily intake of fluoride. Analyses of biological samples, i.e., urine and blood (generally in the form of plasma or serum), provide information on fluoride circulating in the body. Although the plasma fluoride level is a contemporary biomarker for the intake of fluoride, urine has still been considered a valuable biomarker, as fluoride excretion is primarily through urine. The urinary fluoride level represents the cumulative exposure to fluoride through all sources, including water, diet and environmental pollutants. It is relatively simple to collect and non-invasive. Urine fluoride provides dependable and valid dose−response relationships, although for individuals and different age groups, it varies with renal function and acid−base balance [36]. Many studies have reported that the effects of urinary fluoride adjusted for creatinine are negligible, as renal function is generally effective and similar in the considered age groups; therefore, it only mildly affects the estimates of the relationship between intelligence and urinary fluoride [37–39]. High levels of urine fluoride were recorded in the present study compared with those reported in previous studies (0.41 ± 0.49 mg/L to 7.01 ± 1.02 mg/L) [18, 40, 41] and maybe attributed to the substantial dependence of subjects on locally grown vegetarian food for their day-to-day needs and regular intake of tea and usage of fluoridated toothpastes.

Most of the studies assessing any association between fluoride and human body tissues have employed three measures of fluoride exposure, namely, the water-fluoride concentration at the area of residence, the urine-fluoride level of the participants and, finally, the degree of dental fluorosis. Although water and urinary F represent current exposure to fluoride, dental fluorosis serves as a sensitive index of antenatal and early postnatal fluoride exposure and can provide information regarding lapping time windows for the development of dental fluorosis and other human tissues. All three parameters were assessed in the present study. Although, water-fluoride and urine-fluoride has been found to be statistically related to hemoglobin and IQ respectively, association of both parameters could not be established with dental fluorosis in present analysis.

Chronic fluoride overexposure has been linked to potential neurotoxic effects in children due to its accumulation in brain regions responsible for memory and learning [17–21]. Fluoride exposure has also been linked to hypothyroidism, negatively affecting early neurodevelopment [42]. In fact, while the blood-brain barrier, to some extent, can protect the adult brain from various toxic agents, it is less efficient in fetuses, newborns, and young children [43]. Several prospective birth cohort studies indicated that the antenatal period is a more critical time for potential neurotoxic effects of fluoride [18, 44–46]. A recent meta-analysis revealed that although an inverse association was observed between fluoride exposure and intelligence in most studies, there was a general trend toward weaker or null associations in the most precisely conducted studies [47]. The credibility of studies is questioned due to shortcomings such as imprecise exposure assessment (especially prenatal exposure), insufficient statistical power to allow identification of any important IQ deficit, the study design (high-quality longitudinal cohort versus cross-sectional studies), and the lack of acceptable consideration of major confounders, thus increasing the uncertainty about the actual association between fluoride exposure and children's cognitive neurodevelopment and reaffirming the strong need for properly designed and higher-quality research on this topic. In the present study, utmost care was taken to minimize the effects of these confounders by following strict inclusion criteria.

Previous meta-analyses have concentrated on studies conducted in impoverished rural communities in China, Mongolia, and Iran, and the findings cannot be generalized to developed countries [43, 47]. These rural areas may not have advanced healthcare systems, lower educational, socioeconomic, and nutritive status, and frequent exposure to environmental pollutants that have an implicit impact on intelligence. Conversely, relatively rich communities with access to better education and/or advanced socioeconomic status may invest in high-quality drinking water to avoid fluoride concentrations above 1.5 mg/L to reduce the threat of dental fluorosis. Several community study reports and meta-analyses revealed that fluoride exposure, which is applicable to community water fluoridation, is not associated with lower IQ scores in children [48–51].

In the present study, we did not observe a significant association between IQ and dental fluorosis or water fluoride; however, a significant association between IQ and urinary fluoride was noted after extensive evaluation of confounding factors. The negative findings for dental fluorosis and intelligence were consistent with those of a few former studies [52], but were inconsistent with several studies of school-aged children [40, 41, 53]. The significant association between urinary fluoride and intelligence was consistent with the findings of numerous previous studies [18, 20, 41] but clashes with few studies [52].

Age at the time of outcome evaluation varied extensively across the studies, potentially affecting both the cumulative exposure and acceptability of the intelligence tests that were administered. However, a subgroup analysis stratified by age categories found no correlation between age and IQ status.

In the present study, a negative correlation between hemoglobin levels and water fluoride was observed, but there was no significant association with urinary fluoride and dental fluorosis. Numerous studies have been conducted to estimate the effects of fluoride on hematological parameters in experimental animals as well as in human subjects residing in endemic fluorosis zones. Fluoride can cause haematological abnormalities in children, including abnormal blood cell counts and lower hemoglobin content [9, 15]. This is due to endogenous oxidative stress, depletion of Vitamin B12, and damage to intestinal microvilli. Chronic fluoride exposure also enhances the generation of reactive oxygen and nitrogen species in human red blood cells, leading to oxidation of hemoglobin, decreased antioxidant power, and inhibition of transmembrane electron transport and glucose metabolism. Some studies from India reported that anaemia in school children and pregnant women was attributed to the consumption of drinking water with high fluoride levels and that there was an inverse relationship between urinary fluoride and haemoglobin levels [54]. Females with elevated urinary fluoride levels have increased chances of gestation complications, such as preterm and small-for-gestational-age babies, and an increased prevalence of perinatal mortality [55, 56]. Another study reported that maternal anaemia and child anaemia are related to derangement of nutrient absorption due to damage to the GI mucosa by the ingestion of fluoride through food, water and other sources [10–13, 57]. Several studies have reported that withdrawing fluoride from consumption could correct the damage caused to the gastrointestinal mucosa/loss of microvilli, leading to nutrient absorption and an increase in hemoglobin and correction of anemia [9, 58]. While the present study observed an inverse relationship between hemoglobin levels and water fluoride concentrations, this finding is not consistent with all previous research, and potential confounders should be considered.

This study has several limitations, including using Raven's colored progressive matrices test for basic cognitive function estimation, which only measures fluid intelligence, not crystal intelligence or other cognitive abilities. Comprehensive tests that measure different intelligence constructs of children's cognitive abilities should be employed in future studies. The observational cross-sectional design of the study may be a relevant source of bias, primarily due to unmeasured or residual confounding. Moreover, cross-sectional studies cannot establish causality and long-term implications. However, randomized clinical trials investigating long-term exposure are not feasible because of ethical issues. Nevertheless, these children's current urinary fluoride levels might not represent the exposure that occurred in early childhood or in the prenatal period when the developing nervous system was vulnerable to environmental toxicants. The effects of additional naturally occurring contaminants (arsenic, mercury, lead, etc.) must be studied in detail to elucidate the actual detrimental effects of fluoride. Several factors considered in previous studies of the intelligence–fluoride relationship, such as birth weight, abnormal birth, maternal age at delivery, and parents' education level, were not estimated in this study [26, 59]. The implicit misclassification of dental fluorosis status could have biased the study results. Dental fluorosis is a sensitive effect biomarker for excessive fluoride intake during critical periods of tooth development up to 7–8 years of age, except in the third molars [60]. However, 71% of the children included in this study had mixed dentition, and 29% had permanent teeth only, according to the results of the oral examination. In this cross-sectional study, we were not able to evaluate whether the children's exfoliated primary teeth or unerupted permanent teeth were affected by fluorosis and, therefore, might have misclassified the participants' dental fluorosis status.

Despite these limitations, the study has strengths, including assessing individual-level fluoride exposure measures, namely, water fluoride, urine fluoride, and the degree of dental fluorosis, which serve as markers of both present and early-life fluoride exposure, controlling for potential confounders by strict inclusion criteria (such as socioeconomic status, residence, breast feeding, and low birth weight), and having a larger sample size and greater statistical power compared to previous studies.

The findings of past studies are intimidating, and the seriousness of this debate urges expedition of policymaking and awareness campaigns for public safety [17–22,42–47,61,62]. In countries with excessive groundwater fluoride concentrations, it is imperative to promote water defluoridation schemes to protect the public from skeletal and dental fluorosis and from possible 'linked disorders'. While water fluoridation continues to be recommended, the benefits appear to be minimal owing to the use of topical fluoride products, especially fluoridated toothpaste, which have led to significant decline in dental caries incidence as fluoride's predominant benefit comes from topical contact with the surface of enamel, not from ingestion, as was formerly believed [31,63]. A multicenter study with a large sample size that involves maximum strata of the population to further validate the results of the present study may be planned. Future studies that focus on exposures prenatally, during infancy, and in later childhood may allow more detailed assessment of the vulnerable time windows for fluoride toxicity. The results may be used to sensitize policymakers, health administrators, doctors, and grassroots-level functionaries to view the health issues caused by fluorosis and focus on improving the health of patients by early detection and appropriate management.

Conclusion

The study suggests a potential association between fluoride exposure and adverse effects on hematological parameters and cognitive neurodevelopment. Water fluoride intake was inversely associated with hemoglobin level and intelligence was inversely related to urinary fluoride levels, both at significant level. However, dental fluorosis cannot be used as a definitive assessment marker for these conditions, as it is not significantly correlated with these conditions. However, the limitations of this study, with particular reference to the risk of residual confounding, raise uncertainties about both the causal nature of such a relationship and the exact thresholds of exposure involved. Thus, well-designed, high-quality longitudinal cohort studies involving more comprehensive assessments of all variables and confounding factors are urgently needed to better interpret the implicit effects of chronic fluoride exposure and their long-term implications.

Supplementary Information

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Supplementary Material 1

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Author contributions

R.S.- Study conception and design, writing, review & editing; R.N. and A.B.- Supervision and manuscript editing; A.K.- Analysis and interpretation of results; S.S.- Psychological evaluation of subjects.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki of 1975, revised in 2013, and the protocol was approved by the Biomedical and Health Research Committee, PGIDS, Rohtak vide letter no PGIDS/BHRC/21/4. Written informed assent from the participants and consent from their parents/guardians for inclusion were obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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