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Review Paper

Association between water fluoride and the level of children's intelligence: a dose–response meta-analysis

Q. Duan, J. Jiao, X. Chen, X. Wang*

Department of Medical Imaging, The Affiliated Hospital of Guizhou Medical University, Guiyang, China

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ABSTRACT

Objectives: Higher fluoride concentrations in water have inconsistently been associated with the levels of intelligence in children. The following study summarizes the available evidence regarding the strength of association between fluoridated water and children's intelligence.
Study design: Meta-analysis.
Methods: PubMed, Embase, and Cochrane Library databases were systematically analyzed from November 2016. Observational studies that have reported on intelligence levels in relation to high and low water fluoride contents, with 95% confidence intervals (CIs) were included. Further, the results were pooled using inverse variance methods. The correlation between water fluoride concentration and intelligence level was assessed by a dose–response meta-analysis.
Results: Twenty-six studies reporting data on 7258 children were included. The summary results indicated that high water fluoride exposure was associated with lower intelligence levels (standardized mean difference : −0.52; 95% CI: −0.62 to −0.42; $P < 0.001$). The findings from subgroup analyses were consistent with those from overall analysis. The dose–response meta-analysis suggested a significant association between water fluoride dosage and intelligence ($P < 0.001$), while increased water fluoride exposure was associated with reduced intelligence levels.
Conclusions: Greater exposure to high levels of fluoride in water was significantly associated with reduced levels of intelligence in children. Therefore, water quality and exposure to fluoride in water should be controlled in areas with high fluoride levels in water.

Introduction

Fluorosis is a progressive degenerative disease that causes skeletal fluorosis and dental fluorosis.[1] Previous studies have shown that fluoride can cross the blood–brain barrier, induce neurotoxicity, and affect children's cognitive abilities and mental development.[2–4] Currently, about 500 million people are exposed to environments high in fluoride content, while

* *Corresponding author*. Department of Medical Imaging, The Affiliated Hospital of Guizhou Medical University, Guiyang 550001, China. Tel.: +86 18286139851.
E-mail address: wangxiaolin161@163.com (X. Wang).
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the incidence of fluorosis has already reached 200 million people worldwide.[5,6] The inherent limitations related to previous review include the range of fluoridated water intake and the cut-off values varying between studies. Furthermore, the relationships between water fluoridation and intelligence in specific subpopulations were not illustrated.

Recently, numerous studies have evaluated the relationship between fluorosis and the children's intelligence, revealing somewhat inconsistent results.[7,8] Therefore, a new systematic evaluation and meta-analysis are required to determine the strength of this relationship. Although numerous meta-analyses have already assessed the relationship between endemic fluorosis and intelligence levels, new studies have emerged calling for re-evaluation of this relationship.[4,7–9] Moreover, previous meta-analyses failed to provide dose–response curves. Consequently, we conducted an updated dose–response meta-analysis to evaluate the correlation between fluoride dosage and children's intelligence levels.

Methods

Data sources, search strategy, and selection criteria

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009.[10] Any observational study that examined the relationship between water fluoride content and children's intelligence was eligible for inclusion in our study, while there were no restrictions on language or publication status (published, in press, or in progress). The PubMed, Embase, and Cochrane Library electronic databases were searched throughout November 2016 for relevant published articles. The following search terms were used: 'fluoride', 'fluorine', 'intelligence', 'IQ', and 'intelligence quotient'. We also manually searched reference lists from all original and review articles to identify additional eligible studies. The medical subject headings, methods, study population, study design, exposure levels, and outcome variables were used to identify potentially relevant studies.

Two authors identified eligible studies, and all discrepancies were resolved by group discussion. The eligibility criteria included: (1) the study design was observational; (2) the participants were children; (3) the experimental group comprised individuals from areas with high fluoride levels in water, and the control group comprised individuals from areas with normal fluoride levels in water; and (4) the study reported intelligence levels.

Data extraction and quality assessment

The data extraction and quality assessment were conducted independently by two authors. The available information were examined and adjudicated independently by a third author after referring to the original studies. The collected data included the name of the first author, publication year, country, study design, sample size, mean age, percentage of boys, fluoride exposure assessment, intelligence assessment, reported outcomes, and study quality. The Newcastle–Ottawa Scale (NOS), which is comprehensive and partially validated for evaluating the quality of observational studies in a meta-analysis, was used to evaluate the methodological quality.[11] The NOS is based on the following subscales: selection (4 items), comparability (1 item), and outcome (3 items). A 'star system' (range, 0–9) has been developed for the assessment.[12]

Statistical analysis

The inverse variance method was used to pool continuous data, and the results were presented as the standardized mean difference (SMD) with the corresponding 95% confidence intervals (CIs). The relationship between water fluoride intake and intelligence level was examined based on the effect estimate and its 95% CIs published in each study. Fixed or random effects models were initially used to calculate the SMDs and 95% CIs for the high vs normal fluoride concentration of the water. Next, using the generalized least-squares for trend estimation, the category-specific mean estimates were transformed into estimates of the SMD associated with increasing fluoride concentration of water.[11] These estimates were calculated assuming the linear relationship between the natural logarithm of the SMD and the increasing intake of fluoridated water. The value assigned to each fluoride concentration level of water was the mid-point for closed categories, such as the median and mean. Finally, a dose–response meta-analysis was conducted from the correlated natural log of the SMDs across the range of fluoride concentration of the water.[13,14] In order to derive the dose–response curve, the fluoride intake was modeled by using restricted cubic splines with three knots at fixed percentiles of 10%, 50%, and 90% of the distribution.[11] This method requires that the distributions of cases, and effect estimate (SMDs) with the variance estimates for at least three quantitative exposure categories are known. The I^2 statistics was calculated to evaluate the extent of variability attributable to the statistical heterogeneity between trials. In the absence of statistical heterogeneity ($I^2 < 50\%$), fixed effect model was used; otherwise, a random effect model[15] was used. A sensitivity analysis was conducted by removing each individual study from the meta-analysis. Predefined subgroup analyses were performed based on country, sex, age, water fluoride dosage, and intelligence assessment. To investigate the sources of heterogeneity, meta-regression analysis was performed.[16] The publication bias was assessed by visual examination of funnel plots and using the Begg and Mazumdar[17] and Egger tests.[18] Results with two-sided P values less than 0.05 were considered statistically significant. Review Manager (version 5.3) and STATA (version 12.0) were used for data analysis.

Results

Following removal of duplicates, 238 studies were found. Among these, basic researches, comments, reviews, and other irrelevant studies were eliminated, resulting in 76 full-text articles. These were then evaluated in detail, and 50 of them were excluded due to following reasons: comments and reviews (26), no relevant data (10), fluoride from coal burning (4), irrelevant studies (4), fluoride dosage not available (3), the study reported data came from sample population (2), and no control group (1). Finally, 26 studies assessing 7258 children were selected for the final analysis (Fig. 1). Table 1 summarizes the characteristics of the participants and included studies. Four trials were performed in Iran,[1,19–21] Four trials were performed in India,[22–25] and the others were performed in China. One of the trials assessed the fluoride dosage from urine,[26] while the others measured the dosage from water. In most trials, the mean or median fluoride exposure of the test group was >1 mg/l, and <1 mg/l in the control group (Table 1). Two articles used the Wechsler Intelligence test for intelligence assessment,[27,28] one article used the Binet–Simon test,[29] one article used the Iranian version of the Raymond B Cattell test,[21] one article used the Japan intelligence quotient (IQ) test,[30] while the other articles used the Raven related intelligence test. Study quality was evaluated using the NOS (Table 1). Overall, one study had a score of 7,[26] five studies had a score of 6,[27,28,49,50,55] 17 studies had a score of 5,[1,20–22,24,25,29,30,44–48,51–54] and the one study had a score of 4.[23]

As shown in Fig. 2, high fluoride levels in water were associated with lower intelligence levels (SMD: −0.52; 95% CI: −0.62 to −0.42; $P < 0.001$). The random effects model was employed due to the substantial statistical heterogeneity ($I^2 = 69.1\%$; $P = 0.040$). As a result, a sensitivity analysis was conducted, and after sequential exclusion of each study from pooled analyses, the final result was not affected by the exclusion of any specific study. The results of the meta-regression indicated that age significantly affected the relationship between high fluoride content and the children's intelligence level ($P = 0.039$; Fig. 3). Subgroup analysis was performed based on country, age, fluoride dosage, intelligence assessment, and sex (Table 2). High fluoride content was associated with lower levels of intelligence in China (SMD: −0.482; 95% CI: −0.581 to −0.383; $P < 0.001$), Iran (SMD: −0.682; 95% CI: −0.985 to −0.380; $P < 0.001$), and India (SMD: −0.694; 95% CI: −1.250 to −0.138; $P = 0.015$). Moreover, high fluoride content was associated with the children's intelligence levels regardless of the age group they belonged to (age <10.0 years: SMD: −0.331, 95% CI: −0.520 to −0.142, $P < 0.001$; age ≥10.0 years: SMD: −0.451, 95% CI: −0.597 to −0.305, $P < 0.001$). Similarly, the levels of intelligence were significantly lower in children living in areas with high fluoride contents, regardless of sex (boys: SMD: −2.008, 95% CI: −3.069 to −0.946, $P < 0.001$; girls: SMD: −2.053, 95% CI: −2.730 to −1.377, $P < 0.001$). In addition, high fluoride levels were associated with lower levels of intelligence tested using the Chinese standardized Raven's test (SMD: −0.525, 95% CI: −0.668 to −0.382, $P < 0.001$), Raven's intelligence test (SMD: −0.534, 95% CI: −0.688 to −0.381, $P < 0.001$), and other intelligence assessment approaches (including the Wechsler Intelligence test, Binet–Simon test, Japan IQ test, and Raymond B Cattell test) (SMD: −0.524, 95% CI: −0.764 to −0.284, $P < 0.001$). Finally, high fluoride levels were associated with lower levels of intelligence in all the fluoride dosage subsets (1–2 mg/l: SMD: −0.538, 95% CI: −0.931 to −0.144, $P = 0.007$; 2–3 mg/l: SMD: −0.573, 95% CI: −0.731 to −0.415, $P < 0.001$; 3–4 mg/l: SMD: −0.675, 95% CI: −1.012 to −0.338, $P < 0.001$; 4–5 mg/l: SMD: −0.435, 95% CI: −0.613 to −0.257, $P < 0.001$; 5–6 mg/l: SMD: −0.385, 95% CI: −0.579 to −0.190, $P < 0.001$; 8–9 mg/l: SMD: −0.257, 95% CI: −0.444 to −0.070, $P = 0.007$; 11–12 mg/l: SMD: −0.455, 95% CI: −0.710 to −0.201, $P < 0.001$).

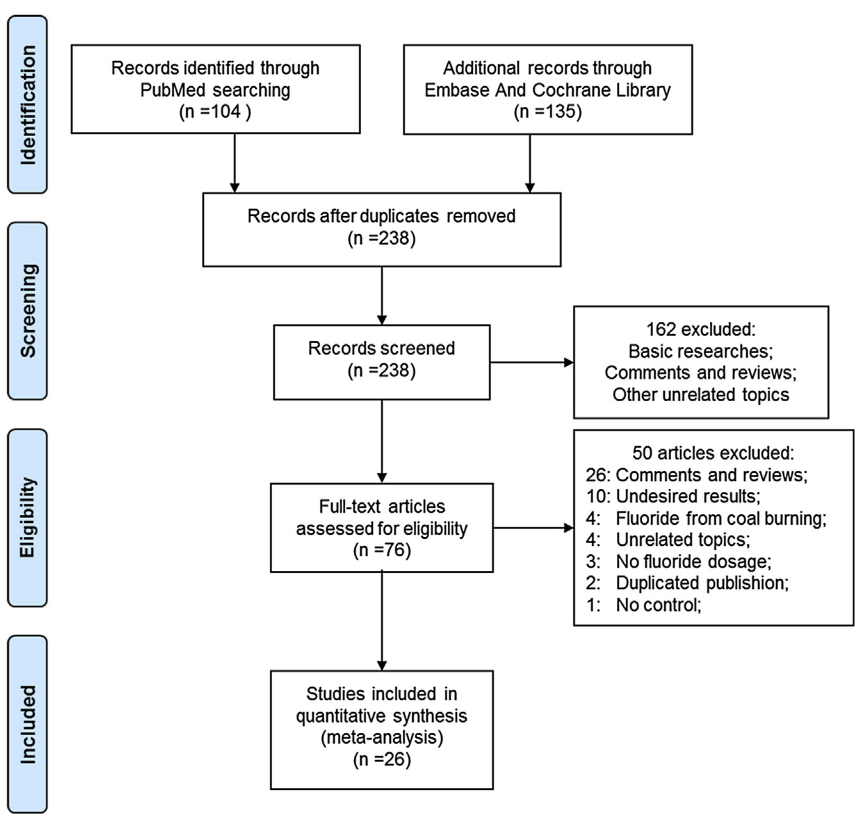

Fig. 1 – Flow chart of the literature search and selection process.

Table 1 – Characteristics of the included studies.

Study	Year	Country	Study design	Age (years)	Percentage of boys	Number of subjects	Expose assessment	F exposure dosage (mg/l)[a]	Control F dosage (mg/l)[a]	Intelligence assessment	Report outcome	NOS, study quality
An JA[27]	1992	China	Observational study	7–16	N/A	242	Water	4.85 (2.1–7.6)	0.8	Wechsler Intelligence test	IQ; IQ of different age; IQ distribution	6
Xu YL[29]	1994	China	Observational study	8–14	N/A	129	Water	1.8	0.8	Binet–Simon test	IQ; IQ distribution	5
Li XS[26]	1995	China	Observational study	8–13	62.80%	907	Urinary	3.2 (1.81–2.69)	0.4	Chinese standardized Raven test	IQ; IQ in age; IQ distribution; IQ in genders	7
Zhao LB[44]	1996	China	Observational study	7–14	50%	320	Water	4.12	0.91	Chinese standardized Raven test	IQ; IQ in age; IQ distribution; IQ in education level	5
Wang GJ[28]	2008	China	Observational study	4–7	50.90%	230	Water	4.8 (1.0–9.6)	0.79 (0.58–1.0)	Wechsler Intelligence test	IQ; IQ less than 90; IQ in different head circumference	6
Yao LM[45]	1996	China	Observational study	8–12	N/A	536	Water	11	0.5 (0–1)	Chinese standardized Raven test	TSH level; IQ; IQ distribution	5
Yao LM[46]	1997	China	Observational study	7–14	50%	502	Water	2	0.4	Chinese standardized Raven test	IQ; IQ in age	5
Zhang JW[30]	1998	China	Observational study	4–10	N/A	103	Water	0.8	0.58	Japan IQ test	IQ; IQ in age	5
Lu Y[47]	2008	China	Observational study	10–12	N/A	118	Water	3.15	0.37	Chinese standardized Raven test	IQ; IQ distribution; Relationship between IQ and F level	5
Hong FG[48]	2008	China	Observational study	8–14	N/A	117	Water	2.9	0.75	Chinese standardized Raven test	IQ; IQ distribution; IQ in education level	5
Wang XH[49]	2001	China	Observational study	8–12	N/A	60	Water	2.97	0.5	Chinese standardized Raven test	IQ; IQ distribution	6
Xiang Q[50]	2003	China	Observational study	8–13	55.10%	512	Water	2.47 (0.57–4.5)	0.47 (0.18–0.76)	Chinese standardized Raven test	IQ; IQ in genders; IQ in serum fluoride level;	6
Seraj B[1]	2006	Iran	Observational study	N/A	N/A	126	Water	2.5	0.4	Raven test	IQ; IQ in age	5
Wang ZH[51]	2006	China	Observational study	8–12	N/A	368	Water	5.54 (3.88)	0.73 (0.28)	Chinese standardized Raven test	IQ; IQ distribution	5
Fan ZX[52]	2007	China	Observational study	7–14	N/A	79	Water	3.15 (1.14–6.09)	1.03	Chinese standardized Raven test	IQ; IQ distribution	5

Wang SX[53]	2007	China	Observational study	8–12	N/A	449	Water	8.3 (3.8–11.5)	0.65 (0.2–1.1)	Chinese standardized Raven test	IQ; IQ distribution	5
Chen YX[54]	2008	China	Observational study	7–14	50%	640	Water	4.55	0.89	Chinese standardized Raven test	IQ; IQ distribution; IQ in genders; IQ in age	5
Hamid Reza Pourelami[20]	2011	Iran	Observational study	7–9	48.30%	120	Water	2.38	0.41	Raven's Progressive Matrices Intelligence Test	IQ; IQ distribution; IQ in genders	5
Pranati Eswar[22]	2011	India	Observational study	12–14	51.90%	133	Water	2.45	0.29	Raven test (Standard Progressive Matrices test)	IQ; IQ distribution	5
Wang GJ[28]	2012	China	Observational study	8–13	54.90%	526	Water	2.45 (0.8)	0.36 (0.11)	Chinese standardized Raven test	IQ; IQ in genders; IQ in fluoride intake level;	6
MH Trivedi[23]	2012	India	Observational study	N/A	61.90%	84	Water	2.25	0.42	Raven test (Standard Progressive Matrices test)	IQ; IQ distribution; IQ in genders	4
B.Seraj[1]	2012	Iran	Observational study	6–11	48.50%	293	Water	5.2 (1.1)	0.8 (0.3)	Raven's Color Progressive Matrices	IQ; IQ distribution; IQ in genders; IQ in fluoride intake level;	5
Zhang Shun[55]	2015	China	Observational study	10–12	41.10%	180	Water	1.4 (1.23–1.57)	0.63 (0.58–0.68)	Chinese standardized Raven test	IQ; IQ in COMT genotype	6
S Karimzade[21]	2014	Iran	Observational study	9–12	100%	39	Water	3.94	0.25	The Iranian version of the Raymond B Cattell test	IQ; IQ distribution	5
D. Mondal[24]	2015	India	Observational study	10–14	50.60%	40	Water	5.39	0.76	Raven Standard Theoretical Intelligence Test	IQ; IQ in genders	5
Shibu Thomas Sebastian[25]	2015	India	Observational study	10–12	N/A	405	Water	2	0.4	Raven's Colored Progressive Matrices	IQ; IQ distribution	5

N/A, not available; IQ, intelligence quotient; NOS, Newcastle–Ottawa Scale; COMT, catechol-O-methyltransferase.

[a] Median (Min.-Max.) or Mean (SD).

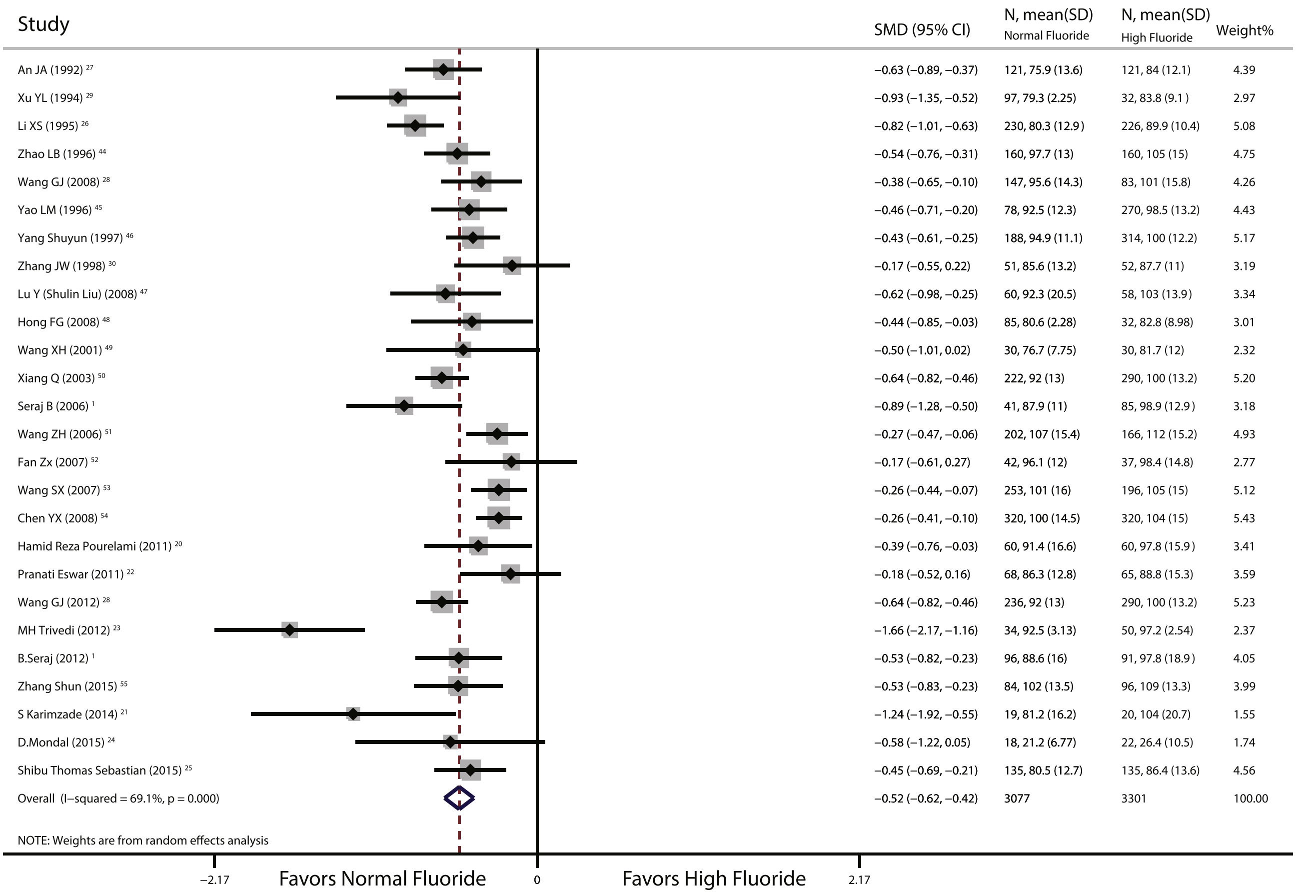

Fig. 2 – Association between water fluoride exposure and intelligence levels in children. CI, confidence intervals; SMD, standardized mean difference; SD, standard deviation.

The dose–response meta-analysis indicated a significant non-linear relationship between fluoride dosage and children's intelligence levels ($P < 0.001$; Fig. 4a). However, a linear relationship was not statistically significant between fluoride dosage and children's intelligence ($P = 0.976$; Fig. 4b). A non-linear relationship was evident between the relative fluoride dosage and the children's IQ ($P < 0.001$; Fig. 4c), and a linear relationship was also noted between relative fluoride dosage and children's intelligence levels ($P < 0.001$) (Fig. 4d).

Review of the funnel plots did not rule out publication bias related to the children's IQ. However, results of the Begg and Egger tests showed no evidence of publication bias related to the children's IQ (Begg test, $P = 0.134$; Egger test, $P = 0.173$) (Fig. 5).

Discussion

A total of 26 studies and 7258 children were included in the present review. In general, we found that high levels of fluoride exposure significantly affected the development of intelligence in children. Additional analysis revealed children's age as a potential source of heterogeneity, since the effect of age was robust in the subgroup analysis performed to account for the effects of covariates. Since the dose–response meta-analysis showed a relationship between the fluoride concentration in water and children's IQ, it is necessary to improve water quality, especially in areas which are economically backward or are faced with serious pollution problems. Government and non-government organizations should pay more attention to control the concentration of fluoride in drinking water to reduce the impact on children's mental development.

Based on animal studies, fluoride has been reported to cross the blood–brain barrier.[31] With the increase of fluoride intake, the fluoride concentrations in the brain increase gradually.[32] Previous studies have shown that high long-term fluoride intake can cause damage to nerve fibers and synapses in the hippocampus and other brain areas, as well as to the blood–brain barrier in rats.[33,34] However, the relationship between high fluoride intake and the mental development in children still needs to be verified. Moreover, there is a variability at the level of individual subjects belonging to different nations, ethnic groups, education and economic brackets, and so on. In the present study, a meta-analysis was conducted to synthesize results from several studies aiming to obtain more reliable conclusions.

In China, fluoride levels in drinking water cannot be more than 1 mg/l.[35] Besides affecting intellectual development in children, long-term exposure to high fluoride levels in the

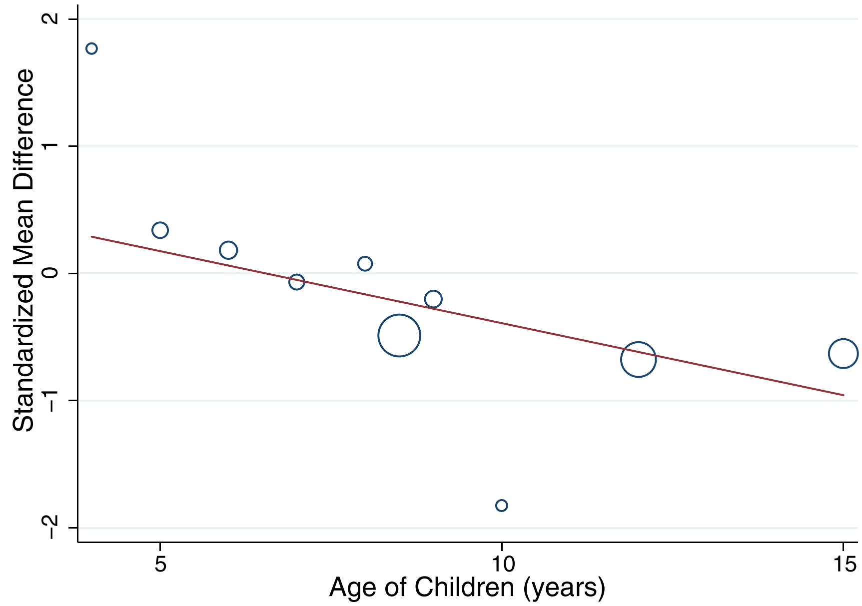

Fig. 3 – Metaregression of the age grades.

drinking water can also cause disorders related to calcium and phosphorus metabolism, leading to calcium loss and fluorosis.[36] Dental fluorosis, characterized by the blackening of teeth and yellowing and roughening of the palate, is the most common in populations living in areas with high fluoride content in drinking water.[37] Skeletal fluorosis is another very common and very serious side-effect of high fluoride intake, characterized by changes in the bone density, skeletal deformation, rickets, paralysis, disability, and even death.[38] Patients with skeletal fluorosis have been reported to show neuronal nuclear vacuoles formations, cell loss in the spinal cord, and loss or solidification of Nissl

Table 2 – Subgroup analysis of the impact of water fluoride content on the children's intelligence levels.

Subgroup		Number of studies	SMD (95% CIs)	P-value	Heterogeneity %	P for heterogeneity
Country	Overall	26	−0.523 (−(0.621 to −0.424)	P < 0.001	69.10%	P < 0.001
	China	18	−0.482 (−0.581 to −0.383)	P < 0.001	64.40%	P < 0.001
	Iran	4	−0.682 (−0.985 to −0.380)	P < 0.001	56.20%	P = 0.077
	India	4	−0.694 (−1.250 to −0.138)	P = 0.015	87.50%	P < 0.001
Gender	Overall	23	−2.053 (−2.730 to −1.377)	P < 0.001	98.60%	P < 0.001
	Male	12	−2.008 (−3.069 to −0.946)	P < 0.001	98.90%	P < 0.001
	Female	11	−2.095 (−2.992 to −1.377)	P < 0.001	98.10%	P < 0.001
Age in years	Overall	8	−0.406 (−0.522 to −0.291)	P < 0.001	0%	P = 0.594
	<10	3	−0.331 (−0.520 to −0.142)	P = 0.001	0%	P = 0.636
	≥10	5	−0.451 (−0.597 to −0.305)	P < 0.001	0%	P = 0.453
Water fluoride dosage	Overall	27	−0.520 (−0.616 to −0.424)	P < 0.001	67.90%	P < 0.001
	1–2 mg/l	3	−0.538 (−0.931 to −0.144)	P = 0.007	71.40%	P = 0.030
	2–3 mg/l	11	−0.573 (−0.731 to −0.415)	P < 0.001	68.60%	P < 0.001
	3–4 mg/l	4	−0.675 (−1.012 to −0.338)	P < 0.001	68%	P = 0.025
	4–5 mg/l	4	−0.435 (−0.613 to −0.257)	P < 0.001	61.20%	P = 0.052
	5–6 mg/l	3	−0.385 (−0.579 to −0.190)	P < 0.001	19.10%	P = 0.291
	8–9 mg/l	1	−0.257 (−0.444 to −0.070)	P = 0.007		
	11–12 mg/l	1	−0.455 (−0.710 to −0.201)	P < 0.001		
Intelligence assessment	Overall	26	−0.523 (−0.621 to −0.424)	P < 0.001	69.10%	P < 0.001
	Chinese standardized Raven test	15	−0.525 (−0.668 to −0.382)	P < 0.001	77.20%	P < 0.001
	Raven's intelligence test	6	−0.534 (−0.688 to −0.381)	P < 0.001	46.20%	P = 0.098
	Other intelligence assessment	5	−0.524 (−0.764 to −0.284)	P < 0.001	54.60%	P = 0.066

CI, confidence interval; SMD, standardized mean difference.

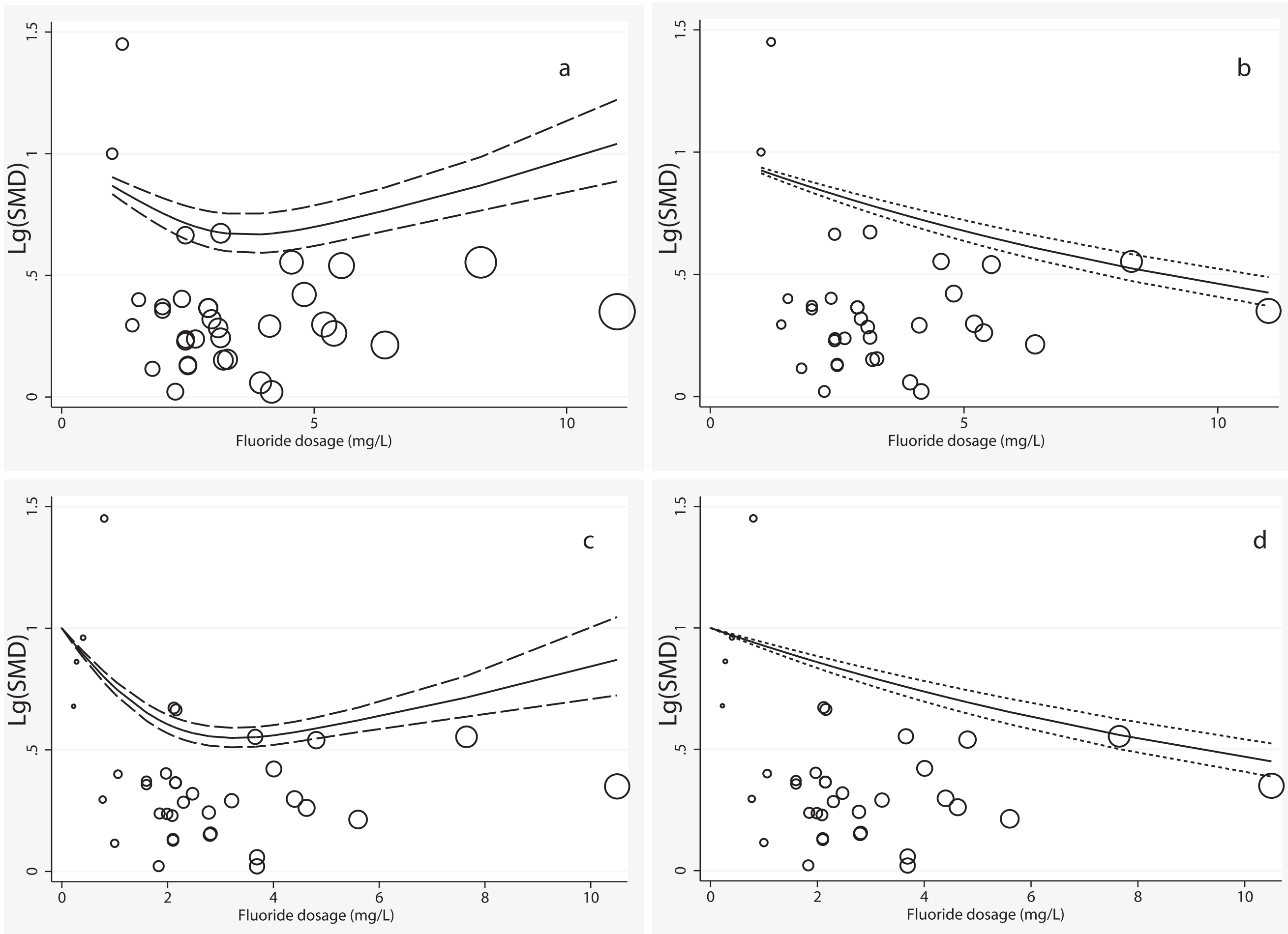

Fig. 4 – (a) Dose–response non-linear association between the absolute concentration of fluoride and the children's intelligence levels. (b) Dose–response linear association between the absolute dosage of fluoride and the children's intelligence levels. (c) Dose–response non-linear association between the relative dosage of fluoride and the children's intelligence levels. (d) Dose–response linear association between the relative dosage of fluoride and the children's intelligence levels. SMD, standardized mean difference.

bodies.[39] Moreover, patients experience fatigue, sleepiness, headache, dizziness, and other symptoms related to the nervous system.

The studies included in the present review were performed in three countries, i.e. China, Iran, and India. Water fluoride content is geographically distributed in a specific manner in the world, and increases of fluoride levels in drinking water are the main cause of fluorosis in these countries.[40] The early development of the brain is synchronous with the development of intelligence. Generally, the age range between 7 and 10 years is an important period for the development of a child's intelligence. According to our results, high fluoride intake would affect the children's intelligence, regardless of their age. Nonetheless, the results of the meta-regression did show that age had an important role in the relationship between high fluoride intake and intelligence level, which furthermore implied that the intelligence level was affected by increasing age. Different intelligence assessment methods can cause heterogeneity among the studies. Subgroup analysis revealed the significant relationship between the fluoride content of drinking water and the intelligence as assessed by general intelligence assessment methods. Certain studies have suggested that estrogen could affect the absorption and metabolism of fluoride,[41] and that the incidence of fluorosis varies among girls and boys. However, in the present review, sex-related differences in the relationship between fluoride intake and intelligence level were not observed.

The dose–response meta-analysis revealed a non-linear regression in both relative and absolute doses. The relationship between fluoride intake and intelligence levels was most obvious above an absolute fluoride concentration of about 4 mg/l or a relative fluoride concentration of about 3 mg/l. The intelligence level of boys residing in areas with medium water fluoride content (3.1 ± 0.9 ppm) was lower compared to boys residing in areas with high water fluoride content (5.2 ± 1.1 ppm); the number of children with below average intelligence levels in the medium fluoride group was higher compared to high fluoride group. Although the result of non-linear model suggested that very high fluoride concentration

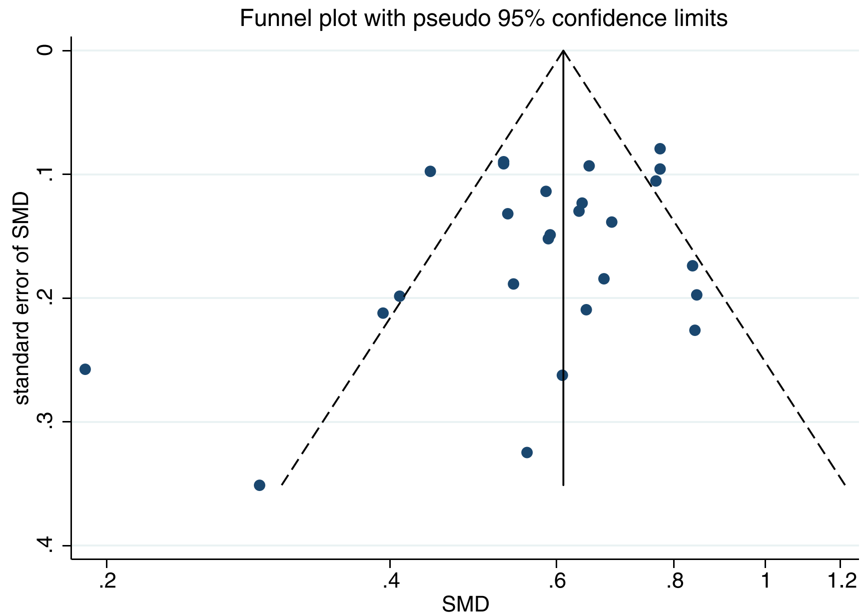

Fig. 5 – Funnel plot for intelligence levels. SMD, standardized mean difference.

in water was associated with higher intelligence level than medium fluoride, the results might variable due to smaller number of cohorts were included. Further, the linear regression model showed that the higher the fluoride concentration, the more the mental development of the children was affected.

In this review, the fluoride intake resulting from coal burning and its effect on the intelligence level was not considered, since the dosage of fluoride in coal is difficult to define, the time impact in children is not clear, and the topic is little studied.[42]

We systematically evaluated the intelligence levels of children living in districts with high fluoride levels in water; however, this analysis had several limitations. First, we lacked specific individual data for all the trials; thus, our statistical analysis could only be performed at a study level. Second, there were several unknown factors that may have caused heterogeneity. Third, the different categories of water fluoride were not included in subgroup analyses, which might have affected the obtained results about the relationship between water fluoride and intelligence level in specific subsets. Fourth, the control doses of water fluoride (i.e. no observed adverse effects) were not illustrated in stratified analyses, which might have led to a potential confounder bias. Finally, socio-economic status is usually a major confounder, and since the socio-economic status was not provided in all original articles, this might have affected the relationship between water fluoride intake and intelligence levels.

High fluoride content in drinking water can affect the intellectual development of children, since the children residing in areas with high fluoride content revealed to have lower levels of intelligence compared to children residing in areas with normal fluoride content. Moreover, the higher the fluoride concentration was, the more obviously the children's intelligence was affected. Furthermore, high fluoride intake was associated with low intelligence levels regardless of country, sex, age, fluoride concentration, and intelligence assessment method employed. Therefore, improving water quality and reducing the fluoride levels in drinking water in areas with high water fluoride content are important measures that could help increase the intelligence levels of children living in these areas.

Author statements

Ethical approval

None sought.

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Competing interests

None declared.

Author contributions

Q.D. contributed to the study concept, manuscript preparation, and drafting the manuscript. J.J., X.C., and X.W. contributed to data collection, analysis, and revising the manuscript for important content. All authors read and approved the final manuscript.

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