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Original Research

Association between low fluoride exposure and children's intelligence: a meta-analysis relevant to community water fluoridation

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ABSTRACT

Objectives: Previous meta-analyses have mainly focused on studies conducted in endemic fluorosis areas with relatively high fluoride concentrations. These are impoverished rural communities in China, India, and Iran, and the findings cannot be generalised to developed countries. Therefore, we investigated the association between fluoride concentrations relevant to community water fluoridation and children's cognition measured with IQ scores by synthesising effect sizes reported in observational studies.
Methods: A previous meta-analysis and the National Toxicology Program database that included a search of multiple databases and the authors' search of PubMed, Google Scholar, and Mendeley provided the data. Cross-sectional and cohort studies examining the association between fluoride and children's cognition and intelligence scores were selected. Two reviewers abstracted data using standard procedures. We performed three meta-analyses to synthesise the effects using the random effects models.
Results: Eight studies of standardized mean difference in IQ scores from non-endemic fluorosis areas found no statistically significant difference between recommended and lower levels of fluoride (standardized mean difference = 0.07; 95% confidence interval: −0.02, 0.17; $I^2 = 0\%$), and no significant fluctuation in IQ scores across the differences in fluoride concentrations by non-linear modeling with restricted cubic spline ($P = 0.21$). Meta-analyses of children's and maternal spot urinary fluoride associated pooled regression coefficients ($Beta_{children} = 0.16$; 95% confidence interval: −0.40, 0.73; $P = 0.57$; $I^2 = 0\%$, $Beta_{maternal} = -0.92$; 95% CI: −3.29, 1.46; $P = 0.45$; $I^2 = 72\%$) were not statistically significant. Further regression analysis by standardizing absolute mean IQ scores from lower fluoride areas did not show a relationship between F concentration and IQ scores (Model Likelihood-ratio test: P-value = 0.34.)
Conclusions: These meta-analyses show that fluoride exposure relevant to community water fluoridation is not associated with lower IQ scores in children. However, the reported association observed at higher fluoride levels in endemic areas requires further investigation.

Introduction

It is well established that fluoride in drinking water has a beneficial effect at lower concentrations in the prevention of tooth decay and detrimental effects on human health at higher concentrations, where it raises the risk for enamel and skeletal fluorosis. Fluoride is added to drinking water worldwide in the 0.5–1.1 mg/l range to prevent tooth decay.[1,2] The US Public Health Service now recommends 0.7 mg/l F for community water fluoridation (CWF).[3] The US Environmental Protection Agency has set the maximum contaminant level of fluoride in drinking water at 4 mg/l to protect against dental and skeletal effects.[4] The World Health Organization (WHO) guideline value for fluoride in drinking water is 1.5 mg/l.[5] Because CWF reaches more than 207 million Americans, its benefits and safety are continually assessed and debated.[6,7] The National Toxicology Program (NTP) asked the National Academies of

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Sciences, Engineering, and Medicine (NASEM) to review draft monographs that assessed the neurodevelopmental hazard associated with fluoride exposure.[8,9] A NASEM committee found the NTP draft monograph fell short of providing a clear and convincing argument that supported its assessment that fluoride is a presumed neurodevelopmental hazard.[10] This appraisal aligns with several other systematic and narrative reviews of the effect of fluoride on neurodevelopmental and cognitive outcomes.[11–17]

Four published meta-analyses of fluoride and neurodevelopmental hazard in humans from mostly endemic fluorosis areas compared the mean IQ scores or odds between higher and lower fluoride exposure groups.[17–20] Duan et al.[20] conducted a meta-analysis of standardised mean difference (SMD) in IQ scores between higher water fluoride communities (mean F = 3.7 mg/l) and normal fluoride communities (mean F = 0.6 mg/l). The summary results indicated high water fluoride exposure was associated with lower intelligence levels (SMD: −0.52; 95% CI: −0.62 to −0.42; $P < 0.001$). However, the dose–response meta-analysis revealed a non-linear relationship with both relative and absolute fluoride doses such that very high fluoride concentrations (5.2 ± 1.1 mg/l F) in water were associated with higher intelligence levels than medium fluoride concentrations (3.1 ± 0.9 mg/l F). The authors cited the lack of socio-economic status data as a limitation that might have affected the relationship between water fluoride intake and intelligence scores. NASEM, in its review of the NTP monograph, recommended that NTP 'emphasize that much of the evidence presented comes from studies that involve relatively high fluoride concentrations and that the monograph cannot be used to draw conclusions regarding low fluoride exposure concentrations (<1.5 mg/l), including those typically associated with drinking water fluoridation.'[10] This highlights a need to assess the association between fluoride exposure relevant to levels observed in communities with CWF and children's intelligence scores. Therefore, the authors posed the following question (Supplementary Table A): *Does fluoride exposure recommended for caries prevention decrease children's cognition and IQ scores?* We assessed fluoride exposure in three ways: 1) an ecological measure based on place of residence; and using fluoride concentration from 2) child; and 3) maternal urine samples. We identify the limitations of the present studies and offer recommendations for future research.

Methods

Search strategy

We started with 26 studies identified by Duan et al.[20] for relevant published articles through November 2016. We then cross-checked the literature search conducted in May 2020 by NTP as part of the report titled Draft NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects to add additional studies.[8] NTP identified 46 studies for the SMD meta-analysis and six studies for the urinary F-IQ meta-analysis. In addition, the authors updated the search using PubMed, Mendeley, and Google Scholar to identify English-language documents published between May 2020 and December 2021. Keywords included combinations of 'fluoride' or 'fluoridation' and 'neurodevelopment' or 'cognition' or 'intelligence' or 'IQ.'

Study selection criteria

Studies were included if they met the following criteria: (1) the exposure variable included water or urinary F; (2) outcomes included information to calculate the SMD and/or regression coefficient for the change in cognition and IQ scores; (3) the study design was an observational study; (4) the article was available in English; and (5) the population was children aged 1–18 years.

Studies were excluded if they met any of the following criteria for assessing the effect at low F levels: (1) studies conducted in endemic fluorosis areas where the higher exposure was greater than 1.5 mg/l F; (2) the exposure variable was other than water or urinary F; and (3) overlapping publications from the same study. We excluded studies that used dental fluorosis as exposure as they were from endemic fluorosis areas (including from coal), or presented IQ outcome and dental fluorosis measurements in a different format than other studies, which made it challenging to synthesise the results.

When multiple publications analysed the same subjects, we included only the article with the largest number of participants. Two authors reviewed each potentially eligible study, and a consensus approach resolved disagreements. We excluded studies where the description of subject recruitment, exposure assessment, and the outcome was not provided.

Data extraction

Two authors abstracted data from the eligible studies using a standard form. For the SMD analysis, the following information was extracted: authors, publication year, study type, age range, fluoride exposure (range and mean), outcome measure, number of children in higher and lower exposure groups, mean IQ, and standard deviation. Where the standard error (SE) was unavailable, we used the method recommended by the Cochrane Handbook for converting confidence intervals and P values to SE.[22]

The following information was extracted for the urinary fluoride analysis: authors, publication year, study type, urinary fluoride exposure range, outcome measure, and covariates. In addition, the beta coefficient data for every 0.5 mg/l increase in urinary F and its SE from the multiple regression equation was abstracted for the two analyses.

Data synthesis

SMD in IQ scores

For this meta-analysis, eight studies from non-endemic areas with fluoride exposure in drinking water below ~1.5 mg/l F were available (Table 1).[21–28] These studies provided fluoride concentrations, mean IQ scores, sample size, and standard deviation for calculating the pooled effect size. In addition, upon request, Ibarluzea et al.[25] provided the same data for their study. The characteristics of the studies included in the meta-analysis are shown in Table 2 and Supplementary Table B.

Urinary fluoride and IQ

Two separate analyses were done using children's urinary fluoride (CUF) and maternal urinary fluoride (MUF) to juxtapose studies with similar exposure measures. Three publications each provided CUF- and MUF-associated regression coefficients.[24,25,27,29,30] For the CUF meta-analysis, multiple publications from a study conducted by Yu et al.[30] in Tianjin, China, were excluded. That study provided a regression coefficient for exposure in the 0.01–1.6 mg/l F range. For the MUF meta-analysis, the author included the General Cognitive Index coefficient from the study by Bashash et al..[24] For the Ibarluzea et al.[25] publication, we chose the MUFcr (mg/g) at week 12 associated coefficient, as it was combined for boys and girls.

Table 1
Characteristics of the studies included in the standardized mean difference (SMD) meta-analysis of fluoride and children's IQ scores.

Study Year	Country	Age (years)	Number of subjects	Exposure assessment	Higher level F exposure (mg/l); (range or midpoint)	Lower level F exposure (mg/l) (range or midpoint)	Intelligence assessment test	Reported outcome	Medline Indexed Journal	RoB study quality
An JA 1992	China	7–16	242	Water	4.85 (2.1–7.6)	0.8	Wechsler Intelligence	IQ; IQ by age group; IQ distribution	No	- -
Xu YL 1994	China	8–14	129	Water	1.8 0.8	0.8 0.38	Binet Simon	IQ; IQ distribution	No	- -
Li XS 1995	China	8–13	907	Urine	2.69	1.02	Chinese standardized Raven	IQ; IQ by gender and age; IQ distribution	No	- -
Zhao LB 1996	China	7–14	320	Water	4.12	0.91	Chinese standardized Raven	IQ; IQ by age, gender and education; IQ distribution	No	- -
Wang G 2008	China	4–7	230	Water	4.8 (0.58–8.6)	0.79 (<1.0)	Wechsler Intelligence	IQ by type; IQ less than 90; IQ by head circumference	No	- -
Yao L 1996	China	8–12	536	Water	11 2.0	1.0 1.0	Chinese standardized Raven	IQ; IQ by TSH level; IQ distribution	No	- -
Yao L, Yang S 1997	China	7–12	497	Water	2	0.4	Chinese standardized Raven	IQ; IQ by age	No	- -
Zhang JW 1998	China	4–10	103	Water	0.8	0.58	Japan IQ	IQ; IQ by age	No	- -
Lu Y 2008	China	10–12	118	Water Urine	3.15 4.99	0.37 1.43	Chinese standardized Raven	IQ; IQ distribution	No	- -
Hong FG 2008	China	8–14	117	Water	2.9	0.75	Chinese standardized Raven	IQ; IQ distribution; IQ by education level	No	- -
Wang XH 2001	China	8–12	60	Water	2.97	0.5	Chinese standardized Raven	IQ; IQ distribution	No	- -
Xiang Q 2003	China	8–13	512 290	Water Urine	2.47 (0.57–4.5) 0.75 3.47	0.36 (0.18–0.76) 0.36 1.11	Chinese standardized Raven	IQ; IQ by age, gender and education; IQ distribution	No	–
Seraj B 2006	Iran	N/A	126	Water	2.5	0.4	Raven	IQ	No	- -
Wang ZH 2006	China	8–12	368	Water Urine	5.54 5.5	0.73 1.51	Chinese standardized Raven	IQ; IQ distribution	No	- -
Fan ZX 2007	China	7–14	79	Water Urine	3.15 2.89	1.03 1.78	Chinese standardized Raven	IQ; IQ distribution	No	- -
Wang SX 2007	China	8–12	449	Water Urine	8.3 (3.8–11.5) 5.1	0.5 (0.2–1.1) 1.5	Chinese standardized Raven	IQ; IQ distribution	Yes	- -
Chen YX 2008	China	7–14	640	Water	4.55	0.89	Chinese standardized Raven	IQ; IQ by age; IQ distribution by gender	No	- -
Pourelami 2011	Iran	7–9	120	Water	2.38	0.41	Raven's Progressive Matrices Intelligence	IQ; IQ distribution; IQ in gender	No	- -
Eswar P 2011	India	12–14	133	Water	2.45	0.29	Raven (Standard Progressive Matrices)	IQ; IQ distribution	No	- -
Trivedi MH 2012	India	N/A	84	Water Urine	2.3 2.69	0.84 0.42	Raven (Standard Progressive Matrices)	IQ; IQ distribution; IQ by gender	No	- -
Seraj B 2012	Iran	6–11	293	Water	5.2 (1.1)	0.8 (0.3)	Raven's Color Progressive Matrices	IQ; IQ distribution; IQ by gender	No	- -
Karimzade 2014	Iran	9–12	39	Water	3.94	0.25	The Iranian version of the Raymond B Cattell	IQ; IQ distribution	No	- -
Sebastian 2015	India	10–12	405	Water	2 1.2	0.4 0.4	Raven's Colored Progressive Matrices	IQ; IQ distribution	Yes	- -

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Table 1 (*continued*)

Study Year	Country	Age (years)	Number of subjects	Exposure assessment	Higher level F exposure (mg/l); (range or midpoint)	Lower level F exposure (mg/l) (range or midpoint)	Intelligence assessment test	Reported outcome	Medline Indexed Journal	RoB study quality
Broadbent 2015	New Zealand	7–13	990	Water	0.7–1.0	0.0–0.3	Wechsler Intelligence Scale for Children-Revised	IQ	Yes	+
Bashash M 2017	Mexico	6–12	189	Urine	≥0.80 75th percentile = 1.01	<0.80 25th percentile = 0.54	Wechsler Abbreviated Scale of Intelligence	IQ	Yes	–
Yu X 2018	China	7–13	2380	Water Urine	2.0 1.37	0.5 0.41	Combined Raven's for Rural China	IQ; IQ distribution	Yes	–
Green R 2019	Canada	3–4	400 369	Water Urine	0.59 0.69	0.13 0.40	Wechsler Primary and Preschool Scale of Intelligence-III	IQ; IQ by gender	Yes	–
Ibarluzea J 2021	Spain	4.4 ± 0.1	247	Water	0.8	0.1	McCarthy Scales of Children's Abilities (MSCA)	IQ	Yes	+

Risk of Bias (RoB) rating:+, probably low risk of bias; –, probably high risk of bias; – –, definitely high risk of bias.
Except for Broadbent 2015, Yu 2018, and Ibarluzea 2021, all studies are based on non-probability sampling. Broadbent 2015 and Ibarluzea 2021 are population-based birth cohort studies. Green 2019 and Bashash 2017 are cohort studies based on non-probability sampling. All others are cross-sectional studies.

Risk of bias and quality assessment

Two authors assessed the risk of bias and study quality reported in the previous systematic reviews. We adapted the Office of Health Assessment and Translation Risk of Bias rating tool[31] and included seven questions relevant to cohort and cross-sectional studies. The risk of bias assessment is presented in Supplementary Fig. A.[8] This assessment is consistent with other reviews.[15–17]

Statistical analysis

We performed three meta-analyses: (1) SMD in IQ scores between children in higher fluoride non-endemic areas (less than ~1.5 mg/l F in drinking water or its equivalent exposure; World Health Organization guideline value) and lower fluoride exposure groups based on studies that used group-level exposure; (2) a meta-analysis of the effect (beta regression coefficient) of 0.5 mg/l F increase in urinary fluoride on IQ scores based on studies that used CUF; and (3) a similar meta-analysis using MUF. We used the Cochrane Review Manager (RevMan)[32] and the R Language.

The random effects models were used for calculating the pooled SMD in unadjusted IQ scores and the urinary fluoride-IQ meta-analysis. The non-linear relationship between fluoride exposure and SMD in IQ scores was modeled by restricted cubic splines with three knots at 10th, 50th, and 90th percentiles. The model was weighted by the precision of SMD in IQ score. The 95% confidence interval band was generated. The Likelihood-ratio test was used to assess the goodness of fit of splines.

Results

Overall, 28 studies (31 comparisons) were available for the SMD analysis.[21–23,25,26,28,33–55] Two overlapping publications from the Duan meta-analysis[56,57] and one publication with unusually low IQ scores were excluded.[52] Five new studies were added.[24,25,27,28,30] Of these 28 studies, 23 and 8 provided data from endemic and non-endemic areas, respectively (Fig. 1).[21–28]

Fig. 2 shows that the pooled SMD effect size of 0.07 (95% CI: −0.02, 0.17), favoring higher F, was not statistically significant ($P = 0.14$) in non-endemic areas. Furthermore, there was no observed heterogeneity ($I^2 = 0\%$; $P = 0.64$). This estimate contrasts with an effect size of −0.46 (95% CI: −0.58, −0.35) with substantial heterogeneity ($I^2 = 81\%$; $P < 0.001$) for studies from endemic areas. A 95% prediction interval for the true outcomes is −0.95 to 0.02, which suggests that SMD values are possible on both sides of the null in future studies.

The relationship between F concentration in water or urine and IQ was explored. A meta-analysis of non-linear regression with restricted cubic spline for SMD showed that population fluoride concentration exposure differential between recommended F level and lower areas was not associated with SMD (Supplementary Fig. B). The summarised estimates of linear and non-linear terms from the restricted cubic spline are 0.0959 ($P = 0.59$; 95% CI −0.2498, 0.4416) and 0.1960 ($P = 0.77$; 95% CI −1.1338, 1.5257), and the overall model fitting resulted in a P-value of 0.21 with Wald test. Further regression analysis with restricted cubic spline by standardising the 36 absolute mean IQ scores from lower fluoride areas (28 studies) did not show a relationship between F concentration and IQ scores (model Likelihood-ratio test: P-value = 0.34; Supplementary Fig. C).

Fig. 3A shows that the change in pooled IQ score of 0.16 points (95% CI: −0.40, 0.73) for every 0.5 mg/l increase in children's urinary F was not statistically significant ($P = 0.57$). There was no observed heterogeneity ($I^2 = 0\%$; $P = 0.43$).

Table 2
Characteristics of the studies of urinary fluoride and children's IQ scores (regression coefficient) meta-analysis at lower fluoride levels.

Publication	Year	Study location	Age	N	Fluoride exposure	Fluoride range	Regression coefficient (95% CI)/unit	Outcome measure	Covariates
ELEMENT Study from Mexico									
Thomas D ELEMENT Study (Thesis)	2014	Mexico	6–15	550	Urine Contemporaneous	0.123–2.812 mg/l.	Beta for CUF/1 mg/l F 1.32; $P = 0.33$ **Boys 3.81; *P* = 0.05** Girls −1.57; $P = 0.39$	Wechsler Abbreviated Scale of Intelligence	Sex, maternal age, marital status, maternal education, family possessions, cohort, mother's WASI score
			1–3	431	Maternal urinary F	0.110–3.439 mg/l	Beta for MUF/1 mg/l F −0.631; $P = 0.391$	Mental Development Index (MDI), a subscale of the Bayley Scales of Infant Development-II (BSID-II) test	Maternal age, education, marital status, pregnancy smoking status, child's sex, and child's age
				194	Maternal plasma F	0.00350–0.07700 mg/l	−0.0031; $P = 0.650$		Breastfeeding not included.
Bashash et al. ELEMENT Study	2017	Mexico	6–12	189	Contemporaneous specific gravity −adjusted Urinary F	Mean 0.84 Range 0.18–2.8 mg/l	Beta for CUF/0.5 mg/l F −0.89 (−2.63, 0.85) −0.77 (−2.53, 0.99), adjusted for MUFcr	Wechsler Abbreviated Scale of Intelligence measured at the time of urine collection in children	Age; sex; weight at birth; parity; gestational age; maternal characteristics (smoking history, marital status, age at delivery, IQ), cohort.
				211	Maternal urine	Mean 0.89 mg/l Range 0.23–2.14 mg/l F	Beta for MUF/0.5 mg/l F **−2.50 (−4.12, −0.59)** 'non-linear relation, with no clear association between IQ scores and values below approximately 0.8 mg/l' −1.73 (−3.75, 0.29) adjusted for CUF − non-linear relation	McCarthy Scales of Children's Abilities −General Cognitive Index (GCI)	Breastfeeding not included.
			4	287	Maternal urine	Mean 0.90 mg/l Range 0.23–2.36 mg/l F	Beta for MUF/0.5 mg/l F **−3.15 (−5.42, −0.87)**		
Tianjin, China									
Yu et al.	2018	China	7–13	2380	Urine Contemporaneous	0.01–1.6 mg/l urinary F. 1.60–2.50 mg/l urinary F 2.50–5.54 mg/l urinary F	Beta for CUF/0.5 mg/l F 0.36 (−0.29, 1.01) **−2.67 (−4.67, −0.68)** −0.84 (−2.18, 0.50)	Combined Raven's Test for Rural China	Age; sex; maternal education; paternal education; low birth weight Breastfeeding not included
MIREC Study from six cities in Canada									
Green et al.	2019	Canada	3–4	512	Maternal urine	Maternal urinary F level 0.06–2.44 mg/l; MUF mean and SD 0.40 (0.27) and 0.69 (0.42)	Beta for MUF/1 mg/l F All −1.95 (−5.19 to 1.28)/**Boys −4.49 (−8.38 to −0.60)** Girls 2.40 (−2.53 to 7.33)	Wechsler Primary and Preschool Scale of Intelligence-III	Adjusted for city, HOME score, maternal education, race/ethnicity, and child −sex interaction. City included. Second-hand smoke excluded. Breastfeeding excluded
Till et al.	2020	Canada	3–4	350	Maternal urinary F used for adjustment	Mean Fluoridated Breast fed 0.70 (0.39)	Water Fl (mg/l) adjusted for MUF Model	Wechsler Preschool and Primary Scale of	Water fluoride concentration model. Adjusted for maternal

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Table 2 (*continued*)

Publication	Year	Study location	Age	N	Fluoride exposure	Fluoride range	Regression coefficient (95% CI)/unit	Outcome measure	Covariates
						Formula fed 0.64 (0.37) Non-fluoridated Breast fed 0.42 (0.28) Formula fed 0.38 (0.27)	Beta for MUF/0.5 mg/l F; −1.08 (−1.54, 0.47) −0.54 (−3.04, 0.90) [without two extreme IQ outliers] Fluoride intake from formula Model Beta for MUF/0.5 mg/l F; −1.50 (−3.41, 0.43) −1.49 (−3.37, 0.39) [without two extreme IQ outliers]	Intelligence-III (WPPSI-III)	education, maternal race, child's age at IQ testing, child's sex, HOME total score, and second-hand smoke status in the child's house. City excluded. Second-hand smoke included Breastfeeding duration used to calculate fluoride intake.
Farmus et al.	2021	Canada	3–4	434	Children's urine adjusted for specific gravity $n = 434$	Urinary F Mean 0.51 mg/l F (0.39) Range 0.05–2.89 mg/l F.	Beta for CUF/0.5 mg/l F All 0.23 (−1.75, 1.29) Boys 0.09 (−2.10, 2.28) Girls −0.52 (−2.62, 1.58)	Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III)	Covariates include maternal education, maternal race, total HOME score, age at urine sampling, and prenatal second-hand smoke.
					Maternal urinary F adjusted for specific gravity $n = 526$	Mean 0.53 mg/l (0.37) Range 0.06–2.48 mg/l F	Beta for MUF/0.5 mg/l F All −1.71 (−3.17, −0.24) **Boys −2.48 (−4.30, −0.66)** Girls −0.31 (−2.76, 2.14)		City excluded. Second-hand smoke included. Breastfeeding duration used to calculate fluoride intake.
Gipuzkoa, Spain Ibarluzea et al.	2021	Spain	4.4	248	Maternal urinary fluoride adjusted for creatinine	MUFcr (mg/g) at pregnancy Mean 0.64 (SD = 0.38) Range 0.15–1.91 MUFcr (mg/g) at week 12 Mean 0.55 (SD = 0.40) Range 0.05–2.36 MUFcr (mg/g) at week 32 Mean 0.73 (SD = 0.48) Range 0.13–3.07	Beta for MUF/1 mg/l F Boys **15.4 (6.32, 24.48)** Girls −0.19 (−7.31, 6.93) All 3.37 (−2.09, 8.83) Boys **11.48 (4.88, 18.08)** Girls −0.54 (−5.97, 4.9)	McCarthy Scales of Children's Abilities (MSCA)	Adjusted by age of the child at the time of the test (only for McCarthy), order of the child (between siblings), nursery at 14 months, breastfeeding, maternal social class, IQ and smoking. Breastfeeding included.

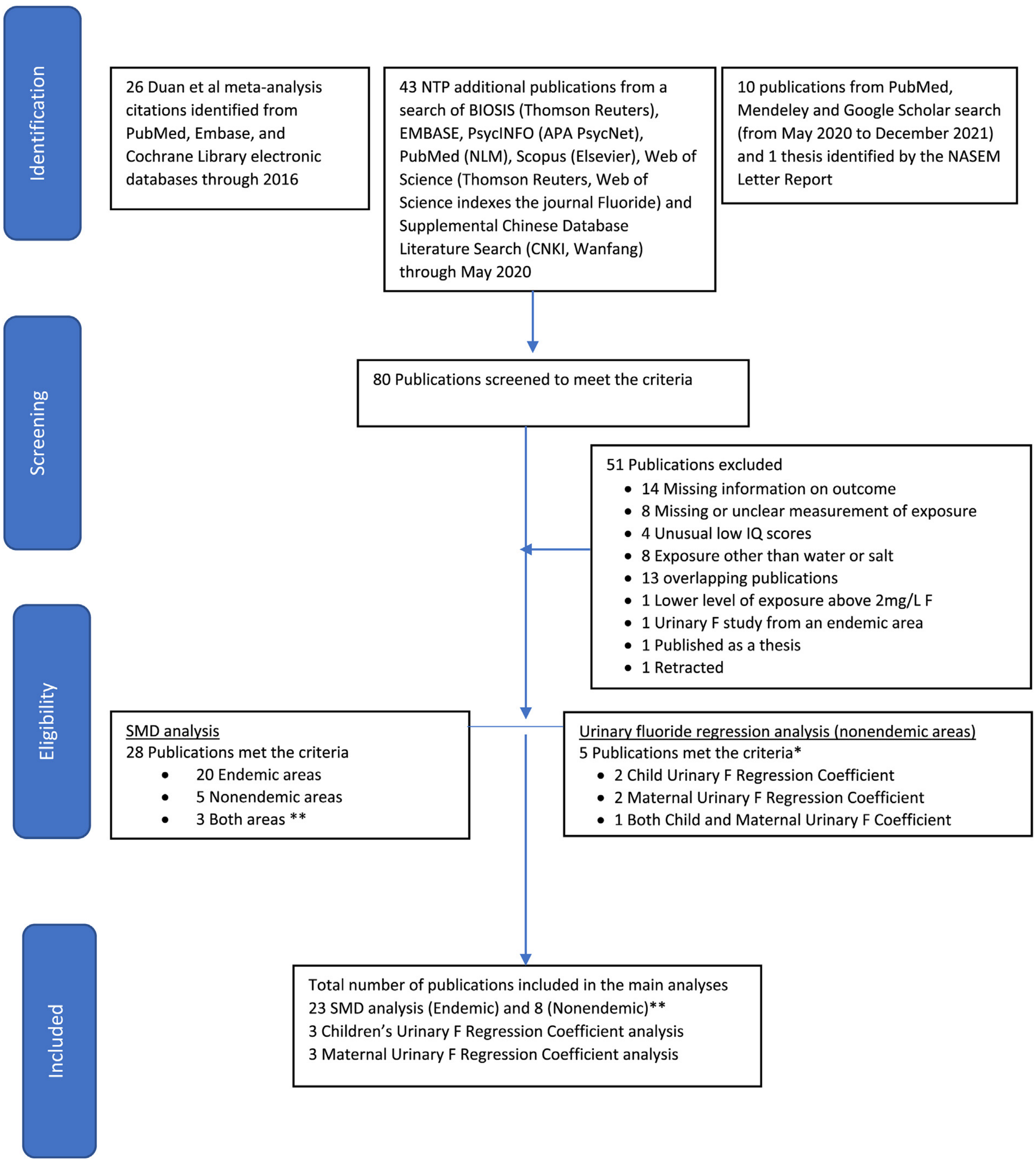
Note: Of 31 coefficients, five negative (two only in boys) and three positive (all in boys) statistically significant coefficients are shown in bold.
TSH, thyroid-stimulating hormone; WAIS, Wechsler Abbreviated Scale of Intelligence.

Fig. 3B shows that the change in pooled General Cognitive Index and IQ scores of −0.92 (95% CI: −3.29, 1.46) was not statistically significant (P = 0.45). However, the substantial heterogeneity (I^2 = 72%; P = 0.03) implies that significant discrepancies exist among studies, and therefore, the studies are not combinable.

In addition, sensitivity analyses by including and omitting other coefficients or studies each time did not influence the interpretation of the pooled regression coefficient outcome, suggesting that the lack of an effect was credible (Supplementary Table C). The funnel plot suggests symmetry. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.5653 and P = 0.06, respectively; Supplementary Fig. D).

Discussion

Meta-analyses of fluoride exposure to levels below 1.5 mg/l in water provide consistent evidence for the lack of an adverse effect on IQ. These results are consistent with the zero effect of fluoride on



Note: *Green 2019 and Farmus 2021 are overlapping publications from the same study, and contributed MUF and CUF data, respectively.
** Xu 1994, Xiang 2003, and Sebastian 2015 provided data for both endemic and non-endemic areas.

Fig. 1. Flow diagram of the publications selected for meta-analyses. Flowchart of studies identified, screened, excluded and included in the meta-analysis.

Study or Subgroup	Higher F Mean	Higher F SD	Higher F Total	Lower F Mean	Lower F SD	Lower F Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.1.1 Higher F (Mean 3.7 mg/L) vs. Lower F (Mean 0.7mg/L)									
An 1992	75.9	13.6	121	84	12.1	121	3.5%	-0.63 [-0.89, -0.37]	1992
Xu YL 1994	79.3	2.25	97	83.8	9.1	32	2.7%	-0.91 [-1.33, -0.50]	1994
Li XS 1995	80.3	12.9	230	89.9	10.4	226	3.9%	-0.82 [-1.01, -0.63]	1995
Yao L 1996	92.5	12.3	78	98.5	13.2	270	3.6%	-0.46 [-0.71, -0.21]	1996
Zhao LB 1996	97.7	13	160	105	15	160	3.7%	-0.52 [-0.74, -0.30]	1996
Yao & Yang S 1997	94.9	11.1	183	100	12.2	314	3.9%	-0.43 [-0.62, -0.25]	1997
Wang XH 2001	76.7	7.75	30	81.7	12	30	2.2%	-0.49 [-1.00, 0.03]	2001
Xiang Q 2003	92	13	222	100	13.2	290	3.9%	-0.61 [-0.79, -0.43]	2003
Seraj B 2006	87.9	11	41	98.9	12.9	85	2.8%	-0.89 [-1.28, -0.50]	2006
Wang ZH 2006	107	15.4	202	112	15.2	166	3.8%	-0.33 [-0.53, -0.12]	2006
Fan ZX 2007	96.1	12	42	98.4	14.8	37	2.6%	-0.17 [-0.61, 0.27]	2007
Wang SX 2007	101	16	253	105	15	196	3.9%	-0.26 [-0.44, -0.07]	2007
Lu Y (Shulin Liu) 2008	92.3	20.5	60	103	13.9	58	2.9%	-0.61 [-0.97, -0.24]	2008
Wang GJ 2008	95.6	14.3	147	101	15.8	83	3.5%	-0.36 [-0.63, -0.09]	2008
Chen YX 2008	100	14.5	320	104	15	320	4.0%	-0.27 [-0.43, -0.12]	2008
Hong FG 2008	80.6	2.28	85	82.8	8.98	32	2.7%	-0.43 [-0.84, -0.02]	2008
Pourelami HR 2011	91.4	15.6	60	97.8	15.9	60	3.0%	-0.40 [-0.77, -0.04]	2011
Eswar P 2011	86.3	12.8	68	88.8	15.3	65	3.1%	-0.18 [-0.52, 0.16]	2011
B. Seraj 2012	88.6	16	96	97.8	18.9	91	3.4%	-0.52 [-0.82, -0.23]	2012
Trivedi MH 2012	92.5	18.25	34	97.2	17.96	50	2.6%	-0.26 [-0.70, 0.18]	2012
Karimzade S 2014	81.2	16.2	19	104	20.7	20	1.6%	-1.20 [-1.89, -0.51]	2014
Sebastian ST 2015	80.5	12.7	135	86.4	13.6	135	3.6%	-0.45 [-0.69, -0.21]	2015
Yu 2018	106.4	12.3	1250	107.4	13	1636	4.3%	-0.08 [-0.15, -0.01]	2018
Subtotal (95% CI)			**3933**			**4477**	**75.2%**	**-0.46 [-0.58, -0.35]**	
Heterogeneity: Tau² = 0.06; Chi² = 118.72, df = 22 (P < 0.00001); I² = 81%								Prediction Interval -0.95 to 0.02	
Test for overall effect: Z = 7.80 (P < 0.00001)									
1.1.2 Recommnded F (Mean 0.90 mg/L) vs. Lower F (Mean 0.30 mg/L)									
Xu 1994	83.83	9.1	32	80.21	8.27	21	2.1%	0.41 [-0.15, 0.96]	1994
Zhang JW 1998	85.6	13.2	51	87.7	11	52	2.8%	-0.17 [-0.56, 0.22]	1998
Xiang 2003	99.56	14.13	9	100.41	13.21	290	1.7%	-0.06 [-0.73, 0.60]	2003
Broadbent (Child) 2015	100	15.1	891	99.8	14.5	99	3.8%	0.01 [-0.19, 0.22]	2015
Sebastian 2015	88.6	14.01	135	86.37	13.58	135	3.6%	0.16 [-0.08, 0.40]	2015
Bashash 2017	96.8	11.16	112	95.37	10.31	77	3.4%	0.13 [-0.16, 0.42]	2017
Green 2019	108.2	13.72	162	108.07	13.31	238	3.8%	0.01 [-0.19, 0.21]	2019
Ibarluzea 2021	101.47	15.5	124	98.67	15.7	123	3.6%	0.18 [-0.07, 0.43]	2021
Subtotal (95% CI)			**1516**			**1035**	**24.8%**	**0.07 [-0.02, 0.17]**	
Heterogeneity: Tau² = 0.00; Chi² = 5.15, df = 7 (P = 0.64); I² = 0%									
Test for overall effect: Z = 1.49 (P = 0.14)									
Total (95% CI)			**5449**			**5512**	**100.0%**	**-0.33 [-0.44, -0.22]**	
Heterogeneity: Tau² = 0.07; Chi² = 178.53, df = 30 (P < 0.00001); I² = 83%								Prediction Interval -0.86 to 0.20	
Test for overall effect: Z = 5.96 (P < 0.00001)									
Test for subgroup differences: Chi² = 48.23, df = 1 (P < 0.00001), I² = 97.9%									

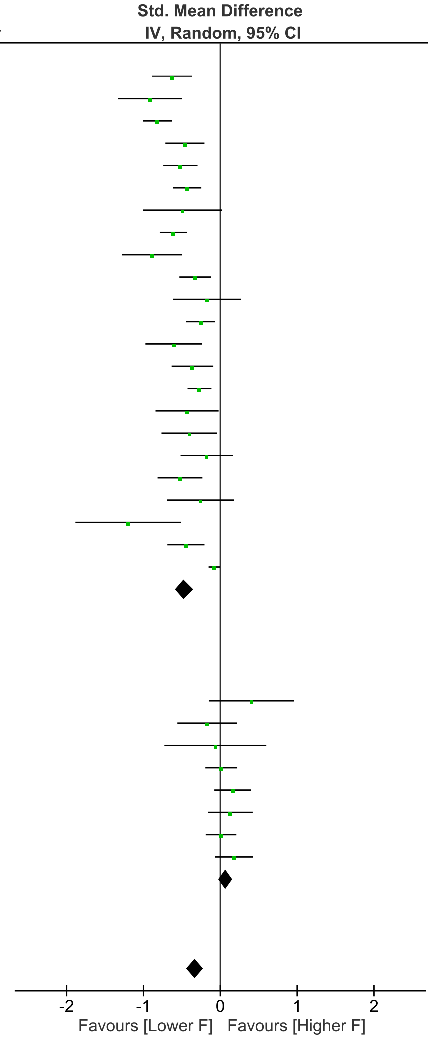


Fig. 2. Random effects analysis of standardized mean difference (SMD) and 95% CI of children's IQ score associated with exposure to higher fluoride. Forest plot of standardized mean difference (SMD) and 95% confidence interval of children's IQ scores according to endemic fluorosis and non-endemic fluorosis study communities. In the endemic areas, the mean F concentration in water or urine for higher and lower exposure groups was ~3.9 mg/l and ~0.7 mg/l, respectively. In the non-endemic areas, the mean F concentration in water or urine for higher and lower exposure groups was ~0.9 mg/l and ~0.3 mg/l, respectively. For each study, squares represent the point estimate, and the horizontal line shows the 95% CIs. Solid diamonds show the pooled estimate. The I^2 and P values for heterogeneity, test for overall effect, respectively, and prediction intervals are shown. The prediction interval reflects the uncertainty we expect in the pooled effect if a new study is included in the meta-analysis.

cognitive ability recently reported by Aggeborn and Ohman,[58] which included 80,000 observations. In addition, a study of school children in Australia showed that exposure to fluoridated water during the first five years of life was not associated with altered measures of child emotional and behavioral development and executive functioning.[59]

SMD analysis comparing higher and lower exposure groups

The meta-analytic finding of no adverse effect at lower F concentrations on IQ scores is not consistent with the meta-analysis of studies at higher F concentrations; thus, these studies should not be combined. Compared with the SMD effect size estimates of −0.45 and −0.52 from higher fluoride areas reported by Duan et al.[20] and Choi et al.,[19] respectively, the SMD effect size at lower F level in this analysis was positive (SMD = 0.07). Several possible explanations exist for the effects observed in studies conducted in endemic fluorosis areas of China, Iran, and India. First, in 23 of 28 studies, the authors did not provide data demonstrating the comparability of higher and lower F groups. These studies were conducted in socio-economically deprived rural areas where access to clean water is a major problem.[36,39,52] Selection bias resulting from non-probability sampling of impoverished population groups, lack of control of confounders and covariates, underestimation of the SE, and unweighted data from complex surveys have distorted the effect.[10] Second, the authors did not explore reverse causality.[10,12,60] Thus, high intelligence may have influenced avoiding fluoride exposure in areas with endemic fluorosis. Third, the exposure dose is much higher in endemic areas than in communities where water is optimally fluoridated. There may be a population threshold effect for IQ similar to severe dental fluorosis in the United States. Several studies have observed non-linear associations and a possible threshold for an IQ effect.[24,30] Fourth, Ioannidis[61] found that effect sizes for many associations, when first discovered and published in the scientific literature, are often inflated and do not reflect the smaller effect sizes reported later. He attributes this to the fact that the 'hallmark of discovery is the performance of exploratory analyses.' Fifth, Egger et al.[62] showed a danger in conducting meta-

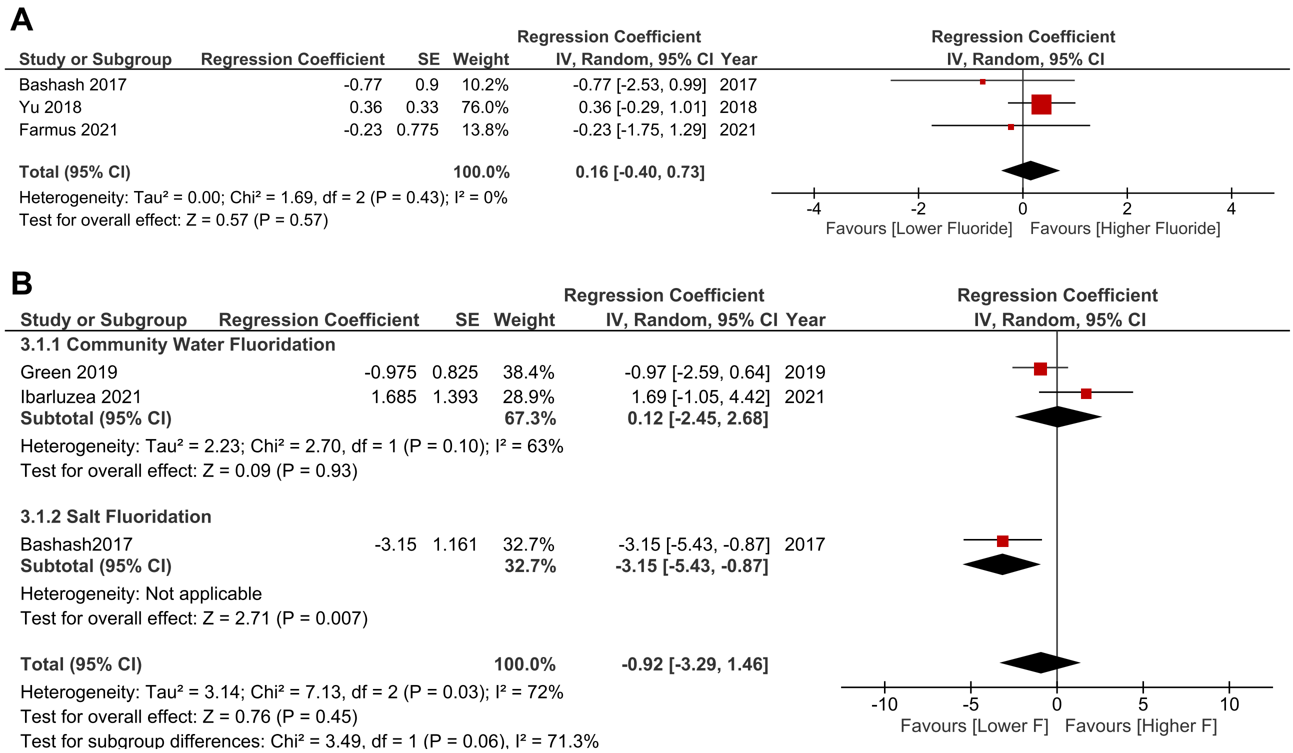


Fig. 3. (A) Random effects analysis of regression coefficients and 95% CI of children's IQ score associated with 0.5 mg/l increase in children's urinary fluoride in non-endemic areas. Forest plot of change in IQ score expressed as regression coefficient for every 0.5 mg/l increase in children's spot urinary fluoride concentrations in non-endemic fluorosis study communities. (B) Random effects analysis of regression coefficients and 95% CI of children's cognition and IQ score associated with 0.5 mg/l increase in maternal urinary fluoride in non-endemic areas. Forest plot of change in IQ score expressed as regression coefficient for every 0.5 mg/l increase in spot MUF concentrations in non-endemic fluorosis study communities according to source of fluoride.

analyses of observational data because they may produce precise but equally spurious results. Thus far, no cogent explanation has emerged for the mechanism of action of fluoride on neurodevelopmental effect.[16] Finally, publication bias is another possible explanation for the effects observed in the previous meta-analyses. The unpublished data showing a beneficial effect of fluoride on IQ in a study by Thomas in Mexico supports the potential for bias.[63]

Meta-analysis of spot CUF as a measure of children's fluoride exposure: postnatal effect

The lack of an adverse effect of fluoride when CUF was used in these studies from non-endemic areas suggests that children's exposure to CWF is not likely to show adverse effects. We selected CUF for the urinary fluoride meta-analysis because it is a direct measure of fluoride exposure to the developing brain. In addition, it likely reflects both prenatal and postnatal exposure if children are lifelong residents of a community.

Meta-analysis of spot MUF as a proxy for fetal fluoride exposure: prenatal effect

Three studies that used MUF as a proxy for fetal fluoride exposure showed inconsistent results characterised by high heterogeneity (Fig. 3B, Supplementary Table B). Ibarluzea et al.[25] could not replicate the previous study findings of prenatal effects. Instead, they found that fluoride exposure during pregnancy increased IQ across all domains among boys. In the Mexico study, Bashash et al.[24] found a threshold effect in older children, whereas Thomas[63] reported that maternal fluoride exposure did not impact children's neurobehavioral development at ages one to three years. A study from China that claimed a prenatal effect (all children had 'normal' intelligence with IQ score >119) was retracted because of methodological issues and misinterpretation of the results.[64] Recently, Farmus et al.[29,65] published a follow-up addendum declaring that exposures during trimesters of pregnancy, infancy, or childhood did not significantly associate with IQ outcomes in their study once the variable city was controlled and adjustments were made for multiple testing.

Salt was the source of fluoride in the Mexico study. Therefore, a high fluoride diet in pregnancy resulting from high salt intake may be confounded by other unhealthy habits.[24,66] However, the most likely explanation for the conflicting and inconsistent results among publications is that spot MUF is not a reliable and valid proxy biomarker of fetal fluoride exposure.[67,68] The limited available data confirm this finding because Thomas et al.[67] reported a weak correlation between MUF and maternal plasma fluoride during the early stage of pregnancy (Spearman correlation coefficient 0.29; $P = 0.004$) and a weak negative correlation in the late stage of pregnancy (Spearman correlation coefficient −0.24; $P = 0.07$) in the ELEMENT cohort. A multiple regression analysis did not show an association between spot MUF and maternal plasma fluoride. Maternal plasma fluoride levels were ~40 times lower than urinary fluoride levels. Gedalia et al.[69,70] found that the fluoride content of the bones, teeth, and cord blood of the fetuses was similar in areas with approximately 1 mg/l of fluoride compared with that of areas with 0.5 mg/l.

Strengths and limitations

We used three different exposure measures, including individual-level measures. This method also allows a direct comparison of the effect size with the Choi et al.[19] and Duan et al.'s[20] SMD meta-analyses of endemic fluorosis areas. The urinary fluoride meta-analysis takes advantage of adjusted beta regression coefficients derived from individual-level exposures. Although we did not find an adverse effect of lower fluoride levels on IQ in this meta-analysis of SMD, it is important to recognize the limitations of this approach.[71] The SMD analysis methodology is designed for data derived from randomised clinical trials where the treatment and control groups are likely to be similar concerning known and unknown variables. This similarity is unlikely to be the case when applied to observational studies, especially when the mean IQ scores presented are unadjusted for covariates. Furthermore, many studies were cross-sectional analyses based on ecological exposure data using convenience sampling, a feature of the study that renders it to the lowest level in the hierarchy of evidence for assessing causal association. Therefore, we used the standardised IQ scores to determine the fluctuations across fluoride concentrations. However, only four studies reported multiple measurements of fluoride concentration to get an accurate assessment of exposure.

There are also limitations to the meta-analysis of pooling the effects of urinary fluoride studies. Fluoride has a short half-life. Riddell et al.[72] found that urinary fluoride levels varied substantially depending on participant behavior before sampling. Therefore, spot urinary fluoride is not a valid biomarker of long-term exposure.[73] At best, an average total daily fluoride intake may be estimated from the average daily urinary fluoride excretion at a group level.[68]

Future direction for research

These weaknesses in existing evidence and a need for confirmatory studies raise the questions for research institutions of whether to support additional research and, if so, what type. A central issue is whether the fluoride-IQ studies can validly measure long-term exposure to prenatal and postnatal fluoride and relevant confounding variables and covariates to detect a difference of 1 or 2 IQ points, which is also not easy to measure reliably. In addition, it is well known that the findings of secondary data analysis using convenience samples or cross-sectional studies are not as reliable as that of randomised clinical trials and cohort studies in establishing a causal relationship. Huang[74] highlighted the problem of selection bias and convenience sample as major inferential threats in the UK Biobank and other big data repository-based studies where collider stratification and back-door paths among variables become highly likely. Animal studies may be undertaken to assess the effect of fluoride on neurodevelopment; however, the previous high-quality study conducted by NTP researchers did not show an effect at lower fluoride exposure concentrations.[75] The challenges of conducting observational studies to establish a cause-and-effect relationship in non-endemic fluoride areas where the range of exposure is narrow may be insurmountable. A better approach is to conduct interventional studies in endemic fluorosis areas of China, India, and Iran to test the fluoride-IQ hypothesis. These studies would provide an opportunity to assess the outcome of reducing fluoride exposure on purported neurodevelopmental effects.

Conclusions

These meta-analyses show that fluoride exposure at the concentration used in CWF is not associated with lower IQ scores. However, the reported association observed at higher fluoride levels in endemic areas requires further investigation. Uncritical acceptance of fluoride-IQ studies, including non-probability sampling, inadequate attention to accurate measurement of exposure, covariates and outcomes, and inappropriate statistical procedures, has hindered methodological progress. Therefore, the authors urge a more scientifically robust effort to develop valid prenatal and postnatal exposure measures and to use interventional studies to investigate the fluoride-IQ hypothesis in populations with high fluoride (endemic) exposure.

Author statements

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Ethical approval

This study was approved by the California Department of Public Health and did not require institutional review board approval. The findings and conclusions in this report are those of the authors and do not necessarily represent the views or opinions of the California Department of Public Health or the California Health & Human Services Agency.

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Competing interests

J.V.K. is a member of the American Dental Association's National Fluoridation Advisory Committee. He was a reviewer of the National Academies of Sciences, Engineering, and Medicine report *Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Letter Report (2021)*. S.F.-O. is a member of the American Academy of Pediatrics' Section on Oral Health. She was a co-author of ‘Fluoride Use in Caries Prevention in the Primary Care Setting’ and ‘Review of Safety, Frequency and Intervals of Preventive Fluoride Varnish Application for Children.’ She consults for Arcora Foundation on medical–dental integration and has research funding for medical–dental integration from Health Resources Services Administration (HRSA) D88HP37553. She serves on an independent DSMB for a study funded by Colgate.

Appendix A. Supplementary data

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