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Fluoride Exposure and Children's IQ Scores
A Systematic Review and Meta-Analysis

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➕ Editorial

➕ Supplemental content

IMPORTANCE Previous meta-analyses suggest that fluoride exposure is adversely associated with children's IQ scores. An individual's total fluoride exposure comes primarily from fluoride in drinking water, food, and beverages.

OBJECTIVE To perform a systematic review and meta-analysis of epidemiological studies investigating children's IQ scores and prenatal or postnatal fluoride exposure.

DATA SOURCES BIOSIS, Embase, PsycInfo, PubMed, Scopus, Web of Science, CNKI, and Wanfang, searched through October 2023.

STUDY SELECTION Studies reporting children's IQ scores, fluoride exposure, and effect sizes.

DATA EXTRACTION AND SYNTHESIS Data were extracted into the Health Assessment Workplace Collaborative system. Study quality was evaluated using the OHAT risk-of-bias tool. Pooled standardized mean differences (SMDs) and regression coefficients were estimated with random-effects models.

MAIN OUTCOMES AND MEASURES Children's IQ scores.

RESULTS Of 74 studies included (64 cross-sectional and 10 cohort studies), most were conducted in China (n = 45); other locations included Canada (n = 3), Denmark (n = 1), India (n = 12), Iran (n = 4), Mexico (n = 4), New Zealand (n = 1), Pakistan (n = 2), Spain (n = 1), and Taiwan (n = 1). Fifty-two studies were rated high risk of bias and 22 were rated low risk of bias. Sixty-four studies reported inverse associations between fluoride exposure measures and children's IQ. Analysis of 59 studies with group-level measures of fluoride in drinking water, dental fluorosis, or other measures of fluoride exposure (47 high risk of bias, 12 low risk of bias; n = 20 932 children) showed an inverse association between fluoride exposure and IQ (pooled SMD, −0.45; 95% CI, −0.57 to −0.33; P < .001). In 31 studies reporting fluoride measured in drinking water, a dose-response association was found between exposed and reference groups (SMD, −0.15; 95% CI, −0.20 to −0.11; P < .001), and associations remained inverse when exposed groups were restricted to less than 4 mg/L and less than 2 mg/L; however, the association was null at less than 1.5 mg/L. In analyses restricted to low risk-of-bias studies, the association remained inverse when exposure was restricted to less than 4 mg/L, less than 2 mg/L, and less than 1.5 mg/L fluoride in drinking water. In 20 studies reporting fluoride measured in urine, there was an inverse dose-response association (SMD, −0.15; 95% CI, −0.23 to −0.07; P < .001). Associations remained inverse when exposed groups were restricted to less than 4 mg/L, less than 2 mg/L, and less than 1.5 mg/L fluoride in urine; the associations held in analyses restricted to the low risk-of-bias studies. Analysis of 13 studies with individual-level measures found an IQ score decrease of 1.63 points (95% CI, −2.33 to −0.93; P < .001) per 1-mg/L increase in urinary fluoride. Among low risk-of-bias studies, there was an IQ score decrease of 1.14 points (95% CI, −1.68 to −0.61; P < .001). Associations remained inverse when stratified by risk of bias, sex, age, outcome assessment type, country, exposure timing, and exposure matrix.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found inverse associations and a dose-response association between fluoride measurements in urine and drinking water and children's IQ across the large multicountry epidemiological literature. There were limited data and uncertainty in the dose-response association between fluoride exposure and children's IQ when fluoride exposure was estimated by drinking water alone at concentrations less than 1.5 mg/L. These findings may inform future comprehensive public health risk-benefit assessments of fluoride exposures.

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Fluoride from natural sources occurs in some community water systems (CWSs), and in the United States and some other countries, fluoride is added to public drinking water systems or salt for the prevention of tooth decay. For CWSs that add fluoride, the US Public Health Service recommends a fluoride concentration of 0.7 mg/L, the US Environmental Protection Agency's (EPA's) enforceable and nonenforceable standards for fluoride in drinking water are 4.0 mg/L and 2.0 mg/L,[1] and the World Health Organization's (WHO's) drinking water quality guideline for fluoride is 1.5 mg/L.[2] Water and water-based beverages are the main source of systemic fluoride intake. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that water and processed beverages (eg, soda and juices) provide approximately 75% of a person's fluoride intake,[3] and EPA estimates that 40% to 70% of a person's fluoride intake comes from fluoridated drinking water.[4] However, an individual's total exposure also reflects contributions from fluoride in other sources, such as food, dental products, industrial emissions, and pharmaceuticals.[4] Accumulating evidence suggests that fluoride exposure may affect brain development. A 2006 report from the National Research Council (NRC) concluded that high levels of naturally occurring fluoride in drinking water may be of concern for neurotoxic effects.[5] This finding was largely based on studies from endemic fluorosis areas in China that had limitations in study design or methods. Following the NRC review, studies from an additional 10 countries have been published (eFigure 1A in Supplement 1).[6-8] Previous meta-analyses[6-8] found an inverse association between fluoride exposure and children's IQ. Since the most recent meta-analysis,[8] 4 new studies on exposure to fluoride and children's IQ have been published, including 3 studies[9-11] that measured individual-level maternal and children's urinary fluoride concentrations.

To incorporate newer evidence and increase transparency, objectivity, and rigor in the analysis of fluoride research, we conducted a systematic review and meta-analysis of studies that provided estimates of group-level and individual-level fluoride exposure in relation to children's IQ scores.

Methods

The search, selection, extraction, and risk-of-bias evaluation of studies were part of a larger systematic review.[12] Brief methods are outlined herein, with detailed methods available in the protocol[13] and the "Detailed Methods" section of eAppendix 1 in Supplement 1. This study follows the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. Data analysis was conducted from June 2020 to January 2024. The most recent analysis update was performed in January and February 2024.

Systematic Literature Review, Study Selection, and Data Extraction
Literature searches were conducted in BIOSIS, Embase, PsycInfo, PubMed, Scopus, Web of Science, CNKI, and Wanfang. The searches were performed through October 2023 without language restrictions.[13] Studies were independently screened by 2 reviewers against inclusion and exclusion criteria described in the "Detailed Methods" section of eAppendix 1 in Supplement 1 and the protocol.[13] Data were extracted from included studies by 1 extractor and verified by a second extractor into the Health Assessment Workspace Collaborative (HAWC) system. Data are publicly available and downloadable (https://hawcproject.org/assessment/405/).

Quality Assessment: Risk of Bias
Quality of individual studies, also called risk of bias, was independently evaluated by 2 trained assessors following criteria prespecified in the protocol,[13] using the National Toxicology Program's or Division of Translational Toxicology's OHAT approach.[14] Risk-of-bias questions concerning confounding, exposure characterization, and outcome assessment were considered key. If not addressed appropriately, these questions were thought to have the greatest potential impact on the results.[13] The remaining risk-of-bias questions were used to identify other concerns that may indicate serious risk-of-bias issues (eg, selection bias, inappropriate statistical analysis). No study was excluded from the meta-analysis based on concerns for risk of bias; however, subgroup analyses were conducted with and without high risk-of-bias studies (ie, studies rated probably high risk of bias for ≥2 key risk-of-bias questions or definitely high risk of bias for any single question) to assess their potential impact, in terms of magnitude and direction of bias, on the results. Ratings and justification are available in HAWC (https://hawcproject.org/assessment/405/).

Statistical Analysis
We conducted the following analyses, planned a priori in the protocol: (1) mean-effects meta-analysis, (2) dose-response mean-effects meta-analysis, and (3) regression slopes meta-analysis (detailed methods are provided in the "Detailed Methods" section of eAppendix 1 in Supplement 1).

Key Points

Question Is fluoride exposure associated with children's IQ scores?

Findings Despite differences in exposure and outcome measures and risk of bias across studies, and when using group-level and individual-level exposure estimates, this systematic review and meta-analysis of 74 cross-sectional and prospective cohort studies found significant inverse associations between fluoride exposure and children's IQ scores. For fluoride measured in water, associations remained inverse when exposed groups were restricted to less than 4 mg/L or less than 2 mg/L but not when restricted to less than 1.5 mg/L; for fluoride measured in urine, associations remained inverse at less than 4 mg/L, less than 2 mg/L, and less than 1.5 mg/L; and among the subset of low risk-of-bias studies, there were inverse associations when exposed groups were restricted to less than 4 mg/L, less than 2 mg/L, and less than 1.5 mg/L for analyses of fluoride measured both in water and in urine.

Meaning This comprehensive meta-analysis may inform future risk-benefit assessments of the use of fluoride in children's oral health.

The mean-effects meta-analysis included studies that reported mean IQ scores and group-level exposures for at least 1 exposed group and 1 reference group. The effect estimates were standardized mean differences (SMDs) for heteroscedastic population variances.[15-17] SMDs were calculated from the difference in mean IQ scores between an exposed group and a reference group. If an individual study reported mean IQ scores for multiple exposure groups, the highest exposure group was considered the exposed group and the lowest exposure group was considered the reference group. A sensitivity analysis was performed to evaluate the impact of all exposure groups combined compared with a reference group. Pooled SMDs and 95% CIs were estimated using random-effects models. To determine whether the data support an exposure-response association, we conducted a dose-response mean-effects meta-analysis that included studies from the mean-effects meta-analysis and used a 1-step approach as described in the protocol.[13,18-20] A pooled dose-response curve was estimated using a restricted maximum likelihood estimation method. Potential nonlinear associations were examined using quadratic terms and restricted cubic splines. Model comparison was based on the maximum likelihood Akaike information criterion (AIC).[21] To examine associations at lower fluoride levels, subgroup analyses were restricted to 0 to less than 4 mg/L (comparable to EPA's enforceable drinking water standard for fluoride of ≤4 mg/L), 0 to less than 2 mg/L (comparable to EPA's nonenforceable standard for fluoride in drinking water of ≤2 mg/L), and 0 to less than 1.5 mg/L (comparable to WHO's guideline for fluoride in drinking water of ≤1.5 mg/L).[4]

The regression slopes meta-analysis included studies that reported regression slopes to estimate associations between individual-level fluoride exposures and children's IQ. Data from individual studies were pooled using a random-effects model.[22]

Heterogeneity was assessed by Cochran Q test[23] and the I^2 statistic.[24] Subgroup analyses stratified studies by risk of bias (high or low), study location (country), outcome assessment, exposure matrix (eg, urine, water), sex, and age to further investigate sources of heterogeneity. An analysis stratified by prenatal or postnatal exposure was suggested post hoc. Potential publication bias was assessed with funnel plots and Egger tests.[25-27] If publication bias was present, trim-and-fill methods[28,29] were used to estimate the number of hypothetical "missing" studies and predict the impact of the missing studies on the pooled effect estimate.

Statistical analyses were performed using Stata version 17.0 statistical software (StataCorp LLC).[30] The combine, meta esize, meta set, meta summarize, drmeta, meta funnel, meta bias, meta trimfill, and metareg packages were used.[31]

Results

Study Sample

A total of 74 publications (64 cross-sectional studies and 10 prospective cohort studies) met the inclusion criteria, with 65 included in the primary analyses and an additional 9 included in sensitivity analyses (eFigure 1B in Supplement 1; see eTable 2 in Supplement 1 for excluded publications). Characteristics of the 74 publications and the study-specific effect estimates used in the meta-analyses are shown in eTable 1 in Supplement 1. Most studies were conducted in China (n = 45); other locations included Canada (n = 3), Denmark (n = 1), India (n = 12), Iran (n = 4), Mexico (n = 4), New Zealand (n = 1), Pakistan (n = 2), Spain (n = 1), and Taiwan (n = 1). No studies were conducted in the United States. Of these, 59 publications reported mean IQ scores for group-level exposures[10,11,32-95] and 19 reported regression slopes for individual-level exposures based on urinary or water fluoride concentrations and fluoride intake.[9-11,32-38,96-104] Additional details on study characteristics are provided in the "Results" section of eAppendix 1 in Supplement 1. Sixty-four studies reported inverse associations between fluoride exposure measures and children's IQ. Fifty-two studies were rated high risk of bias. Twenty-two studies were rated low risk of bias, with 13 rated low risk of bias across all 7 risk-of-bias domains and 9 rated low risk of bias in 6 domains and probably high risk of bias in no more than 1 domain. Results from risk-of-bias evaluations are presented in eFigure 2 in Supplement 1. Interactive versions of the figures and risk-of-bias evaluations are available in HAWC (links provided in the "Results" section of eAppendix 1 in Supplement 1). Further details and justification about low risk-of-bias studies are presented in eAppendix 2 in Supplement 1.

Mean-Effects Meta-Analysis

The meta-analysis of 59 studies (47 high risk of bias, 12 low risk of bias; n = 20 932 children) that provided mean IQ scores showed that, when compared with children exposed to lower fluoride levels, children exposed to higher fluoride levels had statistically significantly lower IQ scores (random-effects pooled SMD, −0.45; 95% CI, −0.57 to −0.33; $P < .001$) (Table 1 and Figure 1). There was evidence of high heterogeneity (I^2 = 94%; $P < .001$; Table 1) and publication bias (funnel plot and Egger $P < .001$, Begg $P = .03$; eFigures 3 and 4 in Supplement 1). Adjusting for possible publication bias through trim-and-fill analysis supported the statistically significant inverse association after imputation of 2 additional studies to the right side (adjusted SMD, -0.39; 95% CI, −0.58 to −0.20) or 17 studies to the left side (adjusted SMD, -0.63; 95% CI, -0.76 to -0.50) (eFigures 5 and 6 in Supplement 1). Fifty-two of the 59 studies (88%) reported an inverse association with SMDs ranging from −5.34 (95% CI, −6.34 to −4.34) to −0.04 (95% CI, −0.45 to 0.36) (Figure 1). Seven studies that did not report inverse associations reported SMDs ranging from 0.00 (95% CI, −0.25 to 0.25) to 0.43 (95% CI, 0.07 to 0.80).[10,32,37,39-42] Three studies[43-45] lacked clear descriptions of their intelligence assessment methods; however, sensitivity analyses did not reveal substantial changes in the pooled SMD estimate when these studies were excluded or when a study[103] that reported the cognitive subset of evaluations using Bayley and McCarthy tests was included (eTable 3 in Supplement 1).

Among the low risk-of-bias studies,[10,11,32-35,37,42,47-50] the random-effects pooled SMD was −0.19 (95% CI, −0.35 to −0.04;

Table 1. Pooled Standardized Mean Differences (SMDs) From Random-Effects Meta-Analyses of the Association Between Group-Level Measures of Fluoride Exposure and IQ Scores in Children

Analysis	Studies, No.	SMD (95% CI)	Heterogeneity P value	I^2, %
Overall association with IQ	59	−0.45 (−0.57 to −0.33)	<.001	94
Subgroup analysis				
Risk of bias				
Low	12	−0.19 (−0.35 to −0.04)	.01	87
High	47	−0.52 (−0.68 to −0.37)	<.001	94
Sex				
Female	15	−0.45 (−0.65 to −0.25)	<.001	78
Male	16	−0.53 (−0.77 to −0.29)	<.001	88
Age, y				
<10[a]	14	−0.38 (−0.57 to −0.19)	<.001	82
≥10	17	−0.52 (−0.67 to −0.37)	<.001	71
Country				
China	41	−0.42 (−0.51 to −0.33)	<.001	86
India	8	−1.09 (−2.23 to 0.06)	<.001	98
Iran	4	−0.68 (−0.99 to −0.38)	.08	57
Canada	2	0.01 (−0.14 to 0.16)	NA	0
Pakistan	2	0.10 (−0.57 to 0.77)	.01	83
New Zealand	1	0.01 (−0.19 to 0.22)	NA	NA
Taiwan	1	0.10 (−0.10 to 0.29)	NA	NA
Assessment type				
CRT-RC	31	−0.35 (−0.45 to −0.25)	<.001	85
Non–CRT-RC tests	28	−0.59 (−0.88 to −0.29)	<.001	96
Raven tests	12	−0.72 (−1.48 to 0.04)	<.001	99
Other tests	16	−0.52 (−0.72 to −0.32)	<.001	87
Exposure matrix				
Water fluoride	34	−0.35 (−0.45 to −0.24)	<.001	87
Dental fluorosis	9	−0.86 (−1.91 to 0.19)	.11	99
Other exposures[b]	16	−0.54 (−0.71 to −0.37)	<.001	81

Abbreviations: CRT-RC, Combined Raven Test–The Rural Edition in China; NA, not applicable.

[a] Both An et al[55] and Li et al[56] included 10-year-old children in the group listed as younger than 10 years (ages 7-10 years reported).

[b] Includes iodine,[44,52-54,57,58] arsenic,[36,51,59] aluminum,[60] and non–drinking water fluoride (ie, fluoride from coal burning[61-69]).

P = .01) with high heterogeneity (I^2 = 87%) (Table 1; eFigure 7 in Supplement 1) and no evidence of publication bias (funnel plot and Egger P = .56; eFigures 8 and 9 in Supplement 1). Among the high risk-of-bias studies, the random-effects pooled SMD was −0.52 (95% CI, −0.68 to −0.37; P < .001) with high heterogeneity (I^2 = 94%) (Table 1; eFigure 7 in Supplement 1). There was evidence of publication bias (funnel plot and Egger P < .001; eFigures 8 and 9 in Supplement 1); the trim-and-fill analysis had an adjusted pooled SMD of −0.47 (95% CI, −0.72 to −0.23) (eFigures 10 and 11 in Supplement 1).

Subgroup analyses by sex, age, study location, outcome assessment type, and exposure assessment matrix found inverse associations between measures of fluoride exposure and children's IQ (Table 1; eFigures 12-16 in Supplement 1). The subgroup analyses did not explain a large amount of the overall heterogeneity; however, the degree of heterogeneity was lower for studies restricted to Iran (I^2 = 57%), children aged 10 years or older (I^2 = 71%), and girls (I^2 = 78%) ("Results" section of eAppendix 1 in Supplement 1). The results of the metaregression models indicate that year of publication and mean age of children did not explain a large degree of heterogeneity ("Results" section of eAppendix 1 in Supplement 1).

Dose-Response Mean-Effects Meta-Analysis

The dose-response mean-effects meta-analysis included data from 38 studies (eTable 1 in Supplement 1). We excluded studies for which there was evidence that coexposures to arsenic or iodine might be differential.[36,41,44,51-54,105] Results from both the analysis of 31 studies with group-level fluoride measurements in drinking water (24 high risk of bias, 7 low risk of bias; n = 12 487 children) and the analysis of 20 studies with group-level mean urinary fluoride levels (10 high risk of bias, 10 low risk of bias; n = 9756 children) found that lower children's IQ scores were associated with increasing levels of fluoride exposure. Based on the linear models, the mean SMD between exposed and reference groups was −0.15 (95% CI, −0.20 to −0.11; P < .001) for water fluoride levels and −0.15 (95% CI, −0.23 to −0.07; P < .001) for urinary fluoride levels (Table 2; eTable 4 in Supplement 1). Based on the AIC, the best model fit was achieved when restricted cubic spline levels were added to the linear models for drinking water. Given the small difference in AICs between the different models, and considerations of parsimony and ease of interpretability, the linear model results were chosen for the purposes of discussion and are presented in Table 2, although results from all models are

Figure 1. Forest Plot for Random-Effects Meta-Analysis of Standardized Mean Differences (SMDs) of the Association Between Group-Level Measures of Fluoride Exposure and IQ Scores in Children

Source	SMD (95% CI)
Ren et al,[57] 1989 (translated in 2008[58])	-0.94 (-1.17 to -0.72)
Chen et al,[70] 1991 (translated in 2008[71])	-0.26 (-0.41 to -0.10)
Guo et al,[61] 1991 (translated in 2008[62])	-0.44 (-0.80 to -0.08)
Lin et al,[44] 1991	-0.17 (-0.35 to 0.00)
Sun et al,[60] 1991	-0.93 (-1.13 to -0.73)
An et al,[55] 1992	-0.63 (-0.89 to -0.37)
Li et al,[45] 1994 (translated in 2008[46])	-0.75 (-1.20 to -0.31)
Xu et al,[72] 1994	-0.93 (-1.35 to -0.52)
Li et al,[73] 1995	-0.82 (-1.01 to -0.63)
Wang et al,[63] 1996 (translated in 2008[64])	-0.38 (-0.65 to -0.10)
Yao et al,[74] 1996	-0.46 (-0.71 to -0.20)
Zhao et al,[75] 1996	-0.54 (-0.76 to -0.31)
Yao et al,[76] 1997	-0.43 (-0.61 to -0.25)
Zhang et al,[51] 1998	-0.17 (-0.56 to 0.22)
Lu et al,[77] 2000	-0.62 (-0.98 to -0.25)
Hong et al,[78] 2001 (translated in 2008[79])	-0.44 (-0.85 to -0.03)
Hong et al,[52] 2001b	-0.48 (-0.99 to 0.03)
Wang et al,[53] 2001	-0.50 (-1.01 to 0.02)
Li et al,[80] 2003 (translated in 2008[81])	-0.10 (-0.25 to 0.04)
Xiang et al,[47] 2003	-0.64 (-0.82 to -0.46)
Wang et al,[82] 2005	-0.30 (-0.49 to -0.11)
Seraj et al,[83] 2006	-0.89 (-1.28 to -0.50)
Wang et al,[84] 2006	-0.27 (-0.47 to -0.06)
Fan et al,[85] 2007	-0.17 (-0.61 to 0.27)
Trivedi et al,[86] 2007	-1.10 (-1.40 to -0.79)
Wang et al,[59] 2007	-0.28 (-0.47 to -0.09)
Li et al,[65] 2009	-0.50 (-1.12 to 0.13)
Li et al,[56] 2010	-0.07 (-0.22 to 0.08)
Ding et al,[34] 2011	-0.04 (-0.45 to 0.36)
Eswar et al,[87] 2011	-0.18 (-0.52 to 0.16)
Kang et al,[41] 2011	0.00 (-0.25 to 0.25)
Poureslami et al,[88] 2011	-0.39 (-0.76 to -0.03)
Shivaprakash et al,[89] 2011	-0.50 (-0.81 to -0.18)
Seraj et al,[48] 2012	-0.53 (-0.82 to -0.23)
Trivedi et al,[49] 2012	-0.26 (-0.69 to 0.18)
Wang et al,[90] 2012	-0.36 (-0.47 to -0.24)
Bai et al,[66] 2014	-0.45 (-0.67 to -0.23)
Karimzade et al,[91] 2014	-1.23 (-1.92 to -0.55)
Broadbent et al,[39] 2015	0.01 (-0.19 to 0.22)
Khan et al,[43] 2015	-5.34 (-6.34 to -4.34)
Sebastian and Sunitha,[92] 2015	-0.45 (-0.69 to -0.21)
Zhang et al,[35] 2015b	-0.53 (-0.83 to -0.23)
Zhang et al,[68] 2015c	-1.81 (-2.41 to -1.21)
Das and Mondal,[93] 2016	-0.56 (-1.63 to 0.51)
Mondal et al,[94] 2016	-0.58 (-1.22 to 0.05)
Yu et al,[33] 2018	-0.08 (-0.15 to -0.01)
Zhao et al,[54] 2018	-0.37 (-0.61 to -0.13)
Green et al,[32] 2019	0.01 (-0.19 to 0.21)
Cui et al,[50] 2020	-0.18 (-0.52 to 0.16)
Wang et al,[69] 2020	-0.68 (-0.94 to -0.43)
Lou et al,[67] 2021	-0.66 (-1.07 to -0.25)
Saeed et al,[36] 2021	-0.25 (-0.65 to 0.16)
Wang et al,[95] 2021	-0.45 (-0.62 to -0.28)
Ahmad et al,[40] 2022	0.43 (0.07 to 0.80)
Feng et al,[37] 2022	0.09 (-0.06 to 0.24)
Tian et al,[38] 2022	-0.07 (-0.38 to 0.23)
Dewey et al,[42] 2023	0.01 (-0.22 to 0.23)
Lin et al,[10] 2023	0.10 (-0.10 to 0.29)
Xia et al,[11] 2023	-0.35 (-0.49 to -0.20)
Overall	**-0.45 (-0.57 to -0.33)**

Effect size is expressed as the standardized weighted mean difference for heteroscedastic population variances (SMD). The random-effects pooled SMD is shown as a diamond. Error bars represent 95% CIs for the study-specific SMDs. Studies are presented in chronological order as found in eTable 1 in Supplement 1.
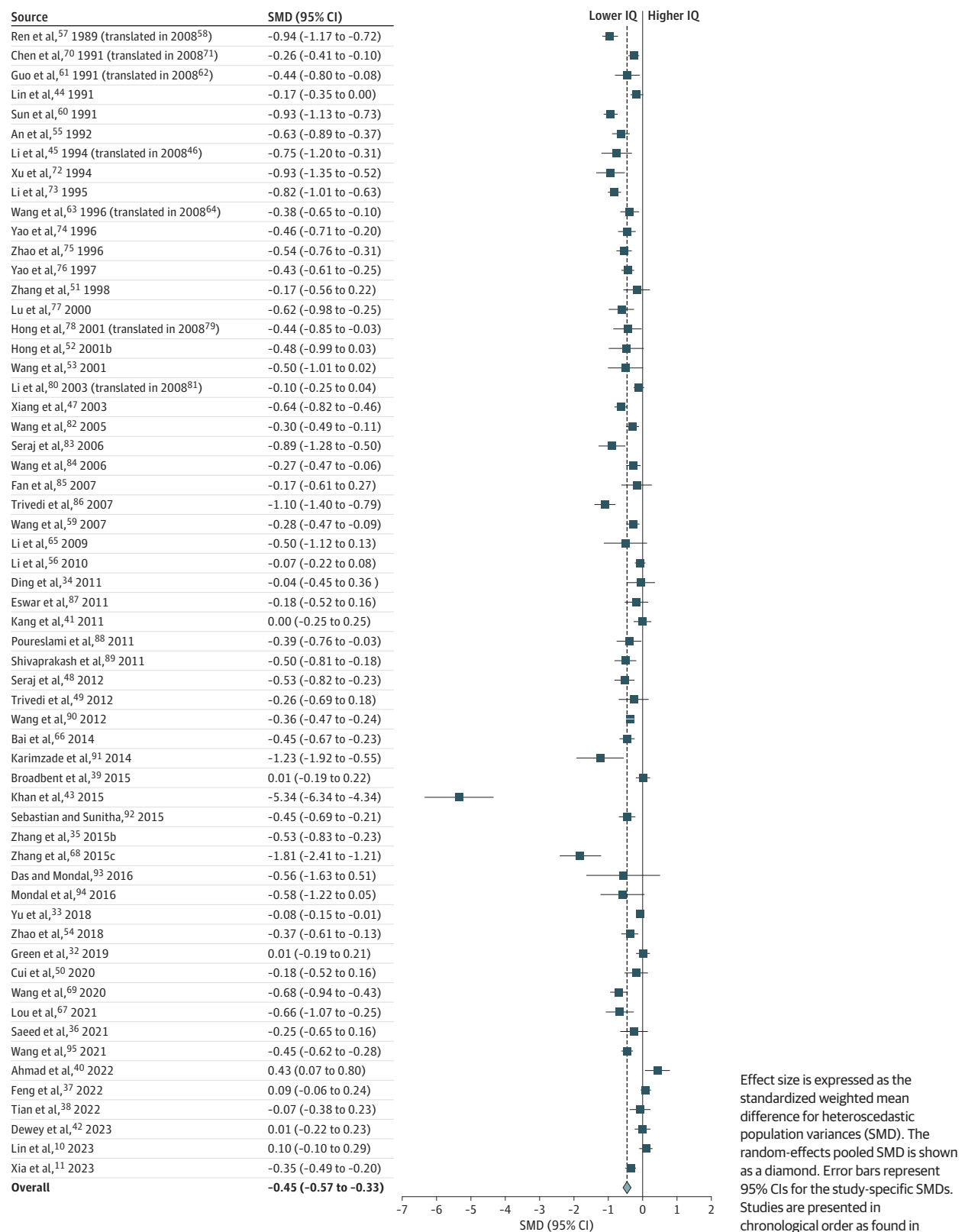
Table 2. Pooled Changes in Standardized Mean Differences (SMDs) From the Linear Model From the Dose-Response Mean-Effects Meta-Analyses Using Group-Level Measures of Fluoride Exposure

Fluoride exposure, mg/L	Studies, No.	Effect estimates, No.[a]	Children, No.	Parameter estimates[b]	
				β (95% CI)	P value
Water fluoride, all studies					
All data	31	41	12 487	−0.15 (−0.20 to −0.11)	<.001
<4	23	29	9554	−0.22 (−0.27 to −0.17)	<.001
<2	8	10	3682	−0.18 (−0.40 to 0.03)	.10
<1.5	7	7	2832	0.05 (−0.36 to 0.45)	.82
Water fluoride, low risk-of-bias studies					
All data	7	12	5066	−0.21 (−0.33 to −0.09)	.001
<4	7	10	4962	−0.23 (−0.34 to −0.11)	<.001
<2	4	5	1632	−0.33 (−0.53 to −0.13)	.001
<1.5	3	3	879	−0.32 (−0.91 to 0.26)	.28
Urinary fluoride, all studies					
All data	20	32	9756	−0.15 (−0.23 to −0.07)	<.001
<4	14	25	8019	−0.20 (−0.31 to −0.08)	.001
<2	6	10	4692	−0.08 (−0.15 to −0.005)	.04
<1.5	5	8	4219	−0.08 (−0.15 to −0.003)	.04
Urinary fluoride, low risk-of-bias studies					
All data	10	14	6847	−0.13 (−0.23 to −0.03)	.01
<4	10	14	6847	−0.13 (−0.23 to −0.03)	.01
<2	4	7	4179	−0.08 (−0.15 to −0.002)	.04
<1.5	4	7	4179	−0.08 (−0.15 to −0.002)	.04

[a] This represents the number of effect estimates (SMDs) from all the studies included in the analysis. Studies with more than 2 exposure levels provided more than 1 SMD for inclusion in the dose-response meta-analysis.

[b] Parameter estimates are changes in SMDs (β [95% CI]) for the linear model based on the restricted maximum likelihood models.

presented in eTable 4 in Supplement 1. For fluoride in water, the associations remained inverse when exposed groups were restricted to less than 4 mg/L (16 high risk-of-bias studies, 7 low risk-of-bias studies) or less than 2 mg/L (4 high risk-of-bias studies, 4 low risk-of-bias studies); however, the association was null at less than 1.5 mg/L (4 high risk-of-bias studies, 3 low risk-of-bias studies) (Table 2; eTable 4 in Supplement 1). When we included only studies with low risk of bias, the associations remained inverse at less than 4 mg/L, less than 2 mg/L, and less than 1.5 mg/L fluoride in water, and the linear model was the best fit (Table 2; eTable 4 in Supplement 1). For urinary fluoride, the associations remained inverse when exposed groups were restricted to less than 4 mg/L (4 high risk-of-bias studies, 10 low risk-of-bias studies), less than 2 mg/L (2 high risk-of-bias studies, 4 low risk-of-bias studies), and less than 1.5 mg/L (1 high risk-of bias study, 4 low risk-of-bias studies). When we included only the low risk-of-bias studies, the associations remained inverse at less than 4 mg/L, less than 2 mg/L, and less than 1.5 mg/L for urinary fluoride, and the linear model was the best fit (Table 2; eTable 4 in Supplement 1).

Regression Slopes Meta-Analysis

Each of the 19 studies with individual-level fluoride measures (2 high risk-of-bias studies, 17 low risk-of-bias studies) (eTable 1 in Supplement 1) reported urinary fluoride levels,[9-11,32-38,96-104] 2 reported fluoride intake,[32,97] and 2 reported water fluoride levels.[32,33] Thirteen studies were included in the primary regression slopes meta-analysis. The 6 remaining studies, including 3 studies[96-98] with populations that overlapped with already-included studies[32,33,101] and 3 that reported scores based on Bayley assessments,[102-104] were included in sensitivity analyses (eTable 5 in Supplement 1).
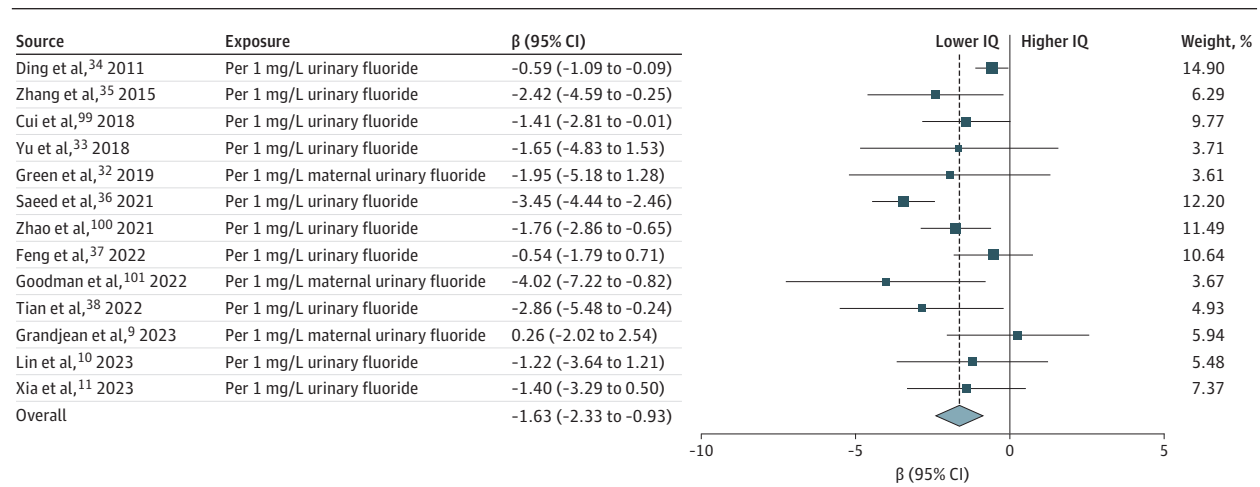
In the primary regression slopes meta-analysis, the pooled effect estimate from the 13 studies (2 high risk-of-bias studies, 11 low risk-of-bias studies; n = 4475 children) with individual-level data showed that a 1-mg/L increase in urinary fluoride was associated with a statistically significant decrease in IQ score of 1.63 points (95% CI, −2.33 to −0.93; P < .001) (Figure 2) with evidence of heterogeneity (I^2 = 60%; P < .001; Table 3) and no indications of publication bias (eFigures 17 and 18 in Supplement 1). When restricted to low risk-of-bias studies, the decrease in IQ score was 1.14 points (95% CI, −1.68 to −0.61; P < .001) with evidence of low heterogeneity (I^2 = 23%; P = .28; Table 3; eFigure 19 in Supplement 1) and a slight indication of publication bias (eFigure 20 in Supplement 1). The trim-and-fill analysis had an adjusted estimate of −0.78 (95% CI, −1.33 to −0.22) (eFigures 21 and 22 in Supplement 1).

Subgroup analyses by risk of bias, sex, country, exposure matrix, outcome assessment type, and prenatal or postnatal exposure found inverse associations between measures of fluoride exposure and children's IQ (Table 3; eFigures 23-27 in Supplement 1). The sensitivity analyses including reporting scores based on Bayley assessments[102-104] showed no substantial changes in the pooled effect estimates (eTable 5 in Supplement 1).

Discussion

This systematic review and meta-analysis found statistically significant inverse associations between measures of fluoride exposure and children's IQ. These inverse associations were observed in all 3 sets of meta-analyses: the mean-effects meta-analysis (47 high risk-of-bias studies, 12 low risk-of-bias studies) and dose-response mean-effects meta-

Figure 2. Forest Plot for Random-Effects Meta-Analysis of Regression Slopes
of the Association Between Individual-Level Urinary Fluoride Measures and IQ Scores in Children

Source	Exposure	β (95% CI)		Weight, %
Ding et al,[34] 2011	Per 1 mg/L urinary fluoride	-0.59 (-1.09 to -0.09)		14.90
Zhang et al,[35] 2015	Per 1 mg/L urinary fluoride	-2.42 (-4.59 to -0.25)		6.29
Cui et al,[99] 2018	Per 1 mg/L urinary fluoride	-1.41 (-2.81 to -0.01)		9.77
Yu et al,[33] 2018	Per 1 mg/L urinary fluoride	-1.65 (-4.83 to 1.53)		3.71
Green et al,[32] 2019	Per 1 mg/L maternal urinary fluoride	-1.95 (-5.18 to 1.28)		3.61
Saeed et al,[36] 2021	Per 1 mg/L urinary fluoride	-3.45 (-4.44 to -2.46)		12.20
Zhao et al,[100] 2021	Per 1 mg/L urinary fluoride	-1.76 (-2.86 to -0.65)		11.49
Feng et al,[37] 2022	Per 1 mg/L urinary fluoride	-0.54 (-1.79 to 0.71)		10.64
Goodman et al,[101] 2022	Per 1 mg/L maternal urinary fluoride	-4.02 (-7.22 to -0.82)		3.67
Tian et al,[38] 2022	Per 1 mg/L urinary fluoride	-2.86 (-5.48 to -0.24)		4.93
Grandjean et al,[9] 2023	Per 1 mg/L maternal urinary fluoride	0.26 (-2.02 to 2.54)		5.94
Lin et al,[10] 2023	Per 1 mg/L urinary fluoride	-1.22 (-3.64 to 1.21)		5.48
Xia et al,[11] 2023	Per 1 mg/L urinary fluoride	-1.40 (-3.29 to 0.50)		7.37
Overall		-1.63 (-2.33 to -0.93)		

Lower IQ | Higher IQ

β (95% CI)

The effect measures are regression slopes (β) per 1-mg/L increase in urinary fluoride. The βs for individual studies are shown with boxes representing the weight, and the pooled estimate is shown as a diamond. Error bars represent 95% CIs for the study-specific βs. Studies are presented in chronological order as found in eTable 1 in Supplement 1.

Table 3. Pooled Changes in IQ Scores From Random-Effects Meta-Analyses of the Association
Between Individual-Level Measures of Urinary Fluoride and IQ Scores in Children

Analysis	Studies, No.	β (95% CI)	Heterogeneity	
			P value	I², %
Overall association with IQ	13	−1.63 (−2.33 to −0.93)	<.001	60
Subgroup analysis				
Risk of bias				
Low	11	−1.14 (−1.68 to −0.61)	.28	23
High	2	−3.38 (−4.30 to −2.45)	.68	0
Sex				
Female	3	−1.07 (−2.20 to 0.05)	.33	0
Male	3	−1.21 (−3.80 to 1.37)	.09	65
Country				
Canada	1	−1.95 (−5.19 to 1.28)	NA	NA
China	8	−1.20 (−1.79 to −0.61)	.25	31
Denmark	1	0.26 (−2.02 to 2.54)	NA	NA
Mexico	1	−4.02 (−7.22 to −0.82)	NA	NA
Pakistan	1	−3.45 (−4.44 to −2.46)	NA	NA
Taiwan	1	−1.22 (−3.64 to 1.21)	NA	NA
Assessment type				
CRT-RC	9	−1.19 (−1.75 to −0.63)	.34	27
Non-CRT-RC tests	4	−2.32 (−4.26 to −0.37)	.03	66
Exposure matrix				
Urinary fluoride	13	−1.63 (−2.33 to −0.93)	<.001	60
Intake	2	−3.87 (−7.15 to −0.59)	.74	0
Water fluoride	2	−4.77 (−9.09 to −0.45)	.71	0
Exposure timing				
Prenatal	3	−1.70 (−4.23 to 0.84)	.09	57
Postnatal	10	−1.65 (−2.39 to −0.90)	<.001	64

Abbreviations: CRT-RC, Combined Raven Test–The Rural Edition in China; NA, not applicable.

analysis (27 high risk-of-bias studies, 11 low risk-of-bias studies) of group-level fluoride exposure, and the regression slopes meta-analysis (2 high risk-of-bias studies, 11 low risk-of-bias studies) of individual-level urinary fluoride. Within each of these meta-analyses, we used prespecified criteria to assess study quality and classify studies into low and high risk of bias.

Stratified analyses found similar inverse associations in both study quality strata. Further subgroup analyses by sex, age, timing of exposure, study location, outcome assessment type, and exposure assessment matrix also found inverse associations between fluoride exposure and children's IQ.

Studies in these meta-analyses included cross-sectional and prospective cohort designs, each study having its own strengths and limitations. Although all studies contribute to our understanding of the overall association, well-designed studies that accurately measure exposure and outcome and adequately account for potential confounding variables are particularly informative. In these meta-analyses, we followed the OHAT approach[14] to extract data from each of the published studies and to classify studies into high risk of bias and low risk of bias based on carefully predefined criteria.[13] To make our process and decisions transparent, we provide full public access to the extracted data, risk-of-bias ratings, and rationale for those ratings for each individual study. These data can be used by other investigators to evaluate or extend our process and analysis (https://hawcproject.org/assessment/405/).

Studies using group-level exposures were assessed in the mean-effects meta-analysis. An advantage of such studies is that they can, for example, examine communities with different CWS fluoride levels. Although in the United States 40% to 70% of a person's fluoride intake comes from fluoridated drinking water, there are other sources of fluoride exposure.[4] Therefore, relying on CWS levels alone may underestimate an individual's total fluoride exposure, which may vary considerably among members of a group depending on individual behaviors. Most of the studies in the mean-effects meta-analysis were cross-sectional; however, we have higher confidence in cross-sectional studies when there is evidence of temporality.[14] Among the low risk-of-bias cross-sectional studies, most provided information to establish that exposure likely preceded the outcome (eg, only including children who had lived in a community since birth or children who had dental fluorosis).

Studies using individual-level exposures were assessed in the regression slopes meta-analysis, which included 13 studies with urinary fluoride measures, a more precise exposure assessment measure than group-level exposures. Unlike drinking water levels, individual-level urinary fluoride concentrations include all ingested fluoride and are considered a valid estimate of total fluoride exposure.[106,107] Fluoride in urine is measured from both single or spot samples and multiple collections. When compared with 24-hour urine samples, spot samples are more prone to the influence of timing of exposure and can be affected by differences in dilution. However, correlations between urinary fluoride concentrations from 24-hour samples and spot samples adjusted for urinary dilution have been described.[108] There were several recent North American prospective cohort studies conducted in Canada and Mexico[32,96,97,101] that reported maternal urinary fluoride levels comparable to those in the United States.[109,110] These studies combined multiple urinary measurements over the course of pregnancy to examine prenatal fluoride exposure during a critical period of brain development. Although the estimated decreases in IQ found in the regression slopes meta-analysis may seem small (1.63 IQ points per 1-mg/L increase in urinary

fluoride), research on other neurotoxicants has shown that subtle shifts in IQ at the population level can affect people who fall within the high and low ranges of the population's IQ distribution.[111-115] For context, a 5-point decrease in a population's IQ would nearly double the number of people classified as intellectually disabled.[116]

Finally, studies with group-level exposure measurements were used in the dose-response mean-effects meta-analysis of water or urinary fluoride levels. Although we examined 2 nonlinear models, a linear model almost always provided the best fit for both water and urinary data. There was a statistically significant dose-response association between group-level fluoride measures and children's IQ. In stratified analyses of low risk-of-bias studies, the association remained inverse when exposure was restricted to less than 4 mg/L, less than 2 mg/L, and less than 1.5 mg/L fluoride in water or urine; except for fluoride concentrations less than 1.5 mg/L in water, these results were statistically significant. There was some inconsistency in the best-fit model and a lack of statistical significance at lower levels for water fluoride exposures, leading to uncertainty in the shape of the dose-response curve. This uncertainty is not surprising given the lower number of observations for fluoride concentrations in water (n = 879 from 3 studies) compared with urinary fluoride concentrations (n = 4218 from 5 studies). The ability to detect a true effect is reduced at lower exposure levels when exposure contrasts are diminished.[117] Although the same cutoffs were used for the water and urine subgroup analyses, fluoride levels in water likely underestimate total fluoride exposures that are better estimated by levels in urine. Variable fluoride exposures from nonwater sources may also decrease the precision of the effect estimates at lower fluoride concentrations in water. In contrast, the best model fit for urinary fluoride concentrations was consistently linear.

Elevated naturally occurring fluoride levels in groundwater (>1.5 mg/L) are prevalent globally and include central Australia, eastern Brazil, sub-Saharan Africa, the southern Arabian Peninsula, south and east Asia, and western North America.[118] Although to our knowledge no epidemiological studies addressing fluoride exposure and children's IQ have been conducted in the United States, significant inequalities in CWS fluoride levels exist by county sociodemographic characteristics, including racial and ethnic composition, especially among Hispanic and Latino communities.[119] Of note, there are regions of the United States where CWS and private wells contain natural fluoride concentrations greater than 1.5 mg/L,[120] serving more than 2.9 million US residents.[119] In addition, the US Geological Survey estimates that 172 000 US residents are served by domestic wells that exceed EPA's enforceable standard of 4.0 mg/L fluoride in drinking water, and 522 000 are served by domestic wells that exceed EPA's nonenforceable standard of 2.0 mg/L fluoride in drinking water.[1] To reduce risk of moderate-to-severe dental fluorosis, the CDC recommends that parents use an alternative source of water for children aged 8 years or younger and for bottle-fed infants if their primary drinking water contains greater than 2 mg/L of fluoride.[121] Currently, there are no recommendations or restrictions on fluoride levels in drinking water based on cognitive neurodevelopmental outcomes.[121]

To our knowledge, no studies of fluoride exposure and children's IQ have been performed in the United States, and no nationally representative urinary fluoride levels are available, hindering application of these findings to the US population. Although this meta-analysis was not designed to address the broader public health implications of water fluoridation in the United States, these results may inform future public health risk-benefit assessments of fluoride.

Strengths and Limitations

Strengths of this systematic review and meta-analysis include a large body of literature, a predefined systematic search and screening process, risk-of-bias assessment of individual studies, prespecified subgroup analyses, and use of both group-level and individual-level exposure data. The consistency of the inverse associations across the high and low risk-of-bias studies, different intelligence assessment methods, different exposure matrices, different study locations, different analytical approaches, and evidence of a dose-response association strengthen confidence in the conclusion of an overall inverse association between fluoride exposure and children's IQ. It is notable that there is a diversity of study design factors across studies, which could be described as overall heterogeneity of the body of evidence. In this case, the heterogeneity supports the robustness of the conclusions and is different from heterogeneity in the results, which we did not find in this meta-analysis.

The body of existing literature has limitations in that many of the studies were classified as having high risk of bias. Most of the studies included in the mean-effects and dose-response mean-effects meta-analyses were cross-sectional and

had study design and/or methodological limitations. However, the consistency in meta-analytic associations across the high and low risk-of-bias studies and the other subgroup analyses reduced the likelihood that specific biases or potential confounders in individual studies could explain the inverse association between fluoride exposure and children's IQ.

While several recent studies conclude that fluoride exposures from community water fluoridation are not associated with children's IQ or other neurodevelopmental outcomes,[122-124] the results of the mean-effects meta-analysis were consistent with 6 previous meta-analyses[6-8,122,125,126] that reported statistically significant inverse associations between fluoride exposure and children's IQ scores (see the "Characteristics of Previous Meta-Analyses" section of eAppendix 1 and eTable 6 in Supplement 1).

Conclusions

This meta-analysis found inverse associations and an inverse dose-response association between fluoride exposure and children's IQ across the multicountry epidemiological literature. There were limited data and uncertainty in the dose-response association between fluoride exposure and children's IQ when fluoride exposure was estimated by drinking water alone at concentrations less than 1.5 mg/L. Confidence in the associations at lower fluoride levels could be increased by additional prospective cohort studies with individual fluoride exposure measures. These results may inform future comprehensive public health risk-benefit assessments of fluoride.

REFERENCES

1. US Geological Survey. Fluoride in groundwater: too much of too little of a good thing? Water Resources Mission Area, Colorado Water Science Center; 2020. Accessed May 3, 2020. https://www.usgs.gov/news/comprehensive-assessment-fluoride-groundwater

2. US Department of Health and Human Services Federal Panel on Community Water Fluoridation. U.S. Public Health Service recommendation for fluoride concentration in drinking water for the prevention of dental caries. *Public Health Rep*. 2015; 130(4):318-331. doi:10.1177/003335491513000408

3. Centers for Disease Control and Prevention. Recommendations for using fluoride to prevent and control dental caries in the United States. *MMWR Recomm Rep*. 2001;50(RR-14):1-42.

4. US Environmental Protection Agency. Fluoride: exposure and relative source contribution analysis. US Environmental Protection Agency; 2010. Accessed August 19, 2019. https://www.epa.gov/sdwa/fluoride-risk-assessment-and-relative-source-contribution

5. National Research Council. Fluoride in drinking water: a scientific review of EPA's standards. National Research Council; 2006. Accessed August 19, 2019. https://nap.nationalacademies.org/catalog/11571/fluoride-in-drinking-water-a-scientific-review-of-epas-standards

6. Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environ Health Perspect*. 2012;120(10):1362-1368. doi:10.1289/ehp.1104912

7. Duan Q, Jiao J, Chen X, Wang X. Association between water fluoride and the level of children's intelligence: a dose-response meta-analysis. *Public Health*. 2018;154:87-97. doi:10.1016/j.puhe.2017.08.013

8. Veneri F, Vinceti M, Generali L, et al. Fluoride exposure and cognitive neurodevelopment: systematic review and dose-response meta-analysis. *Environ Res*. 2023;221:115239. doi:10.1016/j.envres.2023.115239

9. Grandjean P, Meddis A, Nielsen F, et al. Dose dependence of prenatal fluoride exposure associations with cognitive performance at school age in three prospective studies. *Eur J Public Health*. 2024;34(1):143-149. Published online October 5, 2023. doi:10.1093/eurpub/ckad170

10. Lin YY, Hsu WY, Yen CE, Hu SW. Association of dental fluorosis and urinary fluoride with intelligence among schoolchildren. *Children (Basel)*. 2023;10(6):987. doi:10.3390/children10060987

11. Xia Y, Xu Y, Shi M, et al. Effects of high-water fluoride exposure on IQ levels in school-age children: a cross-sectional study in Jiangsu, China. *Expo Health*. 2023;16:885-895. doi:10.1007/s12403-023-00597-2

12. National Toxicology Program. NTP monograph on the state of the science concerning fluoride exposure and neurodevelopment and cognition: a systematic review. *NTP Monogr*. 2024;(8):NTP-MGRAPH-8.

13. National Toxicology Program. Protocol for systematic review of effects of fluoride exposure on neurodevelopment. US Dept of Health & Human Services, Public Health Service, National Institutes of Health; 2020. Accessed May 3, 2020. https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/fluoride/ntpprotocol_revised20200916_508.pdf

14. National Toxicology Program. *OHAT Risk of Bias Rating Tool for Human and Animal Studies*. US Dept of Health & Human Services, Public Health Service, National Institutes of Health; 2015.

15. Bonett DG. Confidence intervals for standardized linear contrasts of means. *Psychol Methods*. 2008;13(2):99-109. doi:10.1037/1082-989X.13.2.99

16. Hedges LV, Olkin I. *Statistical Methods for Meta-Analysis*. Academic Press; 1985.

17. Rosenthal R. Parametric measures of effect size. In: Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. Russell Sage Foundation; 1994.

18. Crippa A, Thomas I, Orsini N. A pointwise approach to dose-response meta-analysis of aggregated data. *Int J Stat Med Res*. 2018;7(2):25-32. doi:10.6000/1929-6029.2018.07.02.1

19. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. *Stat Methods Med Res*. 2019;28(5):1579-1596. doi:10.1177/0962280218773122

20. Orsini N. Weighted mixed-effects dose–response models for tables of correlated contrasts. *Stata J*. 2021;21(2):320-347. doi:10.1177/1536867X211025798

21. Müller S, Scealy JL, Welsh AH. Model selection in linear mixed models. *Stat Sci*. 2013;28(2):135-167. doi:10.1214/12-STS410

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

23. Cochran WG. The combination of estimates from different experiments. *Biometrics*. 1954;10(1):101-129. doi:10.2307/3001666

24. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101. doi:10.2307/2533446

26. Egger M, Smith G, Schneider M, Minder C, eds. *Systematic Reviews in Health Care: Meta-Analysis in Context*. BMJ Publishing Group; 2008.

27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

28. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *J Am Stat Assoc*. 2000;95 (449):89-98.

29. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463. doi:10.1111/j.0006-341X.2000.00455.x

30. StataCorp. *Stata Statistical Software: Release 17.0*. StataCorp LLC; 2021.

31. Palmer TM, Sterne JAC, eds. *Meta-Analysis in Stata: An Updated Collection From the Stata Journal*. 2nd ed. Stata Press; 2016.

32. Green R, Lanphear B, Hornung R, et al. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. *JAMA Pediatr*. 2019;173(10):940-948. doi:10.1001/jamapediatrics.2019.1729

33. Yu X, Chen J, Li Y, et al. Threshold effects of moderately excessive fluoride exposure on children's health: a potential association between dental fluorosis and loss of excellent intelligence. *Environ Int*. 2018;118:116-124. doi:10.1016/j.envint.2018.05.042

34. Ding Y, YanhuiGao, Sun H, et al. The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China. *J Hazard Mater*. 2011;186(2-3):1942-1946. doi:10.1016/j.jhazmat.2010.12.097

35. Zhang S, Zhang X, Liu H, et al. Modifying effect of *COMT* gene polymorphism and a predictive role for proteomics analysis in children's intelligence in endemic fluorosis area in Tianjin, China. *Toxicol Sci*. 2015;144(2):238-245. doi:10.1093/toxsci/kfu311

36. Saeed M, Rehman MYA, Farooqi A, Malik RN. Arsenic and fluoride co-exposure through drinking water and their impacts on intelligence and oxidative stress among rural school-aged children of Lahore and Kasur districts, Pakistan. *Environ Geochem Health*. 2022;44(11):3929-3951. Published online November 9, 2021. doi:10.1007/s10653-021-01141-4

37. Feng Z, An N, Yu F, et al. Do methylenetetrahydrofolate dehydrogenase, cyclohydrolase, and formyltetrahydrofolate synthetase 1 polymorphisms modify changes in intelligence of school-age children in areas of endemic fluorosis? *Chin Med J (Engl)*. 2022;135(15):1846-1854. doi:10.1097/CM9.0000000000002062

38. Tian W, Zhao A, Yu Y, et al. The relationship between IQ and urinary fluoride in children in endemic fluorosis endemic areas polluted by coal burning. *Chin J Endem Dis*. 2022;41(2):117-119. doi:10.3760/cma.j.cn231583-20210125-00025

39. Broadbent JM, Thomson WM, Moffitt TE, Poulton R. Response: community water fluoridation and intelligence response. *Am J Public Health*. 2015;105(4):e3-e4. doi:10.2105/AJPH.2015.302647

40. Ahmad MS, Sarker MNI, Ahmad MN, Ali M, Sadiq AM. Does high fluoride intake cause low IQ? a case of Islamic religious schools (Madrassas) in rural and urban areas of Sindh, Pakistan. *Fluoride*. 2022;55(1):49-62.

41. Kang J, Cheng Y, Wu K, Lin S, He G, Jin Y. Effect of exposure to fluoride and arsenic in drinking water of Hangjinhouqi on children's intelligence. Article in Chinese. *Chin School Health*. 2011:679-681.

42. Dewey D, England-Mason G, Ntanda H, et al; APrON Study Team. Fluoride exposure during pregnancy from a community water supply is associated with executive function in preschool children: a prospective ecological cohort study. *Sci Total Environ*. 2023;891:164322. doi:10.1016/j.scitotenv.2023.164322

43. Khan SA, Singh RK, Navit S, et al. Relationship between dental fluorosis and intelligence quotient of school going children in and around Lucknow District: a cross-sectional study. *J Clin Diagn Res*. 2015;9(11):ZC10-ZC15. doi:10.7860/JCDR/2015/15518.6726

44. Lin F, Ai H, Zhao H, Lin J, Jhiang J, Maimaiti. High fluoride and low iodine environment and subclinical cretinism in Xinjiang. *Endemic Dis Bull*. 1991;6(2):62-67.

45. Li Y, Li X, Wei S. Effects of high fluoride intake on child mental work capacity: preliminary investigation into the mechanisms involved. Article in Chinese. *J West China Univ Med Sci*. 1994;25(2):188-191.

46. Li Y, Li X, Wei S. Effects of high fluoride intake on child mental work capacity: preliminary investigation into the mechanisms involved. *Fluoride*. 2008;41(4):331-335.

47. Xiang Q, Liang Y, Chen L, et al. Effect of fluoride in drinking water on children's intelligence. *Fluoride*. 2003;36:84-94.

48. Seraj B, Shahrabi M, Shadfar M, et al. Effect of high water fluoride concentration on the intellectual development of children in Makoo/Iran. *J Dent (Tehran)*. 2012;9(3):221-229.

49. Trivedi M, Sangai N, Patel R, Payak M, Vyas S. Assessment of groundwater quality with special reference to fluoride and its impact on IQ of schoolchildren in six villages of the Mundra Region, Kachchh, Gujarat, India. *Fluoride*. 2012;45(4):377-383.

50. Cui Y, Yu J, Zhang B, Guo B, Gao T, Liu H. The relationships between thyroid-stimulating hormone and/or dopamine levels in peripheral blood and IQ in children with different urinary iodine concentrations. *Neurosci Lett*. 2020;729:134981. doi:10.1016/j.neulet.2020.134981

51. Zhang J, Yao H, Chen Y. The effect of high levels of arsenic and fluoride on the development of children's intelligence. Article in Chinese. *Chin J Publ Health*. 1998;17(2):119.

52. Hong F, Wang Hui Yang Dong Zhang Z. Investigation on the intelligence and metabolism of iodine and fluoride in children with high iodine and fluoride. *Chin J Endem Dis Control*; 2001:12-14.

53. Wang X, Wang L, Hu P, Guo X, Luo X. Effects of high iodine and high fluorine on children's intelligence and thyroid function. Article in Chinese.

Zhonghua Difangbingxue Zazhi. 2001;20(4): 288-290.

54. Zhao Y, Cui Y, Yu J, et al. Study on the relationship between water-borne high iodine and thyroid hormone and children's intelligence level. *J Environ Health*. 2018;35(1):6-9.

55. An J, Mei S, Liu A, Fu Y, Wang C. Effect of high level of fluoride on children's intelligence. Article in Chinese. *Chin J Control Endem Dis*. 1992;7(2):93-94.

56. Li X, Hou G, Yu B, Yuan C, Liu Y, Hao Z. Investigation and analysis of children's IQ and dental fluorosis in high fluoride area. Article in Chinese. *Chin J Pest Control*. 2010;26(3):230-231.

57. Ren D, Li K, Liu D. A study of the intellectual ability of 8-14 year-old children in high fluoride, low iodine areas. Article in Chinese. *Chin J Control Endem Dis*. 1989;4(4):251.

58. Ren D, Li K, Liu D. A study of the intellectual ability of 8-14 year-old children in high fluoride, low iodine areas. *Fluoride*. 2008;41:319-320.

59. Wang SX, Wang ZH, Cheng XT, et al. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. *Environ Health Perspect*. 2007;115(4):643-647. doi:10.1289/ehp.9270

60. Sun M, Li S, Wang Y, Li F. Measurement of intelligence by drawing test among the children in the endemic area of Al-F combined toxicosis. Article in Chinese. *J Guiyang Med Coll*. 1991;16(3):204-206.

61. Guo XC, Wang RY, Cheng CF, et al. A preliminary investigation of the IQs of 7-13 year-old children from an area with coal burning-related fluoride poisoning. Article in Chinese. *Chin J Epidemiol*. 1991; 10(2):98-100.

62. Guo XC, Wang RY, Cheng CF, et al. A preliminary investigation of the IQs of 7-13 year-old children from an area with coal burning-related fluoride poisoning. *Fluoride*. 2008;41:125-128.

63. Wang G, Yang D, Jia F, Wang H. A study of the IQ levels of four- to seven-year-old children in high fluoride areas. Article in Chinese. *Endemic Dis Bull*. 1996;11(1):60-62.

64. Wang G, Yang D, Jia F, Wang H. A study of the IQ levels of four- to seven-year-old children in high fluoride areas. *Fluoride*. 2008;41:340-343.

65. Li F, Chen X, Huang R, Xie Y. The impact of endemic fluorosis caused by the burning of coal on the development of intelligence in children. *J Environ Health*. 2009;26(4):838-840.

66. Bai A, Li Y, Fan Z, Li X, Li P. Intelligence and growth development of children in coal-burning-borne arsenism and fluorosis areas: an investigation study. Article in Chinese. *Zhonghua Difangbingxue Zazhi*. 2014;33(2):160-163.

67. Lou D, Luo Y, Liu J, et al. Refinement impairments of verbal-performance intelligent quotient in children exposed to fluoride produced by coal burning. *Biol Trace Elem Res*. 2021;199(2): 482-489. doi:10.1007/s12011-020-02174-z

68. Zhang P, Cheng L. Effect of coal-burning endemic fluorosis on children's physical development and intellectual level. *Chin J Endem Dis Control*. 2015;30(6):458-459.

69. Wang J, Yu M, Yang L, Yang X, Deng B. The effect of coal-burning fluoride exposure on children's intelligence and physical development. *J Environ Health*. 2020;37(11):971-974.

70. Chen YX, Han FL, Zhoua ZL, et al. Research on the intellectual development of children in high fluoride areas. Article in Chinese. *Chin J Control Endem Dis*. 1991;6(suppl):99-100.

71. Chen YX, Han FL, Zhoua ZL, et al. Research on the intellectual development of children in high fluoride areas. *Fluoride*. 2008;41:120-124.

72. Xu Y, Lu C, Zhang X. The effect of fluorine on the level of intelligence in children. *Endemic Dis Bull*. 1994;9(2):83-84.

73. Li XS, Zhi JL, Gao RO. Effect of fluoride exposure on the intelligence of children. *Fluoride*. 1995;28:189-192.

74. Yao L, Zhou J, Wang S, Cui K, Lin F. Analysis on TSH and intelligence level of children with dental fluorosis in a high fluoride area. *Lit Inf Prev Med*. 1996;2(1):26-27.

75. Zhao LB, Liang GH, Zhang DN, Wu XR. Effect of a high fluoride water supply on children's intelligence. *Fluoride*. 1996;29:190-192.

76. Yao Y. Comparable analysis on the physical and mental development of children in endemic fluorosis area with water improvement and without water improvement. *Lit Inf Prev Med*. 1997;3(1):42-43.

77. Lu Y, Sun ZR, Wu LN, Wang X, Lu W, Liu SS. Effect of high-fluoride water on intelligence in children. *Fluoride*. 2000;33:74-78.

78. Hong FG, Cao YX, Yang D, Wang H. Research on the effects of fluoride on child intellectual development under different environmental conditions. *Chin Prim Health Care*. 2001;15(3):56-57.

79. Hong FG, Cao YX, Yang D, Wang H. Research on the effects of fluoride on child intellectual development under different environmental conditions. *Fluoride*. 2008;41:156-160.

80. Li YP, Jing XY, Chen D, Lin L, Wang ZJ. Effects of endemic fluoride poisoning on the intellectual development of children in Baotou. Article in Chinese. *Zhongguo Gonggong Weisheng Guanli*. 2003;19(4):337-338.

81. Li YP, Jing XY, Chen D, Lin L, Wang ZJ. Effects of endemic fluoride poisoning on the intellectual development of children in Baotou. *Fluoride*. 2008; 41:161-164.

82. Wang SX, Wang ZH, Cheng XT, et al. Investigation and evaluation on intelligence and growth of children in endemic fluorosis and arsenism areas. Article in Chinese. *Zhonghua Difangbingxue Zazhi*. 2005;24:179-182.

83. Seraj B, Shahrabi M, Falahzade M, Falahzade F, Akhondi N. Effect of high fluoride concentration in drinking water on children's intelligence. *J Dent Med*. 2006;19(2):80-86.

84. Wang Z, Wang S, Zhang X, Li J, Zheng X, Hu C. Investigation of children's growth and development under long-term fluoride exposure. *Chin J Control Endem Dis*. 2006;21(4):239-241.

85. Fan Z, Dai H, Bai A, Li P, Li T, Li G. The effect of high fluoride exposure on children's intelligence. *J Environ Health*. 2007;24(10):802-803.

86. Trivedi MH, Verma RJ, Chinoy NJ, Patel RS, Sathawara NG. Effect of high fluoride water on intelligence of school children in India. *Fluoride*. 2007;40:178-183.

87. Eswar P, Nagesh L, Devaraj CG. Intelligent quotients of 12-14 year old school children in a high and low fluoride village in India. *Fluoride*. 2011;44: 168-172.

88. Poureslami HR, Horri A, Garrusi B. A comparative study of the IQ of children age 7-9 in a high and a low fluoride water city in Iran. *Fluoride*. 2011;44:163-167.

89. Shivaprakash PK, Ohri K, Noorani H. Relation between dental fluorosis and intelligence quotient in school children of Bagalkot district. *J Indian Soc Pedod Prev Dent*. 2011;29(2):117-120. doi:10.4103/0970-4388.84683

90. Wang S, Zhu X. Investigation and analysis of intelligence level of children in high fluoride area. *Chin J Endem Dis Control*. 2012;27(1):67-68.

91. Karimzade S, Aghaei M, Mahvi AH. Investigation of intelligence quotient in 9-12 year-old children exposed to high- and low-drinking water fluoride in West Azerbaijan Province, Iran. *Fluoride*. 2014;47:9-14.

92. Sebastian ST, Sunitha S. A cross-sectional study to assess the intelligence quotient (IQ) of school going children aged 10-12 years in villages of Mysore district, India with different fluoride levels. *J Indian Soc Pedod Prev Dent*. 2015;33(4):307-311. doi:10.4103/0970-4388.165682

93. Das K, Mondal NK. Dental fluorosis and urinary fluoride concentration as a reflection of fluoride exposure and its impact on IQ level and BMI of children of Laxmisagar, Simlapal Block of Bankura District, W.B., India. *Environ Monit Assess*. 2016;188 (4):218. doi:10.1007/s10661-016-5219-1

94. Mondal D, Dutta G, Gupta S. Inferring the fluoride hydrogeochemistry and effect of consuming fluoride-contaminated drinking water on human health in some endemic areas of Birbhum district, West Bengal. *Environ Geochem Health*. 2016;38(2):557-576. doi:10.1007/s10653-015-9743-7

95. Wang R, He N, Wang Y, Hou G, Zhang PJ. Investigation and analysis of children's dental fluorosis and IQ level in high fluoride district of Hengshui City. *Med Anim Control*. 2021;37(8):796-800.

96. Bashash M, Thomas D, Hu H, et al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6-12 years of age in Mexico. *Environ Health Perspect*. 2017;125(9):097017. doi:10.1289/EHP655

97. Till C, Green R, Flora D, et al. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. *Environ Int*. 2020;134:105315. doi:10.1016/j.envint.2019.105315

98. Wang M, Liu L, Li H, et al. Thyroid function, intelligence, and low-moderate fluoride exposure among Chinese school-age children. *Environ Int*. 2020;134:105229. doi:10.1016/j.envint.2019.105229

99. Cui Y, Zhang B, Ma J, et al. Dopamine receptor D2 gene polymorphism, urine fluoride, and intelligence impairment of children in China: a school-based cross-sectional study. *Ecotoxicol Environ Saf*. 2018;165:270-277. doi:10.1016/j.ecoenv.2018.09.018

100. Zhao L, Yu C, Lv J, et al. Fluoride exposure, dopamine relative gene polymorphism and intelligence: a cross-sectional study in China. *Ecotoxicol Environ Saf*. 2021;209:111826. doi:10.1016/j.ecoenv.2020.111826

101. Goodman CV, Bashash M, Green R, et al. Domain-specific effects of prenatal fluoride exposure on child IQ at 4, 5, and 6-12 years in the

ELEMENT cohort. *Environ Res*. 2022;211:112993. doi:10.1016/j.envres.2022.112993

102. Cantoral A, Téllez-Rojo MM, Malin AJ, et al. Dietary fluoride intake during pregnancy and neurodevelopment in toddlers: a prospective study in the progress cohort. *Neurotoxicology*. 2021;87: 86-93. doi:10.1016/j.neuro.2021.08.015

103. Ibarluzea J, Gallastegi M, Santa-Marina L, et al. Prenatal exposure to fluoride and neuropsychological development in early childhood: 1-to 4 years old children. *Environ Res*. 2022;207:112181. doi:10.1016/j.envres.2021.112181

104. Valdez Jiménez L, López Guzmán OD, Cervantes Flores M, et al. In utero exposure to fluoride and cognitive development delay in infants. *Neurotoxicology*. 2017;59:65-70. doi:10.1016/j.neuro.2016.12.011

105. Guo B, Yu J, Cui Y, et al. DBH gene polymorphism, iodine and fluoride and their interactions and their interaction with children's intelligence. *J Environ Hygiene*. 2021;11(2):134-140.

106. Villa A, Anabalon M, Zohouri V, Maguire A, Franco AM, Rugg-Gunn A. Relationships between fluoride intake, urinary fluoride excretion and fluoride retention in children and adults: an analysis of available data. *Caries Res*. 2010;44(1):60-68. doi:10.1159/000279325

107. Watanabe M, Kono K, Orita Y, Usuda K, Takahashi Y, Yoshida Y. Influence of dietary fluoride intake on urinary fluoride concentration and evaluation of corrected levels in spot urine. *Fluoride*. 1995;28(2):61-70.

108. Zohouri FV, Swinbank CM, Maguire A, Moynihan PJ. Is the fluoride/creatinine ratio of a spot urine sample indicative of 24-h urinary fluoride? *Community Dent Oral Epidemiol*. 2006;34 (2):130-138. doi:10.1111/j.1600-0528.2006.00269.x

109. Abduweli Uyghurturk D, Goin DE, Martinez-Mier EA, Woodruff TJ, DenBesten PK. Maternal and fetal exposures to fluoride during

mid-gestation among pregnant women in northern California. *Environ Health*. 2020;19(1):38. doi:10.1186/s12940-020-00581-2

110. Malin AJ, Hu H, Martínez-Mier EA, et al. Urinary fluoride levels and metal co-exposures among pregnant women in Los Angeles, California. *Environ Health*. 2023;22(1):74. doi:10.1186/s12940-023-01026-2

111. Bellinger DC. Interpretation of small effect sizes in occupational and environmental neurotoxicology: individual versus population risk. *Neurotoxicology*. 2007;28(2):245-251. doi:10.1016/j.neuro.2006.05.009

112. Needleman HL. What can the study of lead teach us about other toxicants? *Environ Health Perspect*. 1990;86:183-189. doi:10.1289/ehp.9086183

113. Rose G. Sick individuals and sick populations. *Int J Epidemiol*. 1985;14(1):32-38. doi:10.1093/ije/14.1.32

114. Rose G. Sick individuals and sick populations. *Int J Epidemiol*. 2001;30(3):427-432. doi:10.1093/ije/30.3.427

115. Weiss B. Vulnerability of children and the developing brain to neurotoxic hazards. *Environ Health Perspect*. 2000;108(suppl 3):375-381.

116. Braun JM. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nat Rev Endocrinol*. 2017;13(3):161-173. doi:10.1038/nrendo.2016.186

117. Cooper GS, Lunn RM, Ågerstrand M, et al. Study sensitivity: evaluating the ability to detect effects in systematic reviews of chemical exposures. *Environ Int*. 2016;92-93:605-610. doi:10.1016/j.envint.2016.03.017

118. Podgorski J, Berg M. Global analysis and prediction of fluoride in groundwater. *Nat Commun*. 2022;13(1):4232. doi:10.1038/s41467-022-31940-x

119. Hefferon R, Goin DE, Sarnat JA, Nigra AE. Regional and racial/ethnic inequalities in public

drinking water fluoride concentrations across the US. *J Expo Sci Environ Epidemiol*. 2024;34(1):68-76. doi:10.1038/s41370-023-00570-w

120. McMahon PB, Brown CJ, Johnson TD, Belitz K, Lindsey BD. Fluoride occurrence in United States groundwater. *Sci Total Environ*. 2020;732:139217. doi:10.1016/j.scitotenv.2020.139217

121. Centers for Disease Control and Prevention. Community water fluoridation FAQs: infant formula. Centers for Disease Control & Prevention; 2015. Accessed February 10, 2022. https://www.cdc.gov/fluoridation/faq/?CDC_AAref_Val=https://www.cdc.gov/fluoridation/faqs/infant-formula.html#cdc_faqs_cat5-infant-formula

122. Kumar JV, Moss ME, Liu H, Fisher-Owens S. Association between low fluoride exposure and children's intelligence: a meta-analysis relevant to community water fluoridation. *Public Health*. 2023; 219:73-84. doi:10.1016/j.puhe.2023.03.011

123. Guth S, Hüser S, Roth A, et al. Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses. *Arch Toxicol*. 2020;94(5):1375-1415. doi:10.1007/s00204-020-02725-2

124. Do LG, Spencer AJ, Sawyer A, et al. Early childhood exposures to fluorides and child behavioral development and executive function: a population-based longitudinal study. *J Dent Res*. 2023;102(1):28-36. doi:10.1177/00220345221119431

125. Tang QQ, Du J, Ma HH, Jiang SJ, Zhou XJ. Fluoride and children's intelligence: a meta-analysis. *Biol Trace Elem Res*. 2008;126(1-3):115-120. doi:10.1007/s12011-008-8204-x

126. Miranda GHN, Alvarenga MOP, Ferreira MKM, et al. A systematic review and meta-analysis of the association between fluoride exposure and neurological disorders. *Sci Rep*. 2021;11(1):22659. doi:10.1038/s41598-021-99688-w