



Review article

Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis

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ABSTRACT

Many uncertainties still surround the possible harmful effect of fluoride exposure on cognitive neurodevelopment in children. The aim of this systematic review and meta-analysis was to characterize this relation through a dose-response approach, by comparing the intelligence quotient (IQ) scores in the highest versus the lowest fluoride exposure category with a random-effects model, within a one-stage dose-response meta-analysis based on a cubic spline random-effects model.

Out of 1996 potentially relevant literature records, 33 studies were eligible for this review, 30 of which were also suitable for meta-analysis. The summary mean difference of IQ score, comparing highest versus lowest fluoride categories and considering all types of exposure, was -4.68 (95% confidence interval-CI -6.45 ; -2.92), with a value of -5.60 (95% CI -7.76 ; -3.44) for drinking water fluoride and -3.84 (95% CI -7.93 ; 0.24) for urinary fluoride. Dose-response analysis showed a substantially linear IQ decrease for increasing water fluoride above 1 mg/L, with -3.05 (95% CI -4.06 ; -2.04) IQ points per 1 mg/L up to 2 mg/L, becoming steeper above such level. A weaker and substantially linear decrease of -2.15 (95% CI -4.48 ; 0.18) IQ points with increasing urinary fluoride emerged above 0.28 mg/L (approximately reflecting a water fluoride content of 0.7 mg/L). The inverse association between fluoride exposure and IQ was particularly strong in the studies at high risk of bias, while no adverse effect emerged in the only study judged at low risk of bias. Overall, most studies suggested an adverse effect of fluoride exposure on children's IQ, starting at low levels of exposure. However, a major role of residual confounding could not be ruled out, thus indicating the need of additional prospective studies at low risk of bias to conclusively assess the relation between fluoride exposure and cognitive neurodevelopment.

1. Introduction

The trace element fluoride (F) has been used since 1930 for the prevention and management of dental caries, which is considered a global health issue, especially in pediatric populations (ten Cate and Buzalaf, 2019; World Health Organisation, 2021). In nature, this mineral can be found in different amounts in water, plants, and food.

Fluoride compounds are also used in aluminum, petroleum, chemical, and plastics industries, therefore workers in such industries may be exposed to higher levels of fluoride than the standard population (Choubisa and Choubisa, 2016). As a dental caries preventive approach, fluoride can be delivered through topical self- or professional applications (e.g. toothpastes, mouth rinses, gels, and varnishes), which are considered safe and cost-effective at the recommended amount, thus

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many scientific health authorities have endorsed their use (Iheozor-Ejiofor et al., 2015; NHS - National Health System, 2021; NIH - National Institute of Health, 2021; World Health Organization, 2017). Community-based strategies (e.g. water, salt, and milk fluoridation), as well as individually prescribed drops or tablet supplementation, however, raise concerns on their efficacy and safety both for dental and general health (European Commission, 2011; U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation, 2015). Also, since a considerable amount of fluoridated water is not actually used for direct oral uptake and rather ends up in the environment, contamination from fluoride is addressed as a possible source of biohazard for plants and animals (Aguirre-Sierra et al., 2013; Banerjee et al., 2021; Ranjan et al., 2008). Most fluoride consumption comes from fluoridated water and from foods and beverages prepared with fluoridated water, although a small part also comes from the accidental ingestion of fluoride-containing dental products (CDC - Center for Disease Control and Prevention, 2021). One of the public health policies that has been adopted to supplement children and adults with fluoride has been community water fluoridation (CWF), consisting of the controlled addition of fluoride to the public water supply, typically at concentrations ranging from 0.7 mg/L to 1.2 mg/L. However, in 2015 the Centers for Disease Control and Prevention (CDC) updated its water fluoridation guidelines setting such level at 0.7 mg/L in the U.S. (U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation, 2015). CWF policy was first introduced in the United States in 1945 and is currently applied in many regions worldwide, covering approximately 400 million people in over 25 countries (British Fluoridation Society, 2013; CDC - Center for Disease Control and Prevention, 2021). In addition to the beneficial effects of fluoride on dental caries, some adverse health effects deriving from the chronic overexposure to this element have long been documented (Dhar and Bhatnagar, 2009; European Commission, 2011; Vieira, 2022). Among these, dental and skeletal fluorosis are well known and supported by a strong body of evidence (Abanto Alvarez et al., 2009; Saldarriaga et al., 2021; Srivastava and Flora, 2020). In addition, a possible neurotoxic effect of excess fluoride exposure in children has been reported by the U.S. Environmental Protection Agency (EPA) and U.S. National Research Council (NRC) and has continued to be investigated (Bashash et al., 2017; Broadbent et al., 2015; Lu et al., 2000; National Research Council, 2006; Neurath, 2020). These effects could be due to the capacity of fluoride to accumulate in brain regions responsible for memory and learning, affecting them through oxidative stress. In fact, while the blood-brain barrier, to some extent, can protect the adult brain from various toxic agents, it is less efficient in the fetus, newborn, and young child (Grandjean, 2019; Srivastava and Flora, 2020). In addition, fluoride exposure has been linked to hypothyroidism, which negatively affects early neurodevelopment both in fetuses and newborn children (Peckham et al., 2015; Prezioso et al., 2018). Two previous published systematic reviews have investigated the relation between fluoride exposure and neurocognitive development in humans, yielding somewhat inconsistent results, and only one of them performed a dose-response meta-analysis, focusing their assessment on fluoride exposure through drinking water (Duan et al., 2018), while the other only conducted a high-versus-low fluoride analysis (Duan et al., 2018; Miranda et al., 2021). Also, a draft systematic review by the National Toxicology Program (NTP) analyzed such a relationship, but did not perform a meta-analysis (NTP - National Toxicology Program, 2020).

Therefore, the aim of this study was to investigate the relation between exposure to inorganic fluoride, in all forms, and neurodevelopmental toxicity in children, through a comprehensive, updated systematic review and meta-analysis with a dose-response approach.

2. Methods

2.1. Protocol and registration

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines (Page et al., 2021). The protocol was registered in the PROSPERO database (registration no. CRD42022321899).

2.2. Search strategy and study selection

The research framework was defined by the following question: “What is the effect of early or prenatal fluoride exposure on the risk of abnormal neurodevelopment according to a dose-response relation?” According to the PECOS statement (Population, Exposure, Comparator, Outcomes, and Study design), we considered (S) observational studies and clinical trials investigating the relation between (E) early or prenatal fluoride exposure from any source (e.g. water, dietary, and supplemental intake, topical dental products) or evaluating a biomarker of exposure (e.g. urinary, bone, hair fluoride) and (O) neurodevelopmental function in (P) children less than or equal to 18 years of age, compared to (C) exposure to any lower dose of fluoride. We included only studies reporting (i) type and dose/concentration of known fluoride exposure (dose, mean/median levels or category boundaries); (ii) outcome assessment through validated measures of neurodevelopment or cognitive development such as intelligence quotient (IQ), school performance, Standardized Scale for the Intelligence of Children; (iii) outcome in relation to fluoride exposure; (iv) outcome difference for each different fluoride exposure category, such as mean difference, or standardized mean difference, along with the 95% confidence interval (CI) or data allowing their calculation. We considered only original research articles, while conference proceedings, abstracts, letters to the editor, commentaries, case reports, reviews, and meta-analysis were eliminated from consideration. We disregarded papers concerning exposure to fluoride from coal-burning or volcanic eruptions, since they are limited to very specific geographical and socio-cultural situations. Studies based on specific populations, such as children born preterm and institutionalized children, were also excluded, along with studies addressing specific health conditions including autism, Down’s syndrome, attention-deficit/hyperactivity disorder (ADHD) or other behavioral issues, anxiety, and depression. When multiple studies addressed an overlapping population, only the most complete (generally the most recent) report was considered for this review and meta-analysis.

The online literature search was conducted on PubMed/MEDLINE, Web of Science, and Embase databases from inception up to December 30, 2022. No language or date restrictions were applied.

The search was performed using a combination of terms related to “fluoride” and “fluorosis” as exposure and to “neurodevelopmental disorders” or “neurocognitive disorders” as outcomes, by using related MeSH terms, topic terms, and exploded terms on the three databases respectively. The details of the search strategy are reported in [Supplementary Table S1](#).

Backward and forward citation chasing methods were conducted including manually checking the reference lists of all included studies to identify possible additional eligible articles. The screening of titles, abstracts, and full texts for inclusion was performed independently by three authors (FV, MEG, and EM). Another author (TF) was involved in resolving possible disagreements.

2.3. Data extraction

From each of the included studies, whenever available we extracted data regarding location and year, study design, total population, population age and sex, type and dose of exposure, assessment method of exposure, type of neurodevelopment assessment and assessment criteria, the methodology for quantification of the outcome and mean difference

between each exposure category, along with its standard deviation (SD), standard error (SE), or 95% confidence interval (CI). We also extracted details regarding confounding factors or adjustments, when available.

2.4. Risk of bias assessment

We assessed the risk of bias (RoB) of the included studies using the Risk of Bias in Non-Randomized Studies of Exposure (ROBINS-E) tool (Morgan et al., 2019). Two authors (MEG and EM) conducted the evaluation. Any discrepancies were resolved through consensus-based discussion with a third author (TF). Criteria used for this assessment are shown in [Supplementary Table S2](#). In the final tiering of the studies, we considered an overall “low RoB” if all domains of the study were rated at low risk; we considered an overall “moderate” or “high” RoB if one or more domains was at moderate or high RoB, respectively.

2.5. Data analysis

We performed a meta-analysis through forest plots comparing the highest versus lowest fluoride exposure using a random-effects model, computing the weighted mean difference (MD) of IQ and the 95% CI. The analyses were stratified according to type of exposure monitored (e.g. water, urinary fluoride, serum fluoride), type of outcome (e.g. intelligence level, IQ score), overall RoB, study design, sex, and age categories, whenever the data were available.

We also assessed the relation between fluoride exposure and IQ using one-stage dose-response meta-analysis with a cubic spline random-effects model, as previously implemented in other fields (Filippini et al., 2022; Hogervorst et al., 2022; Vinceti et al., 2021), and using the knot placement method recommended by Harrell (2001). In particular, we selected the optimal number of knots according to Akaike's information criterion (AIC), thus we used three knots at fixed percentiles (10th, 50th, and 90th) for both drinking water fluoride and urinary fluoride (Orsini, 2021; Orsini, N. and Spiegelman, D., 2020). For the graphical representation of such relations, the respective median values of the considered doses were used as references (i.e. 1.2 mg/L for water fluoride; 1.4 mg/L for urinary fluoride). We also performed sensitivity analysis using alternative values as reference dose, namely the current U.S. safety threshold for water fluoride in drinking water (0.7 mg/L) and the previous upper boundary, also equivalent to the median value (1.2 mg/L).

According to Villa et al. (2010), the relation between daily urinary fluoride excretion (UF) and total daily fluoride intake (TDFI) in children is approximately $UF = 0.03 + 0.35 * TDFI$, where 0.03 is the intercept and 0.35 is the slope of such linear relationship. Therefore, assuming that most of fluoride intake comes from water fluoride, 1 mg/L of fluoride in drinking water translates in a concentration of fluoride in urine of approximately 0.38 mg/L. Using such formula, we estimated the values for urinary fluoride in children corresponding to the above-mentioned references for water fluoride, resulting respectively in 0.28 mg/L and 0.45 mg/L, and we performed the additional sensitivity analysis accordingly.

For all studies, we fitted a linear regression analysis model and reported its slope per 1 mg/L of fluoride increase alongside with the spline analysis.

Heterogeneity of included studies was assessed using the I^2 statistics (Higgins et al., 2003). We used the Stata software v17.0 (Stata Corp., College Station, TX, 2021) to perform data analyses.

3. Results

3.1. Study selection

The literature search retrieved 1996 potentially relevant records. After the removal of duplicate records ($n = 162$) and the screening of titles and abstracts of the remaining 1834 records, 1773 records were

discarded. After a full text evaluation of the remaining 61 records, additional 32 records were excluded since 3 of them addressed a wrong outcome, 3 were not eligible as publication types, 2 did not have their full texts available, 8 addressed overlapping cohorts of subjects, 10 did not report a correlation between dose and IQ, 5 investigated the correlation between dental fluorosis and IQ, and one addressed only co-exposure to fluoride and arsenic. We eventually further excluded 3 studies that did not allow the analysis of the correlation between dose and IQ. Four papers were instead added to the database after having been retrieved through citation chasing, based on the reference lists of the included studies and the recent meta-analyses.

Overall, 33 publications eventually met the inclusion criteria for the qualitative analysis, 30 of which were included in the meta-analysis. The detailed overall process of study selection is shown as a PRISMA flow-chart ([Fig. 1](#)).

3.2. Study characteristics

The main characteristics of included studies, divided by type of exposure, are summarized in [Table 1](#). The publication year of the included studies ranges from 1991 to 2022. Among the 33 included studies, 29 were designed as cross-sectional studies and 4 as cohort studies. Overall, a total population of 12,263 children was enrolled in 7 countries (China, India, Canada, Iran, Mexico, Pakistan, New Zealand). The age of the participants ranged from 3 to 14 years. Most of the studies ($n = 25$) investigated exposure to fluoride from drinking water and the estimation of exposure was drawn by measuring water fluoride concentration; 14 studies estimated fluoride exposure by measuring urinary fluoride; 2 studies measured serum fluoride and 2 studies addressed total daily fluoride intake. Hair and nail fluoride were analyzed by 1 study, respectively. Only 1 included study addressed exposure from fluoride tablet supplementation.

In our analysis, fluoride concentration in drinking water ranged from 0.13 to 5.55 mg/L. Urinary fluoride ranged from 0.16 to 7 mg/L. For the one study addressing hair and nail fluoride, the considered doses were 6.9 and 27.8 $\mu\text{g/g}$, and 8.3 and 57 $\mu\text{g/g}$ respectively, while serum fluoride ranged from 0.04 to 0.18 mg/L in the two related studies.

With regards to neurodevelopment evaluation, all the included studies assessed intelligence based on IQ measurement. Most of them ($n = 32$) used IQ scores, whereas one of them used an IQ derived scale of intelligence. The most common tests applied to perform IQ evaluation were the Combined Raven's Tests for Rural China (CRT-RC; $n = 14$), Raven's Standard Progressive Matrices test (RSPM; $n = 4$ – RPM; $n = 2$), the Raven's Color Progressive Matrices test (RCPM; $n = 2$), followed by other less frequent IQ tests, such as the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Abbreviated Scale of Intelligence (WASI), the Wechsler Adult Intelligence Scale-Revised (WISC-R), Stanford-Binet Intelligence Scale (SBIS), Rui-Wen's test, and the Raymond B Cattell's test.

All the studies excluded from meta-analysis for not specifying children's doses of exposure reported lower IQ scores in those exposed to higher levels of fluoride (Farmus et al., 2021; Goodman et al., 2022; Rocha-Amador et al., 2007).

3.3. Risk of bias analysis

Details of RoB assessment are displayed in [Table 2](#). Among the included studies, the overall RoB was “high” in 11 studies, “moderate” in 19 studies, and “low” in 3 studies. The main source of high RoB was related to the lack of adjustments for potential confounders ($n = 11$). Participant selection was another critical aspect, as the enrollment was based on different fluoride exposure in most studies (e.g. areas with different fluoride concentration in drinking water), resulting in a moderate RoB in such domain ($n = 25$).

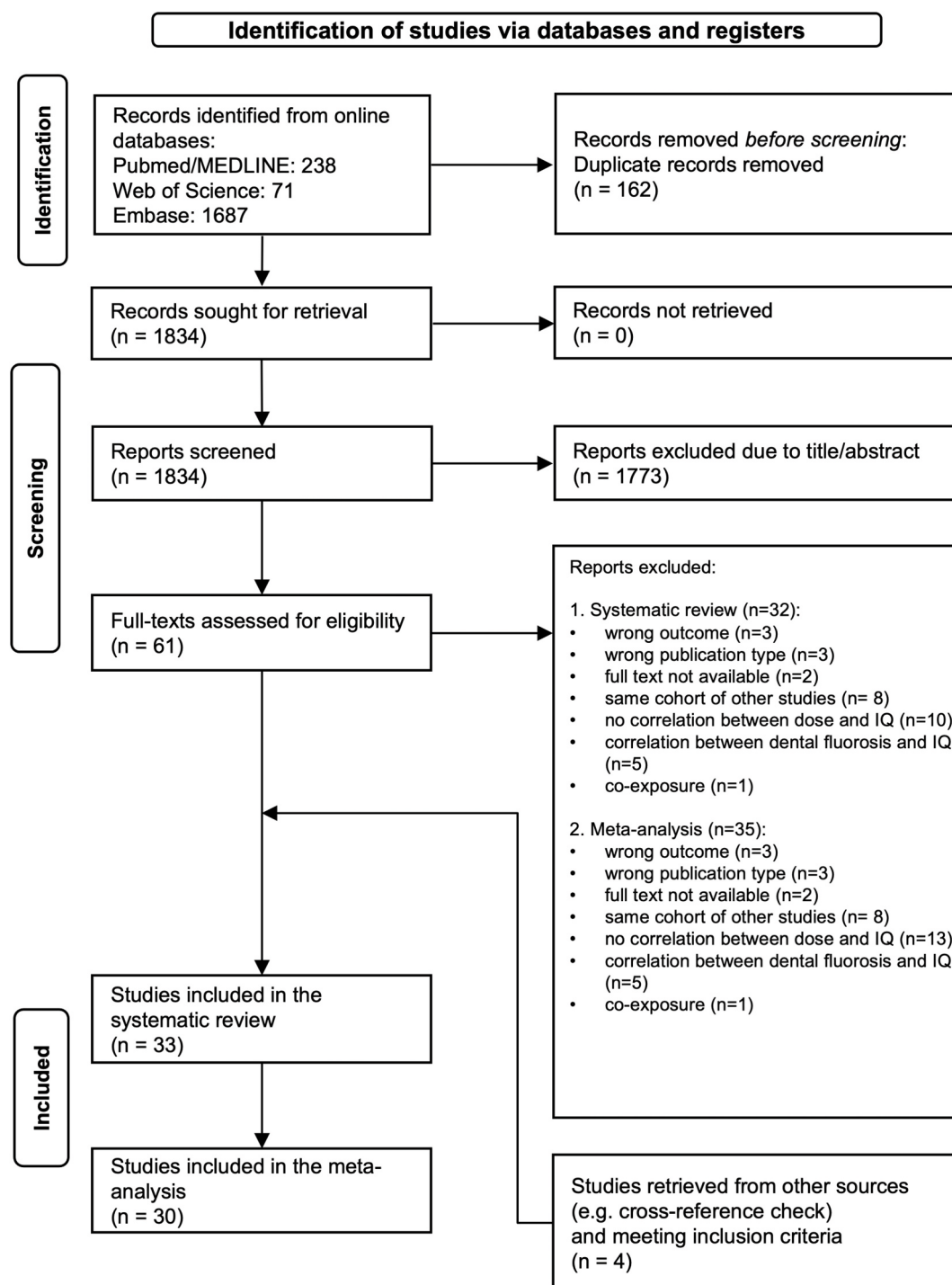


Fig. 1. PRISMA flow-chart of study selection process.

3.4. Quantitative analysis

The summary MD of IQ score, comparing the highest versus lowest fluoride categories considering all types of exposure was -4.68 (95% CI -6.45 ; -2.92). For less represented types of exposure, the summary IQ score MDs were -0.25 (95% CI -3.18 ; 2.68) for fluoride tablet supplementation (1 study), 1.92 (95% CI 1.56 ; 2.28) for hair fluoride (1 study), 0.61 (95% CI 0.30 ; 0.92) for nail fluoride (1 study), and -7.69 (95% CI -9.99 ; -5.38) for serum fluoride (2 studies). The individual and summary mean differences of IQ score, comparing the highest versus lowest fluoride categories considering all types of exposure are

available in [Supplementary Fig. S1](#).

When performing a subgroup analysis by RoB levels, a MD of 1.11 (95% CI -0.67 ; 2.89) emerged for the only low RoB study, -4.27 (95% CI -6.44 ; -2.11) for moderate RoB studies, and -6.31 (95% CI -9.56 ; -3.06) for high RoB studies (Fig. 2). The pooled analysis considering only cohort-designed studies eligible for meta-analysis ($n = 3$) yielded a MD of -0.74 (95% CI -2.90 ; 1.42), while a cumulative MD of -5.21 (95% CI -7.02 ; -3.39) was found for the cross-sectional studies. With regards to exposure to fluoride in drinking water, ranging from 0.13 to 5.55 mg/L, the overall IQ score mean difference was -5.60 (95% CI -7.76 ; -3.44), showing slight differences in subgroup analysis by sex,

Table 1
Characteristics of included studies for by type of exposure: water fluoride, urinary fluoride and other exposures.

Reference	Study design	Country	Age (mean)	Participants	Geographical area	Exposure	Exposure assessment	Unit	Dose	Outcome	Outcome assessment	Main findings	Management of confounders
WATER FLUORIDE													
Ahmad et al., 2022	Cross-sectional	Pakistan	9 to 11	120 (M/F = 86/34)	Karachi and Umerkot, Sindh Province; Pakistan	Water fluoride	Records based on another study	mg/L	1.07; 2.04	IQ score	CRT-RC	No significant differences in the distribution of the IQ scores between the urban (Low F) and rural (High F) areas	Age, sex
Aravind et al., 2016	Cross-sectional	India	10 to 12	288	Karnataka stat; India	Water fluoride	Fluoride ion selective electrode, Orion 9609BN	mg/L	0.96; 1.6; 2.4	IQ score	RSPM	Lower IQ in children from high F areas	Age, sex
Broadbent et al., 2015	Cohort study (DMHDS)	New Zealand	7 to 13	992	Dunedin; New Zealand	Water fluoride	Records based on residential data	mg/L	0.15; 0.85	IQ score	WISC-R	No clear differences in IQ because of fluoride exposure	Age, sex, socioeconomic status based on parental occupation and the educational level and income associated with that occupation, low birth weight, breastfeeding
Chen et al., 2008	Cross-sectional	China	7 to 14	640	Biji and Jiaobei villages; China	Water fluoride	Records based on residential data	mg/L	0.89; 4.55	IQ score	CRT-RC	Significant difference in IQ between endemic and non endemic areas	Sex
Eswar et al., 2011	Cross-sectional	India	12 to 14	133	Ajjihalli and Holesirigere village, District of Karnataka; India	Water fluoride	Records based on residential data	mg/L	0.29; 2.45	IQ score	RSPM	No significant differences between the endemic and non endemic areas, but a trend towards lower IQ in a great number of children from high F village	Age
Hong et al., 2008	Cross-sectional	China	8 to 14	117	Wukang, Boxing, Zouping, Shangdong Province; China	Water fluoride	Conventional chemical assay methods	mg/L	0.75; 2.9	IQ score	CRT-RC	No significant differences between the high F and control areas, but a trend towards lower IQ in a number of children from high F area	NR
Karimzade et al., 2014	Cross-sectional	Iran	9 to 12	39	Poldashi and Piranshahr village, Azerbaijan; India	Water fluoride	SPADNS colorimetric method	mg/L	0.25; 3.94	IQ score	RB Cattell	Lower IQ in children from high F areas	Age (education, economic factors, sociocultural environment, general demographic characteristics)
Li et al., 2008	Cross-sectional	China	6 to 13	956	Inner Mongolia; China	Water fluoride	Records based on residential data		High; Low	IQ score	CRT-RC2	Lower IQ in children from high F areas	NR
Lu et al., 2000	Cross-sectional	China	10 to 12	118	Xiqing District, Tianjin; China	Water fluoride	Fluoride ion selective electrode	mg/L	0.37; 3.15	IQ score	CRT-RC	Lower IQ in children from high F areas	Age (sex, past history of illness, residential history,

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Table 1 (continued)

Reference	Study design	Country	Age (mean)	Participants	Geographical area	Exposure	Exposure assessment	Unit	Dose	Outcome	Outcome assessment	Main findings	Management of confounders
Poureslami et al., 2011	Cross-sectional	Iran	7 to 9	119 (M/F = 57/62)	Koohbanan and Baft city, Kerman Province; Iran	Water fluoride	Records based on residential data	mg/L	0.41; 2.38	IQ score	RPM	Lower IQ in children from high F areas	parents' past history of illness, parents' socioeconomic status, parents' level of education, family income, parents' smoking and drinking habits) Age, sex
Rocha-Amador et al., 2007	Cross-sectional	Mexico	7 to 8	132	Moctezuma, Salitral, 5 de Febrero; Mexico	Water fluoride	TISAB buffer and specific ion electrode method	log	/	IQ score; Performance IQ and Verbal IQ	WISC-RM	Lower IQ in children with high F exposure	Age, Pb blood, socioeconomic status, mother's education, height-for-age z-score, and transferrin saturation
Saxena et al., 2012	Cross-sectional	India	12	170	Madhya Pradesh state; India	Water fluoride	Fluoride ion selective electrode, Orion 9609BN	ppm	1.2; 2.25; 3.8; 5.4	Intelligence grade	RSPM	Lower IQ in children from high F areas	Age, sex, height, weight, residential history, medical history (including illness affecting the nervous system and head trauma), educational level of the head of the family (in years), socioeconomic status
Sebastian and Sunitha, 2015	Cross-sectional	India	10 to 12	405	Mysore District; India	Water fluoride	Records from Rajiv Gandhi National Rural Drinking Water Program (RGNRDWP)	mg/L	0.4; 1.2; 2	IQ score	RCPM	Lower IQ in children from high F areas	Age, sex, parental education, family income
Seraj et al., 2007	Cross-sectional	Iran	7 to 11	126	Dehistan; Iran	Water fluoride	Records based on residential data	mg/L	0.4; 2.5	IQ score	RSPM	Lower IQ in children from high F areas	NR
Seraj et al., 2012	Cross-sectional	Iran	6 to 11	293 (M/F = 142/151)	Makoo; Iran	Water fluoride	SPADNS method utilizing 400 UV-Vis spectrophotometer	mg/L	0.75; 3.1; 5.2	IQ score	RCPM	Lower IQ in children from high F areas	NR
Shivaprakash et al., 2011	Cross-sectional	India	7 to 11	160	Bakalkot, Hungund; India	Water fluoride	Records based on residential data	mg/L	0.4; 3.0	IQ score	RPM	Lower IQ in children from high F areas	Age, sex
Till et al., 2020	Cohort study (MIREC)	Canada	3 to 4 (age of IQ test)	198	Vancouver, Toronto, Hamilton, Halifax, Kingston, Montreal; Canada	Water fluoride	Records based on residential data	mg/L	0.13; 0.59	IQ score; Performance IQ and Verbal IQ	CRT-RC	Lower IQ in children with high F exposure	Sex and age at testing, maternal education, maternal race, second-hand smoke in the home, quality of the

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Table 1 (continued)

Reference	Study design	Country	Age (mean)	Participants	Geographical area	Exposure	Exposure assessment	Unit	Dose	Outcome	Outcome assessment	Main findings	Management of confounders
Trivedi et al., 2007	Cross-sectional	India	12 to 13	190 (M/F = 118/62)	Chandlodia (Ahmedabad) and Sachana (Sanand District of Gujarat); India	Water fluoride	Fluoride ion selective electrode, Orion 9609BN	mg/L	2.01; 5.55	IQ score	SBIS	Lower IQ in children with high F exposure	child's home environment Age, sex
Wang et al., 2007	Cross-sectional	China	8 to 12	449	Rural areas in Shanxi; China	Water fluoride	Fluoride ion selective electrode with an LOD of 50 µg/L ± 2%.	mg/L	0.5; 0.8	IQ score	CRT-RC	Lower IQ in children with high F exposure	Age, income, parental education
Wang et al., 2008	Cross-sectional	China	4 to 7	230	Rural area of Shehezi in Xinjiang Province; China	Water fluoride	Fluoride ion selective electrode method	mg/L	0.8; 1.2	IQ score; Performance IQ and Verbal IQ	WPPSI	Lower IQ in children with high F exposure	Age
Wang et al., 2021	Cross-sectional	China	9.86 ± 1.16	709 (M/F = 381/328)	Rural areas of Tianjin City; China	Water fluoride	Fluoride ion selective electrode (INESA, Shanghai, China)	mg/L	0.24; 0.65; 1.3; 1.92	IQ score	CRT-RC	Lower IQ in children with high F exposure	Age, sex, BMI, low birth weight, paternal education, maternal education, family incomes
Xiang et al., 2003	Cross-sectional	China	8 to 13	512	Wamiao and Xinhuai villages; China	Water fluoride	Fluoride ion selective electrode method	mg/L	0.36; 0.75; 1.53; 2.46; 3.28; 4.16	IQ score	CRT-RC	Lower IQ in children with high F exposure	NR
Yu et al., 2021	Cross-sectional	China	9.8 ± 1.1	952	rural areas of Baodi District, Tianjin; China	Water fluoride	Fluoride ion selective electrode method	mg/L	1.8; 3.65	IQ score	CRT-RC	Lower IQ in children with high F exposure	Age, sex, maternal education, paternal education
Zhang et al., 2015	Cross-sectional	China	10 to 12	180 (M/F = 74/106)	Jinnan District, Tianjin; China	Water fluoride	Ion analyzer EA940 with a fluoride ion selective electrode	mg/L	1.4; 0.63	IQ score	CRT-RC	Lower IQ in children with high F exposure	Age, sex, educational levels of parents
Zhao et al., 1996	Cross-sectional	China	7 to 14	320 (M/F = 160/160)	Sima (Xiaoy city) and Xingua village (Fenyang city); China	Water fluoride	NR	mg/L	0.91; 4.12	IQ score	NR	Lower IQ in children with high F exposure	Age, sex
URINARY FLUORIDE													
Ahmad et al., 2022	Cross-sectional	Pakistan	9 to 11	120 (M/F = 86/34)	Karachi and Umerkot, Sindh Province; Pakistan	Urinary fluoride	NR	mg/L	3.53; 5.99	IQ score	CRT-RC	No significant differences in distribution of IQ scores between rural and urban areas	Age, sex
Bashash et al., 2017	Cohort study (ELEMENT)	Mexico	6 to 12	189 (M/F = 95/116)	Mexico city; Mexico	Urinary fluoride	Ion-selective electrode	mg/L	0.64; 0.96	IQ score	WASI	Higher prenatal fluoride exposure was associated with lower scores on tests of cognitive function in the offspring at age 4 and 6–12 years	Urinary creatinine

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Table 1 (continued)

Reference	Study design	Country	Age (mean)	Participants	Geographical area	Exposure	Exposure assessment	Unit	Dose	Outcome	Outcome assessment	Main findings	Management of confounders
Das and Mondal, 2016	Cross-sectional	India		149 (M/F = 66/83)	Laxmisagar Village, Simlapal Block of Bankura District. W.B.; India	Urinary fluoride	Ion-selective electrode and TISAB	mg/L	2.5; 2.58; 2.91; 2.95; 3.81; 4.82	IQ score	CRT-RC	Exposure dose has a positive correlation with Dental fluorosis and urinary fluoride has a negative correlation with IQ	NR
Ding et al., 2011	Cross-sectional	China	7 to 14	331	Manzhouli City in Hulunbuir, Inner Mongolia; China	Urinary fluoride	Ion-selective electrode and TISAB	mg/L	0.8; 1.11; 1.13; 1.31; 1.46	IQ score	CRT-RC	Low levels of F exposure in drinking water had negative effects on children's intelligence and dental health and confirmed the dose-response relationship between urinary fluoride and IQ scores as well as dental fluorosis	NR
Farmus et al., 2021	Cohort study (MIREC)	Canada	3 to 4	596 (M/F = 291/305)	Vancouver, Toronto, Hamilton, Halifax, Kingston, Montreal; Canada	Urinary fluoride	Records based on residential address data	mg/L	/	IQ score; Performance IQ; Verbal IQ	WPPSI	F was not significantly associated with verbal IQ across any exposure window; associations between fluoride exposure and IQ differed based on timing of exposure	Maternal education, maternal race, total HOME score, age at urine sampling, and prenatal second-hand smoke
Feng et al., 2022	Cross-sectional	China	8 to 12	683 (M/F = 324/359)	Tongxu County, Henan Province; China	Urinary fluoride	Ion-selective electrode	mg/L	0.83; 0.98; 1.56; 2.15	IQ score	CRT-RC	Excessive F exposure may have adverse effects on children's intelligence	Age, sex, BMI, age at which pregnancy occurred, gestational weeks, birth weight, birth modes, paternal and maternal education level
Goodman et al., 2022	Cross-sectional	Mexico	8 to 12	348	Birobouli and Talise sub-villages; Mexico	Maternal urinary fluoride	Ion-selective electrode	mg/mL	/	IQ score; Performance IQ; Verbal IQ	MSCA	The decrease in non-verbal intelligence was assessed to determine the negative association between prenatal fluoride exposure and IQ. This may mean that visual-spatial and perceptual reasoning skills, as opposed to verbal skills, may be affected more by prenatal fluoride exposure	NR
Li et al., 1995	Cross-sectional	China	8 to 13	907 (M/F = 570/337)	Anshu and Zhijin counties of Guizhou	Urinary fluoride	NR	mg/L	1.02; 1.81; 2.01; 2.69	IQ score	Rui-Wen test	High F intake is associated with a lower intelligence	Sex

(continued on next page)

Table 1 (continued)

Reference	Study design	Country	Age (mean)	Participants	Geographical area	Exposure	Exposure assessment	Unit	Dose	Outcome	Outcome assessment	Main findings	Management of confounders
Lu et al., 2000	Cross-sectional	China	10 to 12	118	Province; China Tianjin Xiqing District; China	Urinary fluoride	Ion-selective electrode	mg/L	1.43; 4.99	IQ score	CRT-RC	The IQ of the children in the high-F area was significantly lower than that of the children in the low-F area; an inverse relationship was also present between IQ and the urinary fluoride level. Exposure of children to high levels of fluoride may carry the risk of impaired development and intelligence	Age (sex, past history of illness, residential history, parents' past history of illness, parents' socioeconomic status, parents' level of education, family income, parents' smoking and drinking habits)
Rocha-Amador et al., 2007	Cross-sectional	Mexico	7 to 8	132	Moctezuma, Salitral, 5 de Febrero; Mexico	Urinary fluoride	Ion-selective electrode and TISAB	log	NR	IQ score	WISC-RM	Children exposed to either F or As have increased risk of reduced IQ scores	Age, Pb blood, socioeconomic status, mother's education, height-for-age z-score, and transferrin saturation
Saxena et al., 2012	Cross-sectional	India	12	170 (M/F = 87/83)	Madhya Pradesh state; India	Urinary fluoride	Ion-selective electrode	ppm	2.25; 3.28; 4.85; 7.00	Intelligence grade	RSPM	Children in endemic areas of fluorosis are at risk for impaired development of intelligence; urinary fluoride level was a significant predictor of intelligence	Age, sex, height, weight, residential history, medical history (including illness affecting the nervous system and head trauma), educational level of the head of the family (in years), socioeconomic status
Trivedi et al., 2007	Cross-sectional	India	12 to 13	190 (M/F = 118/72)	Chandlodia (Ahmedabad) and Sachana (Sanand District of Gujarat); India	Urinary fluoride	Ion-selective electrode	mg/L	2.3; 6.13	IQ score	SBIS	Exposure to elevated F can cause lower IQ and the excessive intake of F can produce harmful effects on the developing brain	Age
Wang et al., 2021	Cross-sectional	China	9.86 ± 1.16	709 (M/F = 381/328)	Rural areas of Tianjin City; China	Urinary fluoride	Ion-selective electrode (INESA, Shanghai, China)	mg/L	0.16; 0.34; 0.69; 1.08	IQ score	CRT-RC	Low to moderate F exposure is associated with dysfunction of cholinergic system for children. AchE may partly mediate the prevalence of DF and lower probability of having superior intelligence	Age, sex, body mass index, maternal education, paternal education, household income and low birth weight

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Table 1 (continued)

Reference	Study design	Country	Age (mean)	Participants	Geographical area	Exposure	Exposure assessment	Unit	Dose	Outcome	Outcome assessment	Main findings	Management of confounders
Yu et al., 2021	Cross-sectional	China	9.8 ± 1.1	952 (M/F = 471/481)	Rural areas of Baodi District, Tianjin; China	Urinary fluoride	Ion-selective electrode and TISAB	mg/L	0.81; 2.05; 4.02	IQ score	CRT-RC	F is inversely associated with intelligence; the interactions of F with mitochondrial function-related SNP-set, genes and pathways may also be involved in high intelligence loss	Age, sex, maternal education, paternal education
Zhang et al., 2015	Cross-sectional	China	10 to 12	180 (M/F = 74/106)	Jinnan District, Tianjin; China	Urinary fluoride	Ion-selective electrode	mg/L	1.1; 2.4	IQ score	CRT-RC	Significant high levels of F along with poor IQ score were observed in the high F area	Age, sex, educational levels of parents
OTHER EXPOSURES													
Broadbent et al., 2015	Cohort study (DMHDS)	New Zealand	7 to 13	992	Dunedin; New Zealand	Fluoride Tablets	Parental interviews	mg (ever/never used)	0.5	IQ score	WISC-R	Fluoride exposure does not affect neurologic development or IQ	Age, sex, socioeconomic status, low birth weight, breastfeeding NR
Das and Mondal, 2016	Cross-sectional	India	7 to 18	149	Laxmisagar Village, Simlupal Block of Bankura District. W.B.; India	Intake fluoride	Fluoride ion-selective electrode (model: Thermo Scientific Orion4-Star) and adjustment with buffer (TISAB III)	mg/kg/day	0.069; 0.064; 0.060; 0.099; 0.093	IQ score	CRT-RC	Lower IQ in children from high F areas	
Farmus et al., 2021	Cohort study (MIREC)	Canada	3 to 4 (age at intelligence test)	596	Vancouver, Toronto, Hamilton, Halifax, Kingston, Montreal; Canada	Intake fluoride	Records based on residential data	mg/day	Linear increase of the dose	IQ score; Performance IQ; Verbal IQ	WPPSI	Lower IQ in children exposed to high fluoride concentration; stronger association in fetal exposure than postnatal exposure	Maternal education, maternal race, total HOME score, age at urine sampling, and prenatal second-hand smoke
Xiang et al., 2011	Cross-sectional	China	8 to 13	512 (M/F = 282/230)	Wamiao and Xinhuai villages; China	Serum fluoride	Fluoride ion-selective electrode	mg/L	0.04; 0.065; 0.088	IQ score	CRT-RC	Mean IQ significantly higher and fewer children with an IQ less than 80 in the two quartiles with a serum fluoride level of less than 0.05 mg F/L	Age, sex
Yu et al., 2021	Cross-sectional	China	9.8 ± 1.1	952	Rural areas of Baodi District, Tianjin; China	Hair fluoride; Nail Fluoride	Fluoride ion-selective electrode and adjustment with buffer (TISAB)	µg/g	Hair (6.865; 27.77); Nail (8.29; 57)	IQ score	CRT-RC	The probability of high intelligence was inversely correlated with fluoride contents in water, urine, hair and nail	Age, sex, maternal education, paternal education
Zhang et al., 2015	Cross-sectional	China	10 to 12	180	Jinnan District, Tianjin; China	Serum fluoride	Ion analyzer EA940 with a fluoride ion selective electrode	mg/L	0.06; 0.18	IQ score	CRT-RC	Fluoride exposure negatively associated with children's intelligence	Age, sex, educational levels of parents

NR: not reported; CRT-RC: Combined Raven's Tests for Rural China; RCPM: Raven's Colored Progressive Matrices; RSPM: Raven's Standard Progressive Matrices; WISC-R: Wechsler Adult Intelligence Scale-Revised; WPPSI: Wechsler Preschool and Primary Scale of Intelligence. Parentheses in the column "Management of confounders" indicate that such confounders have been considered, according to the plain text, but data are not shown.

with a MD of -8.02 (95% CI -13.48 ; -2.56) for males, and of -5.96 (95% CI -8.78 ; -3.14) for females (Fig. 3). The stratification by age categories showed some noticeable differences, with an IQ MD of -3.21 (95% CI -8.00 ; 1.58) for preschool children and -5.85 (95% CI -8.20 ; -3.50) for children over 6 years (Supplementary Fig. S2). The individual and summary IQ MD for urinary fluoride as the exposure biomarker, which ranged from 0.16 to 7 mg/L, are shown in Fig. 4 and resulted in -3.84 (95% CI -7.93 ; 0.24), with mild fluctuations for males -5.83 (95% CI -14.71 ; 3.04) and females -6.97 (95% CI -12.49 ; -1.46). The stratification by age categories (Supplementary Fig. S3), was only computable for school aged children over 6 years (MD -3.84 , 95% CI -7.93 ; 0.24). The overall mean difference of IQ scores in studies assessing specific Performance IQ and Verbal IQ (2 studies each), were -6.62 (95% CI -9.73 ; -3.50) and 0.39 (95% CI -6.22 ; 6.99), respectively (Supplementary Fig. S4).

Concerning potential publication bias, the Egger's test suggested a low risk of such bias both for water and urinary fluoride analyses (Supplementary Figs. S5–S6).

In the dose-response meta-analysis based on both non-linear spline regression model and linear regression analysis, we only considered water fluoride and urinary fluoride, as the other types of exposure data were not sufficient to perform such analysis. For the same reason, we limited our dose-response analysis to studies reporting the IQ score as the cognitive outcome. The dose-response curve for water fluoride exposure clearly showed a decrease in IQ score starting at a drinking water fluoride concentration of 1 mg/L, this negative relation becoming considerably steeper over 2 mg/L, though being statistically imprecise (Fig. 5A). In linear regression analysis, the IQ score decrease was 3.05 (95% CI -4.06 ; -2.04) per mg/L. Compared with the analysis based on water fluoride concentrations, the dose-response analysis based on urinary fluoride showed a weaker but substantially linear decrease in IQ scores with increasing urinary fluoride and already starting at very low levels of exposure, with -2.15 (95% CI -4.48 ; 0.18) IQ points per each 1 mg/L in urinary fluoride, again with statistically imprecise estimates at high levels of exposure (Fig. 5B). Additional dose-response splines obtained by the sensitivity analysis using alternative reference values are shown in Supplementary Figs. S7 and S8.

4. Discussion

What is new in this work, as compared to the other systematic reviews and meta-analyses on this topic, is that we applied a recent and novel statistical approach that allows the full modeling of the dose-response relation between fluoride and cognitive endpoints, yielding its shape across the entire range of exposure, considering both exposure from fluoride in drinking water and urinary fluoride as biomarkers of exposure, conducting such analysis separately and allowing a comparison between the two. Also, we added a stratified analysis by RoB, which contributes to the characterization of the overall findings.

This review aimed to investigate all type of fluoride exposure assessments available in the peer-reviewed literature; however, no eligible records or sufficient data were available regarding fluoride exposure from drops or tablets supplementation, and topical dental products. Drinking water and water-based beverages are the main sources of exposure to fluoride in the general population, and fluoride intake from water positively correlates to urinary fluoride concentration (Abduweli Uyghurturk et al., 2020; Till et al., 2018). Naturally occurring and intentionally added water fluoride accounts for up to 90–95% of the total intake in fluoridated areas (Erdal and Buchanan, 2005). However, in young children toothpaste can be another important source of fluoride, reaching up to 25% of the total intake (European Commission, 2011). According to the European Food Safety Authority (EFSA) water intake report, although it is considered underestimated due to scarcity of specific data, children younger than 14 years old have a mean daily water intake of approximately 0.6 L, whereas other estimates report a higher daily water intake of 0.8–1.3 L, since the amount of water intake

Table 2

Risk of bias assessment of included studies.

Studies	Type of exposure assessment	Bias due to confounding	Bias in selecting participants	Bias in exposure classification	Bias in departure from intended exposure	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results	Overall Risk of Bias
Ahmad et al., 2022	W, U	Moderate	Moderate	Moderate Low	Low	Low	Low	Low	Moderate
Aravind et al., 2016	W	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Bashash et al., 2017	U	High	Low	Low	Low	Low	Low	Low	High
Broadbent et al., 2015	W, I	Low	Low	Moderate Moderate	Low	Low	Low	Low	Moderate
Chen et al., 2008	W	High	Moderate	Moderate	Low	Low	Low	Moderate	High
Das and Mondal, 2016	I, U	High	Low	Low Low	Low	Low	Low	Moderate	High
Ding et al., 2011	U	High	Low	Low	Low	Low	Low	Low	High
Eswar et al., 2011	W	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Farmus et al., 2021	I, U	Low	Low	Low Low	Low	Low	Low	Low	Low
Feng et al., 2022	U	Low	Low	Low	Low	Low	Low	Low	Low
Goodman et al., 2022	MUF	Low	Low	Low	Low	Low	Low	Low	Low
Hong et al., 2008	W	High	Moderate	Moderate	Low	Low	Low	Moderate	High
Karimzade et al., 2014	W	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Li et al., 1995	U	High	Moderate	Low	Low	Low	Low	Moderate	High
Li et al., 2008	W	High	Moderate	Moderate	Low	Low	Low	Moderate	High
Lu et al., 2000	W, U	Moderate	Moderate	Moderate Low	Low	Low	Low	Moderate	Moderate
Poureslami et al., 2011	W	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Rocha-Amador et al., 2007	W, U	Low	Moderate	Moderate Low	Low	Low	Low	Moderate	Moderate
Saxena et al., 2012	W, U	Low	Moderate	Moderate Low	Low	Low	Low	Low	Moderate
Sebastian and Sunitha, 2015	W	Low	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Seraj et al., 2012	W	High	Moderate	Moderate	Low	Low	Low	Moderate	High
Seraj et al., 2007	W	High	Moderate	Moderate	Low	Low	Low	Moderate	High
Shivaprakash et al., 2011	W	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Till et al., 2020	W	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Trivedi et al., 2007	W, U	Moderate	Moderate	Moderate Low	Low	Low	Low	Moderate	Moderate
Wang et al., 2008	W	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Wang et al., 2021	W, U	Low	Moderate	Moderate Low	Low	Low	Low	Low	Moderate
Wang et al., 2007	W	Low	Moderate	Moderate	Low	Low	Low	Low	Moderate
Xiang et al., 2003	W	High	Moderate	Moderate	Low	Low	Low	Low	High
Xiang et al., 2011	B	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Yu et al., 2021	W, U, H, N	Low	Moderate	Moderate Low Low	Low	Low	Low	Low	Moderate
Zhang et al., 2015	W, S, U	Low	Moderate	Moderate Low Low	Low	Low	Low	Low	Moderate
Zhao et al., 1996	W	High	Moderate	Moderate	Low	Low	High	Moderate	High

W: water; U: urinary; I: intake; N: nail; H: hair; B: blood; S: serum; MUF: maternal urinary fluoride.

can vary along with different environmental and seasonal temperatures. Based on EFSA report, the European Commission for Health and Food Safety estimated a systemic fluoride intake from water and water-based beverages of approximately 0.4–0.5 mg/day for a water fluoride concentration of 0.8 mg/L and of 0.7–0.9 mg/day for a water fluoride concentration of 1.5 mg/L (European Commission, 2011). For instance in 5 years old child with 20 kg weight, the cumulative exposure, considering all additional sources, can easily be above the adequate daily intake (ADI) of 1 mg/day (i.e. 0.05 mg/kg, as established by EFSA for both adults and children) (EFSA - European Food Safety Authority, 2013). Although the ADI generally aims to provide a balanced effect in preventing dental caries without increasing the risk of dental fluorosis, the results of the present meta-analysis seem to indicate that such an ADI

may not be deemed safe from a cognitive development perspective.

Interestingly and unfortunately, neither among the 33 included studies and the studies excluded during full-texts evaluation, none were conducted in the U.S. or Europe, where community water fluoridation programs are applied extensively. Only some of the included cohort studies were conducted in countries with artificially fluoridated water (Canada and New Zealand). Most of the studies were performed in countries with drinking water naturally rich in fluoride; however concentrations of 1 mg/L and lower were considered, thus making such data comparable to the CWF programs.

Despite some heterogeneity in the effect size and occasionally its direction, we found a consistent indication of a negative association between fluoride exposure and children's intelligence, occurring from

Risk of Bias and IQ

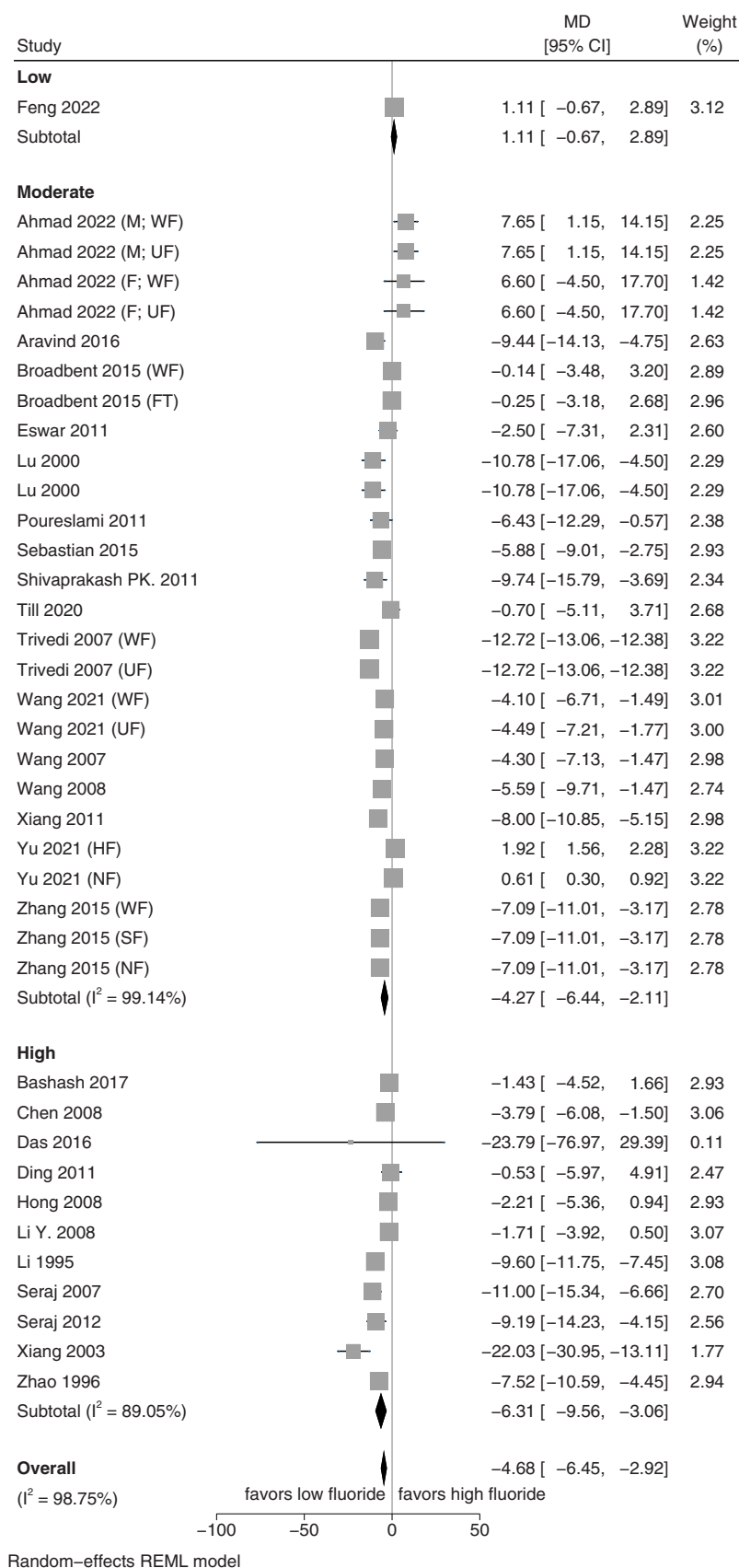


Fig. 2. Forest plot of the included studies stratified by Risk of Bias (RoB). Individual and summary mean differences (MD) of IQ for exposure to fluoride in relation to RoB levels. F: females; M: males; FT: fluoride tablets; HF: hair fluoride; NF: nail fluoride; SF: serum fluoride; UF: urinary fluoride; WF: water fluoride.

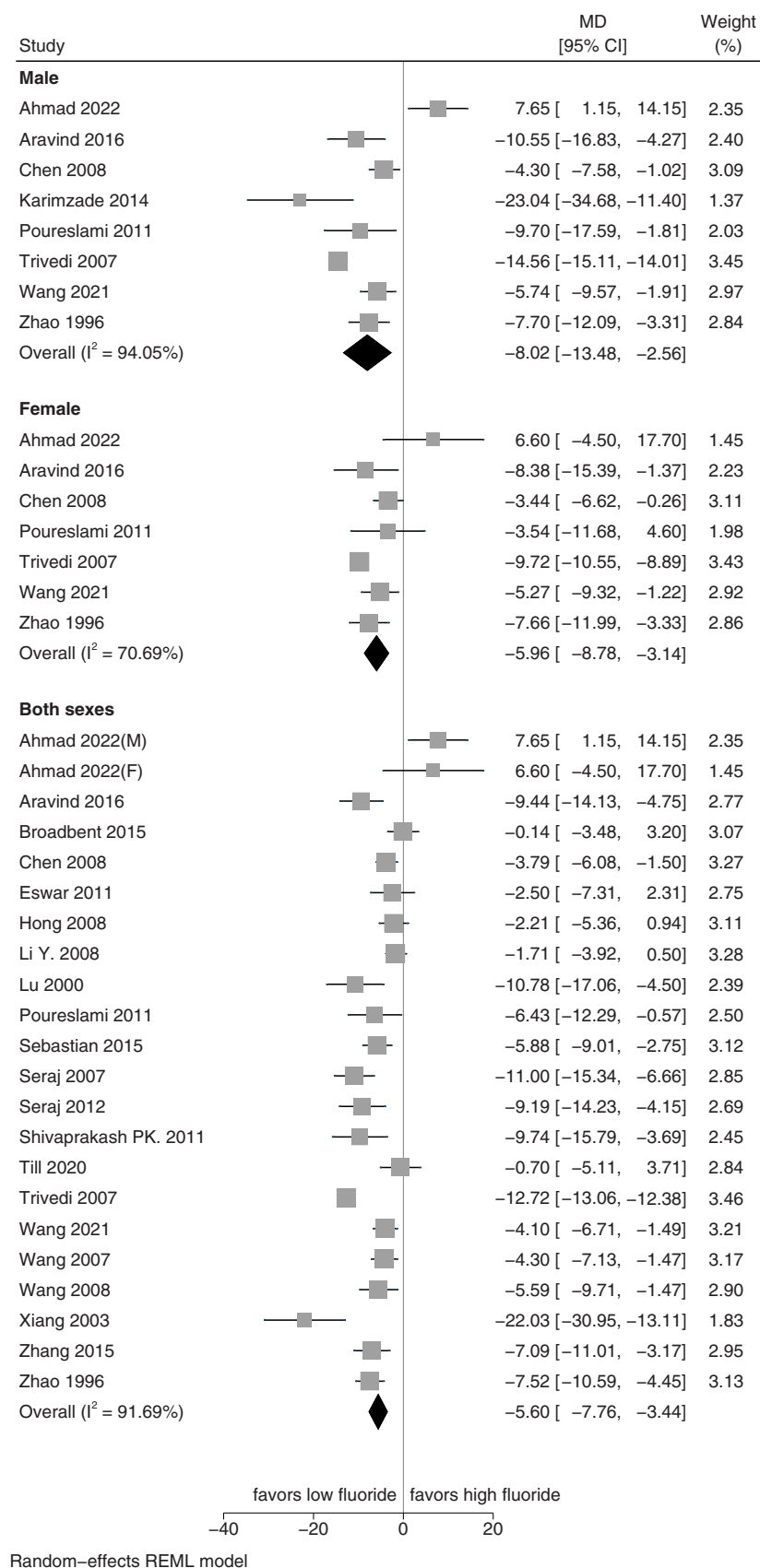
Water fluoride

Fig. 3. Forest plot of the included drinking water studies. Mean difference (MD) in IQ with 95% confidence interval (CI) in relation to exposure to fluoride, stratified by sex. The squares represent risk estimate and horizontal lines represent their 95% CI. The area of each square is proportional to the weight of the study in the meta-analysis. The diamonds represent the combined risk for both sexes, and the solid line represents null value. The inverse-variance estimation method was used for study weighting. M: males; F: females.

Urinary fluoride

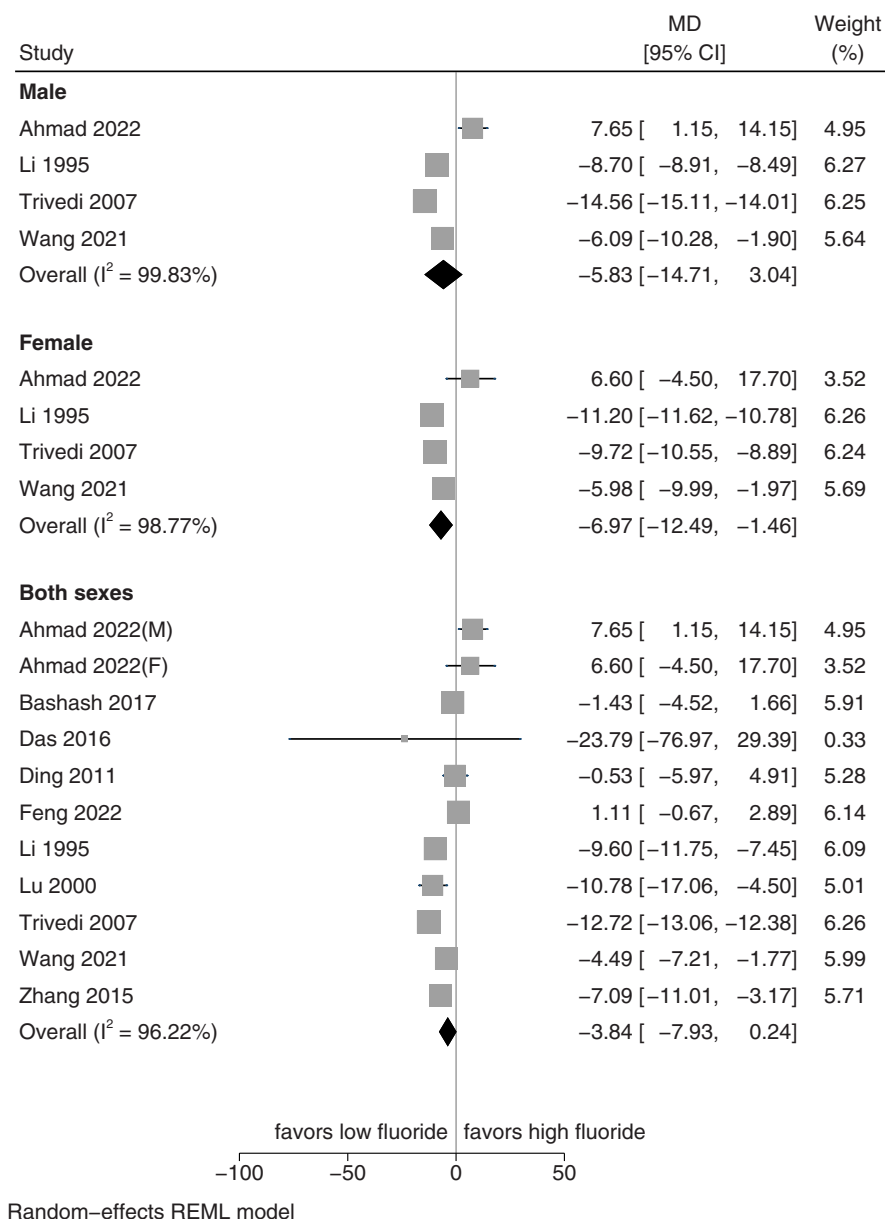


Fig. 4. Forest plots of the included urinary fluoride studies. Mean difference (MD) in IQ with 95% confidence interval (CI), stratified by sex. The squares represent risk estimate and horizontal lines represent their 95% CI. The area of each square is proportional to the weight of the study in the meta-analysis. The diamonds represent the combined risk for both sexes, and the solid line represents null value. The inverse-variance estimation method was used for study weighting. M: males; F: females.

low fluoride concentrations when exposure was assessed through a biomarker (urinary fluoride), while some evidence of a threshold around 1 mg/L emerged from the pooled analysis based on drinking water fluoride. We also found some slight differences in subgroup analysis by sex, with an indication of greater adverse effect on males than on females in some studies (Boyle et al., 2011; Cantoral et al., 2021; Till et al., 2020). This is supported by evidence that there may be a sex-specific presentation of such disorders, as already found for other contaminants (Desrochers-Couture et al., 2018). This difference in prevalence could be due at least in part to referral errors and misdiagnosis in females. Behavioral or intellectual disorders can be modulated by hormonal changes, often resulting in a more complex and blended clinical presentation as compared to males, associated with the development of different coping strategies, thus delaying or hindering the diagnosis

(Young et al., 2020).

Additionally, subgroup analysis by outcome showed a greater adverse association between fluoride exposure and performance IQ, as compared with verbal IQ. This finding may be explained, by the fact that verbal abilities are especially susceptible to home environment and parenting factors, that play a pivotal role on the cognitive development of young children and a positive stimulating environment can somehow act as a buffer for this domain and compensate for the toxicants harmful effect (Goodman et al., 2022). Moreover, thyroid hormones and hippocampal synaptic structures, that are specifically involved in the development of non-verbal, visual-spatial skills, are particularly affected by fluoride (Lee et al., 2012; Levie et al., 2018). Concerning the critical thresholds of exposure involved, the dose-response spline regression analysis for water fluoride suggests a roughly linear adverse effect on IQ

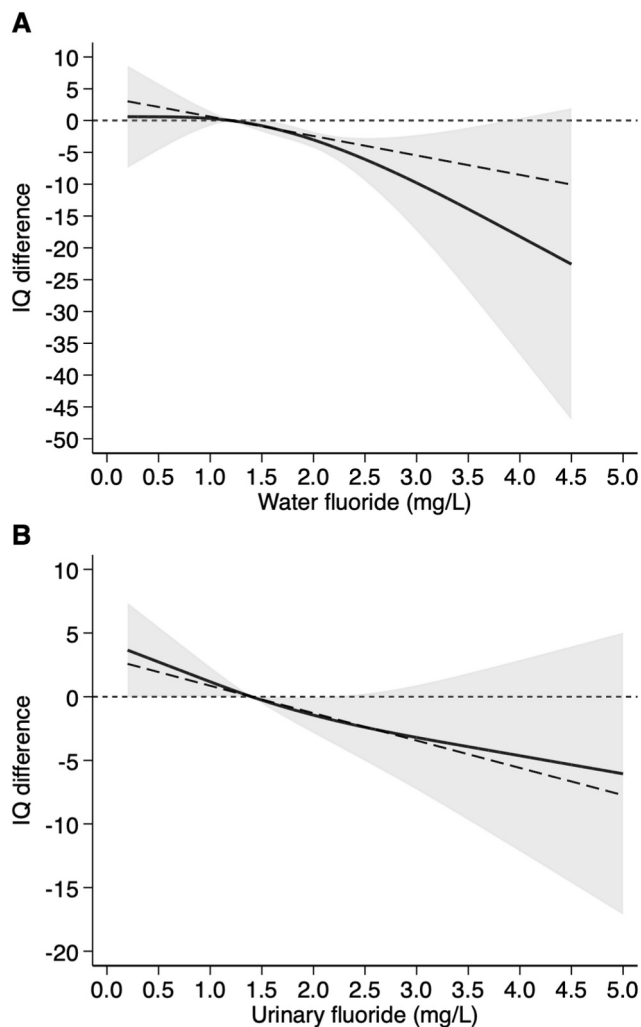


Fig. 5. Dose-response splines of intelligence (IQ score) and exposure to fluoride from drinking water (A) and urinary fluoride (B). Spline curve (black solid line) with 95% confidence limits (grey area), linear relation (black dotted line). Median values used as reference: 1.2 mg/L for drinking water fluoride and 1.4 mg/L for urinary fluoride, respectively.

above an approximate threshold of 1 mg/L, which becomes steeper over 2 mg/L.

The dose-response curve based on urinary fluoride shows a considerably more linear trend of the inverse association with the IQ score, with an early dose-dependent decrease in the endpoint, already detectable at the level corresponding to the current U.S. safety threshold of 0.7 mg/L of fluoride in drinking water. The inconsistency between the indication of a threshold and a more marked IQ decrease at high exposure levels for fluoride in drinking water, and a milder but continuous trend for urinary fluoride, is difficult to explain. It may be interesting to investigate the hypothesis that additional naturally occurring contaminants are also found in drinking water with high levels of naturally occurring fluoride and may either exert a deleterious effect on children's IQ or interact with fluoride by increasing its harmful effects. On the other hand, as a marker of cumulative exposure, urinary fluoride should provide a more reliable assessment and therefore allow a more valid dose-response relation.

Our results differ slightly from those of a recent meta-analysis, based on a linear meta-regression model, that indicated an early and linear decrease of IQ, with -2.94 IQ points per 1 mg/L fluoride increase (Neurath, 2020). However, among other possible common sources of heterogeneity, the fact that they considered water fluoride levels and

urinary fluoride as equivalent for the purpose of pooled analyses, according to the National Toxicology Program guidance, may have affected their estimates, in addition to the choice of a linear regression model. Using instead a non-linear dose-response model, Duan et al. (2018) found an association between increasing water fluoride exposure and IQ decrease, also starting from concentrations as low as 1 mg/L, however they limited their analysis to fluoride exposure from drinking water. Despite the methodological differences and possible limitations, the effect direction resulting from these reviews, in line with our results, suggest a harmful effect from fluoride in drinking water within a concentration range previously considered as safe, such as 0.7–1.2 mg/L (CDC - Center for Disease Control and Prevention, 2021). In 2015, however, the safety threshold for community water fluoridation was set to 0.7 mg/L in the U.S. primarily to lower the risk of dental fluorosis (U. S. Department of Health and Human Services Federal Panel on Community Water Fluoridation, 2015).

In addition to a general indication of an inverse association between fluoride exposure and IQ levels, a key finding of this meta-analysis was provided in the subgroup analysis by risk of bias, which showed noticeable differences of the estimates across categories of overall study quality, with a general trend towards weaker or null associations in the most carefully conducted studies. The fact that the only low RoB study (Feng et al., 2022) reported a non-adverse effect of fluoride on children's IQ, and that studies at intermediate RoB found a weaker association compared with studies affected by more severe biases, raises indeed some doubts on such association, despite the caution that must be given to single studies. Such a pattern may suggest that the serious adverse effect found in lower quality studies according to RoB, could be at least in part due to the methodological limitations of those studies, 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 our meta-analysis, the primary reason for downgrading the studies with reference to the risk of bias was the lack of adequate consideration of major confounders, such as age and socioeconomic status. The domain concerning participant selection was also a common reason for downgrading study quality, since in most the eligible studies the enrollment was primarily based on the participants' different fluoride exposures. In this regard, it should be highlighted that among the 4 cohort-designed studies that did not have such limitation, 3 of them that also adjusted for major confounding (Broadbent et al., 2015; Farmus et al., 2021; Till et al., 2020) found only a mild effect on children's IQ. Likewise, this considerably milder association with IQ score decrease found in these high-quality longitudinal studies (MD -0.74) compared with the cross-sectional studies (MD -5.21) raises additional concerns about the potential influence of biases in the latter estimates, and the key role of methodological issues in the epidemiologic literature.

Age at outcome evaluation, as a possible source of confounding, varied widely over the included studies, possibly affecting both the cumulative exposure and the adequacy of the intelligence tests that were administered, whose results cannot be easily compared, also explaining to some extent the heterogeneous results of the studies and of the subgroup analysis by age groups. We tried to overcome some of such limitations by performing a subgroup analysis stratified by age categories, and we found interestingly a slightly higher IQ loss in children over 6 years of age, compared to preschool children. This could be explained by a higher exposure to fluoride coming from an increased intake of water and water-based beverages of older children compared to younger ones, as supported by a recent report from the Food Safety Authority of Ireland (FSAI - Food Safety Authority of Ireland, 2018). However, current evidence from cohort studies seems to indicate that *in utero* exposure to fluoride has a stronger association to neurodevelopmental issues as compared to post-natal exposure (Bashash et al., 2017; Cantoral et al., 2021; Farmus et al., 2021; Goodman et al., 2022). Another possible limitation of the evidence generated by this review lies in the fact that many studies included in this review assessed water fluoride

concentration and could not give a reliable insight on the total daily intake of fluoride. On the other hand, a considerable number of studies assessed urinary fluoride as the exposure marker, which reflects the cumulative exposure from all sources. Villa et al. (2010) estimated that in children 0–7 years old a daily fluoride intake of 0.07 mg leads to a neutral fluoride balance, being the fluoride retained equals zero. Differently, whatever the total daily fluoride intake might be and regardless of the sources, over approximately 0.5 mg/day a constant 55% of it will be retained, reaching teeth, bones, and brain regions, accounting for an increased 35% excretion through urine for each mg/day. Urinary fluoride excretion is therefore considered a valid biomarker of contemporary fluoride intake for population groups, although for individuals and different age groups it varies with renal function and acid-base balance (EFSA - European Food Safety Authority, 2013; Villa et al., 2010). In this regard, it should be noted that only a few studies reported the urinary fluoride adjusted for creatinine (Bashash et al., 2017; Feng et al., 2022; Wang et al., 2021). The differences, when reported, were however negligible, as renal function is generally efficient and comparable in the age groups considered by this review (Wang et al., 2018), thus only mildly affecting the estimates on the relation between intelligence and urinary fluoride.

Overall, we note that the observational design of all the included studies, mostly having in addition a cross-sectional design, may be a relevant source of bias, primarily due to unmeasured or residual confounding. However, eligible randomized clinical trials on this subject were not available, let alone investigating long-term exposure, understandably because of ethical issues. Therefore, and also in light of the differences found in the related subgroup analysis, well-designed cohort studies with complete data for both exposure and confounding and proper blinding of the study personnel are urgently needed, to adequately assess the relation between fluoride exposure and neuro-cognitive development, and to clarify the current sources of uncertainty, that also limit the adoption of public health measures.

Lastly, we acknowledge that the statistical estimates generated by our meta-analysis at high levels of fluoride exposure were statistically imprecise, thus suggesting additional caution.

In conclusion, we found an overall indication of dose-dependent adverse effects of fluoride on children's cognitive neurodevelopment, starting at rather low exposure. However, the limitations of most studies included in this meta-analysis, with particular reference to the risk of residual confounding, raise uncertainties about both the causal nature of such relation and the exact thresholds of exposure involved. Such key issues can only be confirmed by additional, high-quality longitudinal studies.

Credit author statement

Federica Veneri: conceptualization of the research protocol, methodology, data collection, data analysis, writing-original draft preparation; Marco Vinceti: conceptualization of the research protocol, methodology, data analysis, writing-reviewing and editing; Luigi Generali: supervision, writing-reviewing and editing; Maria Edvige Giannone: methodology, data collection and data synthesis; Elena Mazzoleni: methodology, data collection and data synthesis; Linda Birnbaum: writing-reviewing and editing; Ugo Consolo: writing-reviewing; Tommaso Filippini: conceptualization of the research protocol, methodology, modeling, data analysis, writing-reviewing and editing, supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2023.115239>.

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