Title: Association between fluoride exposure and children's intelligence: A systematic review and meta-analysis

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Abstract

IMPORTANCE Water and water-based beverages are the main source of systemic fluoride intake; however, an individual's total exposure to fluoride also reflects contributions from other sources such as food, dental products, industrial emissions, and some pharmaceuticals. Previous meta-analyses suggest that exposure to fluoride adversely affects children's intelligence.

OBJECTIVE To perform a systematic review and meta-analysis to investigate associations between fluoride exposure and children's intelligence.

DATA SOURCES BIOSIS, EMBASE, PsychINFO, PubMed, Scopus, Web of Science, CNKI, and Wanfang databases were searched for relevant literature published up to November 2021.

STUDY SELECTION Inclusion criteria were assessment of cognitive outcomes, fluoride exposure, and statistical data on effect size.

DATA EXTRACTION AND SYNTHESIS Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines were followed for data extraction. The quality of individual studies was evaluated for risk of bias using a standardized tool. Pooled standardized mean differences (SMDs) and regression coefficients were estimated with random-effects models.

MAIN OUTCOMES AND MEASURES Children's intelligence levels reflected by intelligence quotient (IQ) scores.

RESULTS The meta-analysis of 55 studies (N = 18,845 children) with group-level exposures found that, when compared to children exposed to lower fluoride levels, children exposed to higher fluoride levels had lower mean IQ scores (pooled SMD: −0.46; 95% CI: −0.55, −0.37; p-value < 0.001). There was a dose-response relationship between group-level fluoride exposure measures and mean children's IQ. The meta-analysis of studies that reported individual-level measures of fluoride and children's IQ scores found a decrease of 1.81 points (95% CI: −2.80, −0.81; p-value < 0.001) per 1-mg/L increase in urinary

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fluoride. Overall, the direction of the association was robust to stratification by study quality (high *vs*. low risk of bias), sex, age group, outcome assessment, study location, exposure timing, and exposure metric.

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CONCLUSIONS AND RELEVANCE This meta-analysis confirms results of previous meta-analyses and extends them by including newer, more precise studies with individual-level exposure measures. The consistency of the data supports an inverse association between fluoride exposure and children's IQ.

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Introduction

Fluoride from natural sources occurs in some community water systems and, in the United States and some other countries, fluoride is added to public drinking water systems for the prevention of tooth decay. Water and water-based beverages are the main source of systemic fluoride intake; however, an individual's total exposure also reflects contributions from fluoride in other sources such as food, dental products, industrial emissions, and some pharmaceuticals.[1] 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.[2] This report was largely based on studies from endemic fluorosis areas in China that had limitations in study design or methods (e.g., high risk of bias). Following the NRC review, more evidence has emerged in studies from India, Iran, Pakistan, New Zealand, Spain, and Canada (**Figure 1**). Two previous meta-analyses[3, 4] found an association between high fluoride exposure and lower children's IQ; however, many of the studies in these meta-analyses lacked the information necessary to evaluate study quality and all used group-level estimates of fluoride exposure. Since the most recent meta-analysis,[4] eleven new studies on exposure to fluoride and children's IQ have been published, including three prospective North American birth cohort studies[5-7] that used individual-level measures of maternal and children's urinary fluoride.

To incorporate this newer evidence, and to complement a larger systematic review[8] that concluded there is moderate confidence in the evidence of an inverse association between fluoride exposure and children's IQ, we conducted a meta-analysis of studies that provided group-and individual-level fluoride exposure measurements in relation to children's IQ scores.

Methods

The search, selection, extraction, and risk-of-bias evaluation of studies for this meta-analysis were part of a larger systematic review.[8] Brief methods are outlined below with detailed methods available in the protocol[9] and the **Supplemental Materials**.

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Systematic literature review

Literature searches were conducted in BIOSIS, EMBASE, PsychINFO, PubMed, Scopus, Web of Science, CNKI, and Wanfang databases through November 2021, without language restrictions. Search strategies are available in the protocol.[9]

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Study selection

To be eligible for inclusion, individual study publications had to satisfy review eligibility criteria outlined in the protocol.[9] References retrieved from the literature search were independently screened by two reviewers by title and abstract followed by full-text review. Studies that estimated the association between exposure to fluoride (based on environmental measures or biomonitoring data, reported as either individual-level or group-level measurements) and a quantitative measure of children's intelligence were included. Studies that did not report quantitative effect estimates (mean outcome measures or regression coefficients), measures of variability (95% confidence intervals [CIs], standard errors [SEs], or standard deviations [SDs]), or numbers of participants were excluded. Studies with missing measures of variability but with reported p-values for differences were included, and SDs were calculated using the approach in the Cochrane Handbook for Systematic Reviews.[10] To avoid sample overrepresentation, if the same cohort was followed at multiple timepoints resulting in multiple study publications,[11, 12] only the study publication that included the largest number of participants was included in this meta-analysis (see **eTable 1**).

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Data extraction

Data were collected from included studies by one extractor and verified by a second extractor. Data were extracted in Health Assessment Workspace Collaborative (HAWC), an open source, web-based application for data extraction elements listed in the protocol. Data extraction results for included studies are publicly available and downloadable (https://hawcproject.org/assessment/405/).

Quality assessment: Risk-of-bias evaluation

Quality of individual studies, also called "risk of bias," was assessed using the National Toxicology Program's Office of Health Assessment and Translation approach.[13] Studies were independently evaluated by two trained assessors who answered risk-of-bias questions following prespecified criteria detailed in the protocol.[9] 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.[9] The other risk-of-bias questions were used to identify other concerns that may indicate serious risk-of-bias issues (e.g., selection bias, 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 (i.e., studies rated "probably high" risk of bias for at least two key risk-of-bias questions or "definitely high" for any single question) to assess their impact on the results.

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Statistical analysis

We conducted the following analyses, planned *a priori* in the protocol: (1) *a mean-effects meta-analysis*, (2) *a dose-response mean-effects meta-analysis*, and (3) *a regression slopes meta-analysis.* We also conducted several subgroup and sensitivity analyses.

The *mean-effects meta-analysis* included studies that reported mean IQ scores and group-level exposures for at least one exposed and one reference group. The effect estimates in the primary *mean-effects meta-analysis* were the standardized mean differences (SMDs) for heteroscedastic population variances.[14-16] The SMDs were calculated from the difference in mean IQ scores between an exposed group and a reference group. If mean IQ scores were reported for multiple exposure groups within a single study, 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 to a reference group (see additional details on the approach, effect estimation, and study selection in the **Supplemental Materials**). Predefined subgroup analyses

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were stratified by risk of bias (high or low), study location (e.g., country), outcome assessment, exposure matrix (e.g., urinary fluoride or water fluoride concentrations), sex, and age group. To further evaluate potential sources of heterogeneity, we conducted meta-regression analyses using mean age in years (from the age range reported in each study) and year of publication in each study.

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To determine whether the data support an exposure-response relationship, we conducted a *dose-response mean-effects meta-analysis.* This analysis included studies from the *mean-effects meta-analysis* that reported fluoride exposure levels and used a one-step approach as described in the protocol.[9, 17, 18] This approach uses linear mixed models to analyze all available mean effect estimates for the reference group and one or more exposure group and estimates a pooled dose-response curve using a restricted maximum likelihood estimation method. Model comparison was based on the maximum likelihood Akaike information criterion (AIC).[19] We also examined whether there was a dose-response relationship at lower exposure levels that corresponded with the U.S. Environmental Protection Agency drinking water standards[20] and World Health Organization drinking water guidelines[21] (details provided in the **Supplemental Materials**).

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The *regression slopes meta-analysis* included studies that reported regression slopes to estimate associations between individual-level fluoride exposure and children's IQ. The primary regression slopes meta-analysis used regression slopes from models that adjusted for potential confounders. If results from multiple models were reported within a single study, either the most adjusted results or the main model results as presented by the study authors were selected. The study outcomes were evaluated with respect to a 1-mg/L unit increase in water or urinary fluoride, or 1-mg/day fluoride intake.

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Data from individual studies were pooled using a random-effects model.[22] Heterogeneity was assessed by Cochran's Q test[23] and the I^2 statistic.[24] Forest plots were used to display results and to examine possible heterogeneity between studies. Potential publication bias was assessed by developing funnel plots and performing Egger regression on the estimates of effect size.[25-27] If publication bias was

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Commented [l30]: See Doc05_Meta-analysis, 5.J., page 9 and 10 present, trim-and-fill methods[28, 29] were used to estimate the number of missing studies and to predict the impact of the hypothetical "missing" studies on the pooled effect estimate. Subgroup analyses were performed to investigate sources of heterogeneity. Subgroup analyses were stratified by risk of bias (high or low), study location (e.g., country), outcome assessment, exposure matrix (e.g., urinary fluoride or water fluoride concentrations), pre- or post-natal exposure, and sex.

Statistical analyses were performed using the software STATA version 17.0[30] with the *combine, meta esize*, *meta set*, *meta summarize*, *drmeta*, *meta funnel*, *meta bias*, *meta trimfill* and *metareg* packages.[31]

Results

Study sample

Results of the study identification process are provided in **eFigure 1.** Characteristics of the 60 publications included in the meta-analysis are shown in **Table 1** (see **eTable 1** for list of excluded publications). A total of 55 publications reported mean IQ scores for group-level exposures. Eleven publications reported regression slopes for individual-level exposures based on urinary or water fluoride concentrations.[5-7, 11, 12, 32-37] Additional details on study characteristics are provided in the **Supplemental Materials**. Results from risk-of-bias evaluations are presented in **eFigure 2a** and **eFigure 2b**. Study-specific effect estimates used in the meta-analysis are presented in **eTable 2**.

Mean-effects meta-analysis

The meta-analysis of 55 studies (45 high risk-of-bias studies and 10 low risk-of-bias studies) that provided mean IQ scores shows that, when compared to children exposed to lower levels of fluoride, children exposed to higher fluoride levels had statistically significantly lower IQ scores (random-effects pooled SMD, −0.46; 95% CI: −0.55, −0.37; p-value < 0.001) (**Table 2, Figure 2**). There was evidence of high heterogeneity ($I^2 = 87\%$, p-value < 0.001; **Table 2**) and publication bias (funnel plot and Egger's p-value < 0.001, Begg's p-value = 0.031; **eFigures 3 and 4**). Adjusting for possible publication bias

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Note: Changes in study numbers from reviewer text reflects updated literature search.

Commented [I35]: See Doc02_Meta-analysis, 2.K., page 4 through trim-and-fill analysis suggested the imputation of seven additional studies to the right side, with an adjusted pooled SMD of – 0.36 (95% CI: −0.46, −0.26) (**eFigures 5 and 6**). The pattern of results across the 55 studies was consistent; 52 (95%) reported an inverse association with SMDs ranging from −5.34 (95% CI: −6.34, −4.34) to −0.04 (95% CI: −0.45, 0.36) (**Figure 2**). The (95% CI: −0.19, 0.21),[6] 0.01 (95% CI: −0.19, 0.22),[38] and 0.13 (95% CI: −0.16, 0.42).[5] Three studies[39, 40, 41 [translated in Li et al. 2008b]] 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[43] that reported the cognitive subset of evaluations using Bayley and McCarthy tests was included (**eTable 3**).

Among the low risk-of-bias studies (n = 10), [5, 6, 11, 32, 33, 36, 44-47] the random-effects pooled SMD was −0.22 (95% CI: −0.39, −0.05; p-value = 0.011) with high heterogeneity (I^2 = 83%) (**Table 2 and eFigure 7**). There was no evidence of publication bias (funnel plot and Egger's p-value = 0.93; **eFigures 8 and 9**). Among the high risk-of-bias studies (n = 45), the random-effects pooled SMD was −0.52 (95% CI: −0.63, −0.42; p-value < 0.001) with high heterogeneity (I^2 = 86%,) (**Table 2 and eFigure 7**). There was evidence of publication bias among the high risk-of-bias studies (funnel plot and Egger's p-value < 0.001; **eFigures 8 and 9**); adjusting for possible publication bias through trim-and-fill analysis supports the results with an adjusted pooled SMD estimate of −0.37 (95% CI: −0.48, −0.25) (**eFigures 10 and 11**). Subgroup analyses by sex, age group, study location, outcome assessment type, and exposure assessment type further support the consistent and robust pattern of an inverse association between fluoride exposure and children's IQ (**Table 2, eFigures 12-16**). The subgroup and meta-regression analyses did not explain a large amount of the overall heterogeneity; however, the degree of heterogeneity was lower We also examined whether there was a dose-response relationship at lower exposure levels that corresponded with the U.S. Environmental Protection Agency drinking water standards[20] and World restricted to Iran (I^2=56%), children ages 10 and older (I^2=68%), and girls (I^2=76%) (see **Supplemental Materials**).

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The sensitivity analysis to evaluate the impact of combining all exposed groups and comparing them to the reference group did not appreciably change the effect estimates (**eTable 3**). Sensitivity analyses that removed an outlier study[39] or a study with an unspecified IQ test[41 [translated in Li et al. 2008b]] also did not appreciably change the effect estimates (**eTable 3**).

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Dose-response mean-effects meta-analysis

The *dose-response mean-effects meta-analysis* combining data from 29 studies with group-level fluoride measurements in drinking water (23 high risk-of-bias and 6 low risk-of-bias studies) and 18 studies with group-level mean urinary fluoride levels (9 high risk-of-bias and 9 low risk-of-bias studies) show statistically significantly lower children's IQ scores with increasing fluoride exposures. Based on the linear models, the decrease in mean SMD between exposed and reference groups is −0.15 (95% CI: −0.20, −0.11; p-value < 0.001) for drinking water fluoride levels and −0.16 (95% CI: −0.24, −0.08; p-value < 0.001) for urinary fluoride levels (**eTable 4**). Based on the AIC and likelihood ratio tests, the best model fit was achieved when quadratic or restricted cubic spline exposure levels were added to the linear models for drinking water (**eFigure 17**); the linear model was the best fit for urinary fluoride (**eFigure 18**). Given the small difference in AICs between the different models, and for ease of interpretability, the linear model results were chosen for the purposes of discussion, although results from all models are presented (**eTable 4**). The direction of the associations did not change when the exposed groups were restricted to <4 mg/L or <2 mg/L fluoride in drinking water or fluoride in urine (**eTable 4** and **eTable 5**).

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Regression slopes meta-analysis

The *regression slopes meta-analysis* includes ten studies with individual-level exposure measures (1 high risk-of-bias and 9 low risk-of-bias studies) (**Table 1**). Each of these studies reported urinary fluoride levels,[5-7, 11, 12, 32-37] two reported fluoride intake,[6, 7] and two reported water fluoride levels.[6, 11] Two studies[7, 12] are not included in the primary meta-analysis they had overlapping populations with already-included studies[6, 11 respectively] (see **Supplemental Materials**). Similarly, three studies reporting scores based on Bayley assessments[43, 48, 49] were only included in sensitivity analyses (see **Supplemental Materials**).

The overall pooled effect estimate from the nine studies with individual-level urinary fluoride measures shows that a 1-mg/L increase in urinary fluoride is associated with a statistically significant lower IQ score of 1.81 points (95% CI: −2.80, −0.81; p-value < 0.001) with evidence of heterogeneity (I^2 = 77%, p-value < 0.001; **Table 3, eFigure 19**) and no indications of publication bias (**eFigures 20 and 21**). When restricted to only low risk-of-bias studies, the decrease in IQ score was 1.33 points (95% CI: −2.09, −0.57; p-value < 0.001). There was evidence of moderate heterogeneity (I^2 = 46%, p-value < 0.072; **Table 3, eFigure 22**) and no indications of publication bias. The results for fluoride intake and water fluoride levels are available in **Supplemental Materials**.

Subgroup analyses by risk of bias, sex, country, exposure type, outcome assessment type, and pre- or post-natal exposure further support the consistent and robust pattern of an inverse association between fluoride exposure and children's IQ (**Table 3, eFigures 22–27**). The observed heterogeneity in the overall effect estimate was explained by the subgroup analyses, with no significant heterogeneity remaining in analyses of low-risk-of bias studies, by sex, by country, by assessment type, and by exposure timing (**Table 3**). The sensitivity analyses including reporting scores based on Bayley assessments[43, 48, 49] showed no substantial changes in the pooled effect estimates (**eTable 6**).

Discussion

The results of this meta-analysis support a statistically significant association between higher fluoride exposure and lower children's IQ. The direction of the association was robust to stratification by risk of bias, sex, age group, timing of exposure, study location, outcome assessment type, and exposure assessment type. There is also evidence of a dose-response relationship. Although the estimated decreases in IQ may seem small, research on other neurotoxicants has shown that subtle shifts in IQ at the population level can have a profound impact on the number of people who fall within the high and low

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Commented [I46]: See Doc02_Meta-analysis, 2.P., page 5 ranges of the population's IQ distribution.[50-54] For example, a 5-point decrease in a population's IQ would nearly double the number of people classified as intellectually disabled.[55]

The results of the *mean-effects meta-analysis* are consistent with two previous meta-analyses that, when comparing children exposed to lower fluoride levels, reported statistically significantly lower IQ scores in children exposed to higher fluoride levels ($p < 0.001$) (**Table 2**). However, this meta-analysis included more recently published studies that were considered low risk of bias and studies with different exposure assessment types. We also found a statistically significant dose-response between lower children's IQ with increasing fluoride exposures as measured in both drinking water (p-value < 0.001) and urine (p-value < 0.001). Associations appeared to be non-linear for drinking water and linear for urine. The Duan et al.[4] meta-analysis reported a significant non-linear dose-response relationship above 3 ppm [3 mg/L] in water. A more recent literature review[56] did not comment on the shape of the dose-response curve; however, based on the three publications from Mexico and Canada,[5-7] the author concluded that the association between maternal urinary fluoride and children's neurotoxicity appeared to be "dose dependent."

Whereas the previously published meta-analyses only included group-level exposures, the *regression slopes meta-analysis* included nine studies with individual urinary fluoride measures, a more precise exposure measure. It also included recent North American prospective cohort studies[5-7] with maternal urinary fluoride levels comparable to those found in the United States.[57] In contrast to urinary fluoride measures, drinking water measures capture only a portion of a person's total exposure to fluoride. Consequently, relying on drinking water levels alone likely underestimates an individual's total exposure to fluoride. For community water systems that add fluoride, the Public Health Service recommends a fluoride concentration of 0.7 mg/L; however, it is important to note that there are regions of the United States where public systems and private wells contain natural fluoride concentrations of more than 2 mg/L.[58] In April 2020, the Centers for Disease Control and Prevention (CDC) estimated that community water systems supplying water with ≥2 mg/L naturally occurring fluoride served 0.31% of the U.S.

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Commented [I50]: See Doc01_Meta-analysis, 1.M., page 6 and 7 population (~1 million people).[59] For the purposes of reducing dental fluorosis, the CDC recommends that parents use an alternative source of water for children aged 8 years and younger and for bottle-fed infants if their primary drinking water contains greater than 2 mg/L of fluoride.[60]

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Strengths and Limitations

Strengths of this meta-analysis include a large body of literature and predefined systematic search and screening process, a risk-of-bias assessment of individual studies, a variety of intelligence assessment methods and exposure matrices, varying exposure levels from multiple study locations, prespecified subgroup analyses, and use of both group-level and individual-level exposure data. The direction of the association is consistent across different analytical approaches and subgroup analyses.

There are also limitations to consider. Most of the studies included in the *mean-effects* and *dose-response mean effects meta-analyses* were considered to have study design and/or methodological limitations. For example, all but three studies were cross-sectional in design. However, among the low risk-of-bias cross-sectional studies, most provided information to suggest that exposure preceded the outcome (e.g., including only children who had lived in the area since birth, or children that had dental fluorosis). In addition, subgroup analyses suggest that the association between higher fluoride exposure and lower IQ was consistent even when restricted to low risk-of-bias studies (see **Table 2** and **eFigure 7** for additional details). Although we conducted subgroup analyses by sex, only 1 of the 14 studies that reported IQ scores separately for boys and girls analyzed fluoride exposure for each sex separately.[6] This is essential for evaluating whether a differential change in IQ by sex may be related to higher susceptibility or higher exposure in that sex. With a couple exceptions, the subgroup analyses in the *mean-effects meta-analysis* did not explain a large amount of the overall heterogeneity. However, the heterogeneity in the *regression slopes meta-analysis* was explained by subgroup analyses. This suggests that the aggregate nature of the *mean-effects meta-analysis* might not be sufficiently sensitive to capture potential sources of heterogeneity, as seen possible when using studies with individual-level data in the *regression slopes meta-analysis*. However, the large number of studies included in the *mean-effects meta-*

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Commented [I57]: See Doc06b_Meta-analysis, 6b.O., page 13 and 14 *analysis* and the consistency in the direction of the association across the analyses make this is less of a concern.

Another limitation of the *mean-effects meta-analyses* is that exposure values are assumed to be the same for each child in an exposure group, either because the study used a community-level water fluoride measure or a median, mean, or midpoint in water or urine as the exposure value. Fluoride exposure may vary considerably depending on individual behaviors and is best captured by individual-level measures of total exposure, such as urinary fluoride measures. Because drinking water measures capture only some of a person's total exposure to fluoride, it is reasonable to assume that some children in the meta-analysis had higher exposure to fluoride and those children may have skewed the mean IQ deficits of the entire group. Urinary fluoride levels include all ingested fluoride and are considered a valid measure to estimate total fluoride exposure.[61, 62] When compared with 24-hour urine samples, spot urine samples are more prone to the influence of timing of exposure (e.g., when water was last consumed, when teeth were last brushed) and can also 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,[63] and with one exception[35] all studies in the *regression slopes meta-analysis*, accounted for dilution.

There is inconsistency in which model is the best fit at lower exposure levels (**eTable 4** and **eTable 5**) leading to uncertainty in the shape of the dose-response curve at these levels. More individual-level data would increase our certainty in the shape of the dose-response curve at these lower exposure levels. There are also several limitations to the existing approaches for evaluating potential for publication bias. The funnel plot asymmetry is a subjective assessment and is recommended only when at least 10 studies are included in the meta-analysis.[64] Furthermore, the Egger regression test and Begg's rank tests[25-27] may suffer from inflated type I power and limited power in certain situations.[65] Finally, the small number of studies reporting slopes for association with individual-level exposure data limits the power of the *regression slopes meta-analysis*.

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This meta-analysis complements a larger systematic review[8] that concluded moderate confidence in the body of evidence that fluoride exposure is associated with lower IQ in children. Confidence would be increased with additional prospective cohort studies with individual urinary fluoride measures. Studies conducted in the United States, which as of the writing of this manuscript were not available, would also be valuable.

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Conclusions

This meta-analysis extends the findings of our larger systematic review that concluded, with moderate confidence, that higher fluoride exposure is associated with lower children's IQ. These findings are consistent with prior meta-analyses and demonstrate that the direction of the association is robust to stratifications by risk of bias, sex, age group, outcome assessment, study location, exposure timing, and exposure measurement (including both drinking water and urinary fluoride). Therefore, the consistency of the data supports an inverse association between fluoride exposure and children's IQ.

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Tables and Figures

Table 1. Characteristics of Studies Included in the Meta-analysis

Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure: Assessment (Metric, Exposure Groups)	Fluoride Exposure: Levels	Intelligence Assessment	Overall RoB Rating	Confounders Considered
Ren et al. (1989)[66] [translated in Ren et al. 2008][me, o] *Cross-sectional*	China	8–14	No fluoride measurement Low iodine village/high fluoride and low iodine village	Not specified	Wechsler Intelligence Scale for Children	High	Sex; iodine
Chen et al. (1991)[68] [translated in Chen et al. 2008][me, w] *Cross-sectional*	China	7–14	Drinking water Nonendemic/endemic fluorosis village	0.89 mg/L (nonendemic) 4.55 mg/L (endemic)	Chinese Standardized Raven Test	High	Age; sex
Guo et al. (1991)[70] [translated in Guo et al. 2008a][me, o] *Cross-sectional*	China	7–13	Serum Reference area using wood/coal burning-related fluoride endemic area	0.1044 ± 0.0652 mg/L (reference) 0.1483 ± 0.0473 mg/L (endemic)	Chinese Binet Intelligence Test	High	Age; sex; SES
Lin et al. (1991)[40me, o] *Cross-sectional*	China	7–14	Urine, drinking water Reference area with iodine supplementation/high fluoride and low iodine village	Urine: 1.6 mg/L (reference area with iodine supplementation) 2.56 mg/L (high fluoride, low iodine village) Water: 0.34 mg/L (low iodine village) 0.88 mg/L (high fluoride, low iodine village)	Combined Raven's Test for Rural China	High	SES
Sun et al. (1991)[72me, o] *Cross-sectional*	China	6.5–12	No fluoride measurement Nonendemic/endemic (aluminum-fluoride endemic toxicosis)	Fluorosis: 98.36% (endemic)	Japan's Shigeo Kobayashi's 50-point scoring method	High	Age
An et al. (1992)[73me, w] *Cross-sectional*	China	7–16	Drinking water Nonhigh/high fluoride area	0.6−1.0 mg/L (nonhigh) 2.1−3.2 mg/L (secondary high) 5.2−7.6 mg/L (high) 2.1−7.6 mg/L (combined high)	Wechsler Intelligence Scale for Children-Revised	High	Age; race; SES

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Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure: Assessment (Metric, Exposure Groups)	Fluoride Exposure: Levels	Intelligence Assessment	Overall RoB Rating	Confounders Considered
Li et al. (1994)[41] [translated in Li et al. 2008b][me, o] *Cross-sectional*	China	12–13	Grain (cooked by burning high-fluoride coal) Reference group (no dental fluorosis)/high fluoride group I (no dental fluorosis)/high fluoride group II (dental fluorosis present)/high fluoride group III (dental fluorosis present)	0.5 mg/kg (reference group) 4.7 mg/kg (group I) 5.2 mg/kg (group II) 31.6 mg/kg (group III)	Proofing test	High	Age; sex; SES
Xu et al. (1994)[74me, w*] *Cross-sectional*	China	8–14	Drinking water Reference region/low- and high-fluoride regions[b]	0.8 mg/L (reference region) 0.38 mg/L (low fluoride) 1.8 mg/L (high fluoride)	Binet-Simon Scale	High	–
Li et al. (1995)[75me, o, u] *Cross-sectional*	China	8–13	Urine, dental fluorosis index (DFI) Nonfluorosis/fluorosis area due to soot from coal burning	1.02 mg/L; DFI: <0.4 (nonfluorosis) 1.81 mg/L; DFI: 0.8 (slight fluorosis) 2.01 mg/L; DFI: 2.5 (medium fluorosis) 2.69 mg/L; DFI: 3.2 (severe fluorosis)	China Rui Wen Scaler for Rural Areas	High	Sex
Wang et al. (1996)[76] [translated in Wang et al. 2008b][me, o, w] *Cross-sectional*	China	4–7	Drinking water (well) Low/high fluoride region Fluoride exposure from drinking water, contaminated food, and coal burning	0.58−1.0 mg/L (low) >1.0−8.6 mg/L (high)	Wechsler Preschool and Primary Scale of Intelligence	High	Age; sex
Yao et al. (1996)[78me, w] *Cross-sectional*	China	8–12	Drinking water Nonendemic/endemic fluorosis area	1 mg/L (nonendemic) 2 mg/L (slightly endemic) 11 mg/L (severely endemic)	Raven Test – Associative Atlas	High	Iodine; SES
Zhao et al. (1996)[79me, w] *Cross-sectional*	China	7–14	Drinking water Low fluoride village (Xinghua)/high fluoride village (Sima)	0.91 mg/L (low) 4.12 mg/L (high)	China Rui Wen Scaler for Rural Areas	High	Age; SES
Yao (1997)[80me, w*] *Cross-sectional*	China	7–12	Drinking water Nonfluorosis area/fluorosis area with water improvements/fluorosis area without water improvements	0.4 mg/L (nonfluorosis area) 0.33 mg/L (fluorosis area with water improvement) 2 mg/L (fluorosis area without water improvement)	Raven's Standard Progressive Matrices (China's Rural Version)	High	Iodine; SES
Zhang et al. (1998)[81me, o] *Cross-sectional*	China	4–10	Drinking water Reference/high fluoride group (all observation groups included arsenic exposure)	0.58 mg/L (reference) 0.8 mg/L (high fluoride)	Shigeo Kobayashi 50-pt. test	High	Age; arsenic

Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure: Assessment (Metric, Exposure Groups)	Fluoride Exposure: Levels	Intelligence Assessment	Overall RoB Rating	Confounders Considered
Lu et al. (2000)[82me, w, u] *Cross-sectional*	China	10–12	Urine, drinking water Low/high fluoride area	Urine: 1.43 ± 0.64 mg/L (low) 4.99 ± 2.57 mg/L (high) Water: 0.37 ± 0.04 mg/L (low) 3.15 ± 0.61 mg/L (high)	Chinese Combined Raven Test-C2	High	SES
Hong et al. (2001)[83] [translated in Hong et al. 2008][me, w*] *Cross-sectional*	China	8–14	Drinking water Reference/high fluoride[b]	0.75 mg/L (reference) 2.90 mg/L (high fluoride)	Chinese Standardized Raven Test	High	Iodine; SES; demographics
Hong et al. (2001b)[85me, o] *Cross-sectional*	China	8–14	Urine, drinking water Nonendemic/endemic fluorosis areas (high fluoride, high iodine)	Urine: 0.796 ± 0.53 mg/L (nonendemic) 2.09 ± 1.03 mg/L (endemic) Water: 0.48 mg/L (nonendemic) 2.81 mg/L (endemic)	Combined Raven's Test for Rural China	High	–
Wang et al. (2001)[86me, o] *Cross-sectional*	China	8–12	Urine, drinking water Reference point (low fluoride, low iodine)/investigative point (high fluoride, high iodine)	Urine: 0.82 mg/L (low fluoride, low iodine) 3.08 mg/L (high fluoride, high iodine) Water: 0.5 mg/L (low fluoride, low iodine) 2.97 mg/L (high fluoride, high iodine)	Combined Raven's Test for Rural China	High	–
Li et al. (2003)[87] [translated in Li et al. 2008c][me] *Cross-sectional*	China	6–13	No fluoride measurement Reference/endemic fluorosis areas	Not specified	Chinese Standardized Raven Test	High	–

Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Levels			
Xiang et al. (2003a)[44me, w*, u] *Cross-sectional*	China	8–13	Urine, drinking water Nonendemic/endemic fluorosis areas	Urine: 1.11 ± 0.39 mg/L (reference) 3.47 ± 1.95 mg/L (high fluoride) Water: 0.36 ± 0.15 mg/L (nonendemic) 0.75 ± 0.14 mg/L (endemic fluorosis area group A) 1.53 ± 0.27 mg/L (endemic fluorosis area group B) 2.46 ± 0.3 mg/L (endemic fluorosis area group C) 3.28 ± 0.25 mg/L (endemic fluorosis area group D) 4.16 ± 0.22 mg/L (endemic fluorosis area group E) 2.47 ± 0.79 mg/L (high fluoride)	Combined Raven's Test for Rural China	Low	Age; sex; iodine; lead; SES
Wang et al. (2005)[89me, w, u] *Cross-sectional*	China	8–12	Urine, drinking water Reference/high fluoride group[c]	Urine: 1.51 mg/L(reference) 5.09 mg/L (high fluoride group) Water: 0.48 mg/L (reference) 8.31 mg/L (high fluoride group)	Chinese Combined Raven Test-C2	High	SES
Seraj et al. (2006)[90me, w] *Cross-sectional*	Iran	7–11	Drinking water Low/high fluoride area	0.4 ppm (low) 2.5 ppm (high)	Raven Test	High	Sex
Wang et al. (2006)[91me, w, u] *Cross-sectional*	China	8–12	Urine, drinking water Reference/high (area severely affected by fluorosis)	Urine: 1.51 ± 1.66 mg/L (reference) 5.50 ± 2.40 mg/L (high) Water: 0.73 ± 0.28 mg/L (reference) 5.54 ± 3.88 mg/L (high)	Combined Raven's Test for Rural China	High	–
Fan et al. (2007)[92me, w, u] *Cross-sectional*	China	7–14	Urine, drinking water Low/high fluoride area	Urine: 1.78 ± 0.46 mg/L (low) 2.89 ± 1.97 mg/L (high) Water: 1.03 mg/L (low) 3.15 mg/L (high)	Chinese Combined Raven Test-C2	High	–
Trivedi et al. (2007)[93me, w, u] *Cross-sectional*	India	12–13	Urine, drinking water Low/high fluoride area	Urine: 2.30 ± 0.28 mg/L (low) 6.13 ± 0.67 mg/L (high) Water: 2.01 ± 0.009 mg/L (low) 5.55 ± 0.41 mg/L (high)	questionnaire prepared by Professor JH Shah	High	Age; sex

Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure: Assessment (Metric, Exposure Groups)	Fluoride Exposure: Levels	Intelligence Assessment	Overall RoB Rating	Confounders Considered
Wang et al. (2007)[94me, o, w, u] *Cross-sectional*	China	8–12	Urine, drinking water Low fluoride, low arsenic/high fluoride, low arsenic area	Urine: 1.5 ± 1.6 mg/L (low fluoride, low arsenic) 5.1 ± 2.0 mg/L (high fluoride, low arsenic) Water: 0.5 ± 0.2 mg/L (low fluoride, low arsenic) 8.3 ± 1.9 mg/L (high fluoride, low arsenic)	Combined Raven's Test for Rural China	High	Age; sex; arsenic; SES
Li et al.(2009)[95me, o, u*] *Cross-sectional*	China	8–12	Urine Endemic fluorosis region caused by coal burning (reference/mild/medium/severe) Degree of dental fluorosis (normal/suspected/very mild/mild/medium/severe)	0.962 ± 0.517 mg/L (reference) 1.235 ± 0.426 mg/L (mild) 1.670 ± 0.663 mg/L (medium) 2.336 ± 1.128 mg/L (severe) 0.867 ± 0.233 mg/L (normal) 1.094 ± 0.355 mg/L (suspected) 1.173 ± 0.480 mg/L (very mild) 1.637 ± 0.682 mg/L (mild) 2.005 ± 0.796 mg/L (medium) 2.662 ± 1.093 mg/L (severe)	Combined Raven's Test for Rural China	High	Age; sex
Li et al. (2010)[96me] *Cross-sectional*	China	7–10	No fluoride measurement Nondental fluorosis children/dental fluorosis children	Not specified	Combined Raven's Test for Rural China	High	Sex
Ding et al. (2011)[32me, u*, rs] *Cross-sectional*	China	7–14	Dental fluorosis (normal/ questionable/very mild/mild/moderate) Urine Mean urinary fluoride levels (10 groups)	0.80 ± 0.55 mg/L (normal) 1.13 ± 0.73 mg/L (questionable) 1.11 ± 0.74 mg/L (very mild) 1.31 ± 0.78 mg/L (mild) 1.46 ± 0.79 mg/L (moderate) 0.26 mg/L (group 1) 0.45 mg/L (group 2) 0.56 mg/L (group 3) 0.66 mg/L (group 4) 0.75 mg/L (group 5) 0.89 mg/L (group 6) 1.08 mg/L (group 7) 1.33 mg/L (group 8) 1.74 mg/L (group 9) 2.96 mg/L (group 10) 0.10−3.55 mg/L	Combined Raven's Test for Rural China	Low	Age; arsenic; iodine; lead; SES; demographics

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Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Levels			
Eswar et al.(2011)[97me, w] *Cross-sectional*	India	12–14	Drinking water Low/high fluoride villages	0.29 mg/L (low) 2.45 mg/L (high)	Standard Progressive Matrices	High	Age; sex
Kang et al. (2011)[98me, o] *Cross-sectional*	China	6–12	Drinking water Reference/high fluoride areas (both areas with high arsenic exposure)	1.24 ± 0.74 mg/L (all children) <1.2 mg/L (reference) ≥1.2 mg/L (high fluoride)	Chinese Combined Raven Test-C2	High	Age; sex
Poureslami et al. (2011)[99me, w] *Cross-sectional*	Iran	7–9	Drinking water Reference/endemic dental fluorosis city	0.41 mg/L (reference) 2.38 mg/L (endemic)	Persian version of Raven's Matrices Test	High	Sex
Shivaprakash et al. (2011)[100me, w] *Cross-sectional*	India	7–11	Drinking water No fluorosis/fluorosis severity groups (mild/moderate/severe)/all fluorosis	<0.5 ppm (no fluorosis) 2.5–3.5 ppm (mild) 2.5–3.5 ppm (moderate) 2.5–3.5 ppm (severe) 2.5–3.5 ppm (all)	Raven's Colored Progressive Matrices	High	Health factors; SES
Seraj et al. (2012)[45me, w] *Cross-sectional*	Iran	6–11	Drinking water Normal/medium/high fluoride levels	0.8 ± 0.3 mg/L (normal) 3.1 ± 0.9 mg/L (medium) 5.2 ± 1.1 mg/L (high)	Raven's Colored Progressive Matrices	Low	Age; sex; SES
Trivedi et al. (2012)[46me, w, u] *Cross-sectional*	India	12–13	Urine, ground water Low/high fluoride area	Urine: 0.42 ± 0.23 mg/L (low) 2.69 ± 0.92 mg/L (high) Water: 0.84 ± 0.38 mg/L (low) 2.3 ± 0.87 mg/L (high)	Questionnaire prepared by Professor JH Shah	Low	Sex; SES
Wang et al. (2012b)[101me] *Cross-sectional*	China	Primary school age	No fluoride measurement Reference/high fluoride areas	Not specified	Combined Raven's Test for Rural China	High	–
Bai et al. (2014)[102me, o] *Cross-sectional*	China	8–12	Urine Coal-burning-borne fluorosis areas (reference/lightly-affected/seriously-affected)	0.54 mg/L (reference) 0.81 mg/L (lightly-affected area) 1.96 mg/L (seriously-affected area)	Chinese Combined Raven Test-C2	High	SES
Karimzade et al. (2014)[103me, w] *Cross-sectional*	Iran	9–12	Drinking water Low/high fluoride area	0.25 mg/L (low) 3.94 mg/L (high)	Iranian version of the Raymond B Cattell test	High	Sex

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Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure: Assessment (Metric, Exposure Groups)	Fluoride Exposure: Levels	Intelligence Assessment	Overall RoB Rating	Confounders Considered
Broadbent et al. (2015)[38me, w*] *Prospective Cohort*	New Zealand	7–13	Drinking water Area without community water fluoridation (low)/area with community water fluoridation (high) Fluoride tablet use (never/ever) Fluoride toothpaste use (never/sometimes/always)	Water: 0.0–0.3 mg/L (low) 0.7–1.0 mg/L (high) Tablet use: 0 mg (never used) 0.5 mg (ever used) Range not specified for fluoride toothpaste use (always/sometimes/never)	Wechsler Intelligence Scale for Children-Revised	High	Sex; SES; low birth weight; breastfeeding
Khan et al. (2015)[39me] *Cross-sectional*	India	6–11	Drinking water Low fluoride areas (Tiwariganj)/high fluoride areas (Unnao) Fluorosis grades (normal/very mild/mild/moderate/severe)	0.19 mg/L (Tiwariganj) 2.41 mg/L (Unnao) Ranges not specified by fluorosis grades	Raven's Colored Progressive Matrices	High	Health factors; SES
Sebastian and Sunitha (2015)[104me, w*] *Cross-sectional*	India	10–12	Drinking water Low/normal/high fluoride villages	0.40 mg/L (low) 1.2 mg/L (normal) 2.0 mg/L (high)	Raven's Colored Progressive Matrices	High	Age; sex; SES
Zhang et al.(2015b)[33me, w*, u, rs] *Cross-sectional*	China	10–12	Urine, drinking water, serum Reference/high fluoride areas	Urine: 1.10 ± 0.67 mg/L (reference) 2.40 ± 1.01 mg/L (high) Water: 0.63 (0.58–0.68) mg/L (reference) 1.40 (1.23–1.57) mg/L (high) Serum: 0.06 ± 0.03 (reference) 0.18 ± 0.11 (high)	Combined Raven's Test for Rural China	Low	Age; sex; arsenic; iodine; drinking water fluoride; SES; thyroid hormone levels; COMT genotype
Zhang et al. (2015c)[105me, o] *Cross-sectional*	China	7–13	Urine Coal-burning endemic fluorosis area Reference (no dental fluorosis)/mild dental fluorosis/moderate dental fluorosis/critically ill dental fluorosis	0.83 ± 0.71 mg/L (reference) 1.54 ± 0.57 mg/L (mildly ill) 2.41 ± 0.76 mg/L (moderately ill) 3.32 ± 1.02 mg/L (critically ill)	Combined Raven's Test for Rural China	High	–

Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure: Assessment (Metric, Exposure Groups)	Fluoride Exposure: Levels	Intelligence Assessment	Overall RoB Rating	Confounders Considered
Das and Mondal (2016)[106me, u] *Cross-sectional*	India	6–18	Urine, drinking water intake, dental fluorosis (normal/questionable/very mild/mild/moderate/severe)	Urine: 2.91 ± 1.76 mg/L (normal) 2.50 ± 2.39 mg/L (questionable) 2.58 ± 1.31 mg/L (very mild) 2.95 ± 1.44 mg/L (mild) 4.82 ± 3.57 mg/L (moderate) 3.81 ± 2.51 mg/L (severe) Water: 0.069 ± 0.021 mg/kg-d (normal) 0.064 ± 0.004 mg/kg-d (questionable) 0.060 ± 0.036 mg/kg-d (very mild) 0.060 ± 0.030 mg/kg-d (mild) 0.099 ± 0.063 mg/kg-d (moderate) 0.093 ± 0.040 mg/kg-d (severe)	Combined Raven's Test for Rural China	High	–
Mondal et al. (2016)[107me, w] *Cross-sectional*	India	10–14	Drinking water Low/high fluoride areas	Not reported (low) 0.33–18.08 mg/L (high)	Raven Standard Theoretical Intelligence Test	High	SES
Bashash et al. (2017)[5me, u, rs] *Prospective Cohort*	Mexico	6–12	Maternal urine Reference/high fluoride (based on children urinary fluoride)	<0.80 mg/L (reference) ≥0.80 mg/L (high)	Wechsler Abbreviated Scale of Intelligence	Low	Age; sex; weight at birth; parity; gestational age; maternal characteristics (smoking history, marital status, age at delivery, IQ, education, cohort)
Cui et al. (2018)[34rs] *Cross-sectional*	China	7–12	Urine	Boys: 1.3 (0.9−1.7)[d] mg/L Girls: 1.2 (0.9−1.6)[d] mg/L	Combined Raven's Test for Rural China	Low	Age; maternal education; smoking in family member; stress; anger; dopamine receptor-2 polymorphism

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Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Levels			
Yu et al. (2018)[11me, w, u*, rs] *Cross-sectional*	China	7–13	Maternal urine Low/medium/high fluoride ranges Drinking water Normal/high fluoride	Urine: 0.01–1.60 mg/L (low) 1.60–2.50 mg/L (medium) 2.50–5.54 mg/L (high) Water: ≤1 mg/L (normal) >1 mg/L (high) Overall: 0.01−5.54 mg/L (urine) 0.20−3.90 mg/L (water)	Combined Raven's Test for Rural China	Low	Age; sex; health factors; SES
Zhao et al. (2018)[108me, o] *Cross-sectional*	China	7–12	Urine Reference/exposed areas All areas with iodine exposure	≤2.16 mg/L (reference) >2.16 mg/L (exposed)	Combined Raven's Test for Rural China	High	–
Green et al. (2019)[6me, w*, u*, rs] *Prospective Cohort*	Canada	3−4	Maternal urine, drinking water, maternal fluoride intake Nonfluoridated/fluoridated area	Urine: 0.40 ± 0.27 mg/L (nonfluoridated) 0.69 ± 0.42 mg/L (fluoridated) Water: 0.13 ± 0.06 mg/L (nonfluoridated) 0.59 ± 0.08 mg/L (fluoridated) Intake: 0.30 ± 0.26 mg/day (nonfluoridated) 0.93 ± 0.43 mg/day (fluoridated) Overall: 0.51 ± 0.36 mg/L (urine) 0.54 ± 0.44 mg/day (intake) 0.31 ± 0.23 mg/L (water)	Wechsler Primary and Preschool Scale of Intelligence-III	Low	Sex; city; maternal education; race/ethnicity; HOME score; prenatal secondhand smoke exposure
Cui et al. (2020)[47me, u] *Cross-sectional*	China	7–12	Urine Low/medium/high fluoride levels	<1.6 mg/L (low) 1.6–2.5 mg/L (medium) >=2.5 mg/L (high)	Combined Raven's Test	Low	Sex; arsenic; iodine

Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure: Assessment (Metric, Exposure Groups)	Fluoride Exposure: Levels	Intelligence Assessment	Overall RoB Rating	Confounders Considered
Till et al. (2020)[7rs] *Prospective Cohort*	Canada	3−4	Residence, maternal urine, drinking water, infant fluoride intake from formula Nonfluoridated/fluoridated areas	Urine: 0.38−0.42 mg/L (nonfluoridated) 0.64−0.70 mg/L (fluoridated) Water: 0.13 mg/L (nonfluoridated) 0.58 mg/L (fluoridated) Intake: 0.02−0.08 mg/day (nonfluoridated) 0.12−0.34 mg/day (fluoridated)	Wechsler Primary and Preschool Scale of Intelligence-III	Low	Age; sex; maternal education; maternal race; HOME total score; secondhand smoke status in the child's house
Wang et al. (2020c)[109me, o] *Cross-sectional*	China	7−12	Urine Coal-burning endemic fluorosis area Nonendemic/endemic fluorosis regions	0.461 ± 0.210 mg/L (nonendemic) 0.689 ± 0.502 mg/L (endemic)	Combined Raven's Test for Rural China	High	Age; sex
Xu et al. (2020)[36me, u*, rs] *Cross-sectional*	China	7−13	Urine Reference/high prenatal exposure only/high childhood exposure only/both prenatal and childhood exposure group	0.82 ± 0.30 mg/L (reference) 0.98 ± 0.29 mg/L (high prenatal exposure only) 2.05 ± 0.58 mg/L (high childhood exposure only) 2.13 ± 0.59 mg/L (both prenatal and childhood exposure group)	Combined Raven's Test for Rural China	Low	Age; sex; gestational weeks; maternal education level; paternal education level; children's BMI
Guo et al., (2021)[110me] *Cross-sectional*	China	7−12	Urine Reference/exposed areas (also with iodine exposure)	1.16 mg/L (reference) 1.29 mg/L (iodine area 1) 2.01 mg/L (iodine area 2)	Combined Raven's Test for Rural China	High	–
Lou et al. (2021)[111me, o] *Cross-sectional*	China	8−12	Coal-burning endemic fluorosis area No fluoride measurement Nondental fluorosis children/dental fluorosis children	Not specified	Wechsler Intelligence Scale for Children-Revised in China (WISC-CR)	High	–
Saeed et al. (2021)[35me, o, rs] *Cross-sectional*	Pakistan	5−16	Urine, drinking water Reference/high fluoride areas Co-exposure with arsenic	Urine: 0.24 ± 0.15 mg/L (reference) 3.27 ± 2.60 mg/L (high) Water: 0.15 ± 0.13 mg/L (reference) 5.64 ± 3.52 mg/L (high)	Wechsler scale of intelligence (WISC-IV)	High	Age; sex; parental education; dental fluorosis

Reference[a] *Study Design*	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Levels			
Wang et al. (2021)[112] [me, w] *Cross-sectional*	China	9−11	Drinking water Reference/high fluoride areas	1.0 ± 0.07 mg/L (reference) 2.8 ± 0.06 mg/L (high fluoride)	Combined Raven's Test	High	Age; sex
Zhao et al. (2021)[37rs] *Cross-sectional*	China	6−11	Urine Nonendemic/endemic fluorosis areas	1.03 (0.72, 1.47) mg/L	Combined Raven's Test for Rural China	Low	Age; sex; BMI; paternal educational level; maternal educational level; household income; abnormal birth; maternal age at delivery

Notes:
COMT = catechol-O-methyltransferase; RoB = risk of bias; SES = socioeconomic status; HOME = Home Observation for Measurement of the Environment
[a]An "me" superscript indicates that the studies included in the mean-effects meta-analysis; an "o" superscript indicates a study included in "other" exposures *mean-effects meta-analysis* (see **Table 2** footnote); a "w" superscript indicates studies included in the mean-effects dose-response meta-analysis using fluoride in water; a "u" superscript indicates studies included in the mean-effects dose-response meta-analysis using fluoride in urine; "*" indicates studies included in the mean-effects dose-response meta-analysis at levels < 1.5 mg/L; an "rs" superscript indicates studies included in the regression slopes meta-analysis.
[b]Additional exposure regions including iodine levels were not included in the analysis.
[c]Additional exposure regions including arsenic levels were not included in the analysis.
[d]Median (q1–q3).

Table 2. Pooled SMDs and 95% CIs for Children's IQ Score and Exposures to Fluoride

Analysis	Number of Studies	SMD (95% CI)	Heterogeneity p-value	Heterogeneity I^2
Overall Effect	55	−0.46 (−0.55, −0.37)	<0.001	87%
Subgroup Analyses				
Risk of Bias				
Low	10	−0.22 (−0.39, −0.05)	<0.001	83%
High	45	−0.52 (−0.63, −0.42)	<0.001	86%
Sex				
Males	14	−0.62 (−0.81, −0.42)	<0.001	78%
Females	13	−0.53 (−0.72, −0.34)	<0.001	74%
Age Group				
<10 years[a]	13	−0.41 (−0.60, −0.22)	<0.001	80%
≥10 years	16	−0.55 (−0.70, −0.40)	<0.001	68%
Country				
China	39	−0.43 (−0.52, −0.34)	<0.001	85%
India	8	−0.99 (−1.55, −0.43)	<0.001	93%
Iran	4	−0.68 (−0.99, −0.38)	0.077	56%
Canada	1	0.01 (−0.19, 0.21)	NA	NA
Mexico	1	0.13 (−0.16, 0.42)	NA	NA
New Zealand	1	0.01 (−0.19, 0.22)	NA	NA
Pakistan	1	−0.25 (−0.65, 0.16)	NA	NA
Assessment Type				
CRT-RC tests	29	−0.36 (−0.46, −0.27)	<0.001	82%
Non-CRT-RC tests	26	−0.60 (−0.78, −0.42)	<0.001	89%
Raven's tests	10	−0.76 (−1.10, −0.43)	<0.001	91%
Other tests	16	−0.52 (−0.74, −0.29)	<0.001	89%
Exposure Type				
Water fluoride	32	−0.37 (−0.46, −0.27)	<0.001	82%
Dental fluorosis	7	−0.99 (−1.57, −0.41)	<0.001	96%
Other exposures[b]	16	−0.54 (−0.71, −0.37)	<0.001	81%
Previous Meta-analyses				
Duan et al. (2018)[4]	26	−0.52 (−0.62, −0.42)	<0.001	69%
Choi et al. (2012)[3]	27	−0.45 (−0.56, −0.34)	<0.001	80%

Notes: CI = confidence interval; CRT-RC = Combined Raven's Test–The Rural edition in China; NA = not applicable; SMD = standardized weighted mean difference
[a]An et al. (1992)[73] and Li et al. (2010)[96] include 10-year-old children in the <10 age group (7−10 years reported).
[b]Includes iodine [40, 66 [translated in Ren et al. 2008], 85, 86, 108]; arsenic[35, 81, 94]; aluminum[72]; and non-drinking water fluoride (i.e., fluoride from coal burning[41 [translated in Li et al. 2008b], 70 [translated in Guo et al. 2008a], 75, 76 [translated in Wang et al. 2008b], 89, 95, 102, 105, 109, 111]).
[c] p-value for differences between the estimates based on CRT-RC tests *vs.* non-CRT-RC tests.
[d] p-value for differences between the estimates based on CRT-RC tests, Raven's test and other tests. Note that non-CRT-RC test include Raven's tests and other tests.

Commented [I73]: See Doc06a_Meta-analysis, 6a.E., page 3 and 4

Commented [I74]: See Doc02_Meta-analysis, 2.X., page 7 and 8

Table 3. Pooled Regression Slopes and 95% CIs for Children's IQ Score and Exposures to Fluoride

Analysis	Number of Studies	Beta (95% CI)	Heterogeneity p-value	Heterogeneity I^2
Overall Effect				
Full-scale IQ	9	−1.81 (−2.80, −0.81)	<0.001	77%
Subgroup Analyses				
Risk of Bias				
Low	8	−1.33 (−2.09, −0.57)	0.072	46%
High	1	−3.45 (−4.44, −2.46)	NA	NA
Sex				
Males	2	−2.23 (−5.45, 0.99)	0.092	65%
Females	2	−0.27 (-3.64, 3.10)	0.145	53%
Country				
Canada	1	−1.95 (−5.18, 1.28)	NA	NA
China	6	−1.06 (−1.70, −0.42)	0.191	33%
Mexico	1	−5.00 (−8.53, −1.47)	NA	NA
Pakistan	1	−3.45 (−4.44, −2.46)	NA	NA
Assessment Type				
CRT-RC tests	6	−1.06 (−1.70, −0.42)	0.191	33%
Non-CRT-RC tests	3	−3.43 (−4.35, −2.52)	0.457	0%
Exposure Type				
Urinary fluoride	9	−1.81 (−2.80, −0.81)	<0.001	77%
Intake	2	−3.87 (−7.15, −0.59)	0.737	0%
Water fluoride	2	−4.77 (−9.09, −0.45)	0.707	0%
Exposure timing				
Pre-natal exposure	3	−3.08 (−5.43, −0.72)	0.351	5%
Post-natal exposure	7	−1.84 (-2.97, -0.72)	<0.001	78%

Notes: CI = confidence interval; NA = not applicable

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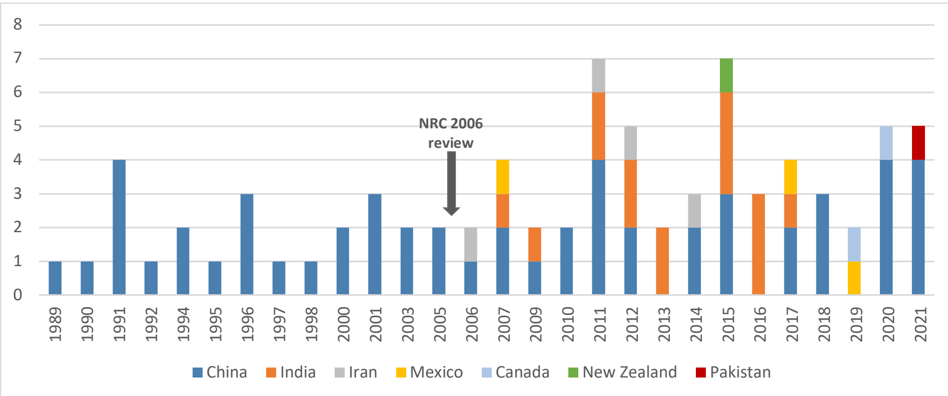

Figure 1. Number of Studies of Fluoride Exposure and IQ in Children by Country and Year of Publication

Note: Figure includes 80 epidemiological studies that were identified during the larger systematic review and the November 2021 literature search update that evaluated the effects of fluoride exposure on children's IQ.

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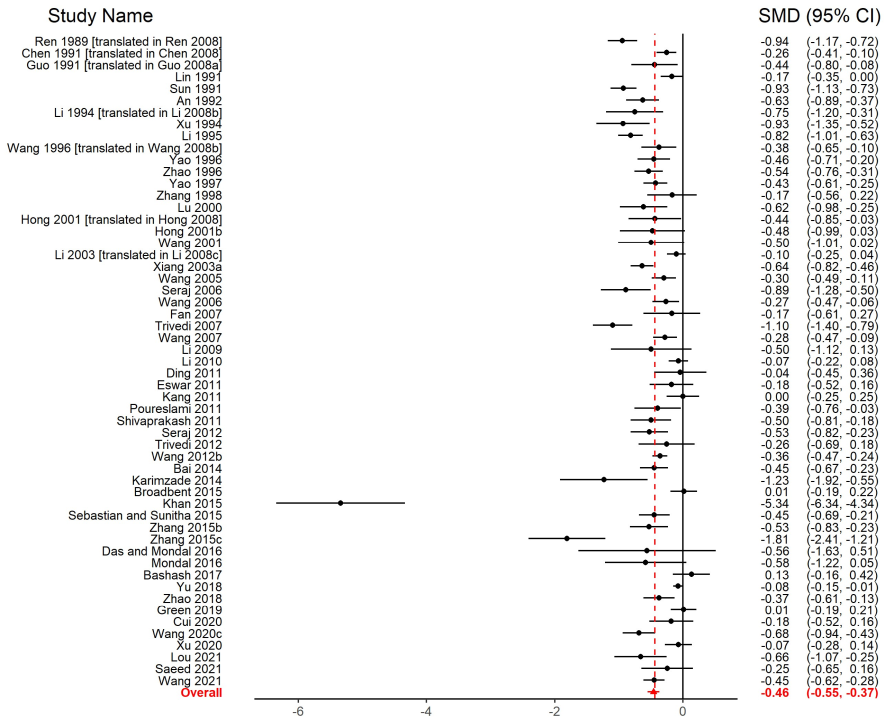

Figure 2. Association Between Fluoride Exposure and IQ Scores in Children

Commented [I78]: See Doc06b_Meta-analysis, 6b.R., page 15 and 16

Note: Forest plot for random-effects meta-analysis of the association between fluoride exposure and child's IQ scores. Effect size is expressed as the standardized weighted mean difference for heteroscedastic population variances (SMD). The random-effects pooled SMD is shown as a solid triangle. Horizontal lines represent 95% CIs for the study-specific SMDs.

SUPPLEMENTAL MATERIALS

List of Tables

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Additional Detail on Methods

Systematic Literature Review

Literature searches were conducted in the following databases: BIOSIS, EMBASE, PsychINFO, PubMed, Scopus, Web of Science, CNKI, and Wanfang. Search strategies tailored for each database are available in the protocol (https://ntp.niehs.nih.gov/go/785076). The last search was performed on May 1, 2020. The identification of studies for the meta-analysis was part of a larger systematic review.[1]

Study Selection

In order to be eligible for inclusion in the systematic literature review, individual study publications (referred to in this paper as "studies") had to satisfy eligibility criteria outlined in the protocol (i.e., address PECO statement in Table 1 and specific exclusion criteria in Table 2, https://ntp.niehs.nih.gov/go/785076).

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The following exclusions were made:

(1) Case studies and case reports.

(2) Articles without original data (e.g., reviews, editorials, commentaries). Reference lists from these materials, however, were reviewed to identify potentially relevant studies not identified from the database searches. New studies identified were assessed for eligibility for inclusion.

(3) Conference abstracts or reports and dissertations.

References retrieved from the literature search were independently screened by two trained screeners at the title and abstract level to determine whether a reference met the evidence selection criteria. Studies that were not excluded during the title and abstract screening were further screened for inclusion with a full-text review by two independent reviewers. Translation assistance was obtained to assess the relevance of non-English studies. Following full-text review, the remaining studies were "included" and used for the evaluation.

Results of the study identification process are provided in **eFigure 1**.

Statistical Analysis

Mean-effects meta-analysis

A sensitivity analysis was performed to evaluate the impact of using any exposed group compared to the reference group. This was accomplished by using the approach outlined in the Cochrane Handbook for Systematic Reviews[2] which combines the data from all available exposure groups (n, mean, and standard deviation [SD]). Subgroup analyses were stratified by risk of bias (high or low), outcome assessment, exposure matrix (e.g., urine or water), pre- or post-natal exposures, outcome, gender, and age group. If results were not reported by gender or age-specific subgroups (<10, ≥10 years), they were calculated (if possible) by combining smaller subgroups. If SDs were not reported, but mean effects, sample sizes (n values), and p-values for differences between groups were available, SDs were calculated using the SE and t-statistic (assuming equal variances). To avoid sample overrepresentation, if the same cohort was followed at multiple timepoints resulting in multiple study publications (e.g., Yu et al.[3] and Wang et al.[4]), only the study publication that included the largest number of participants was included in the meta-analysis (see **eTable 1** for list of excluded studies and rationales). For studies with overlapping populations (i.e., multiple study publications that used the same cohort), results from one study publication were selected considering the following factors: most appropriate exposure metric, exposure range, exposure period, number of subjects, and statistical adjustment for potential confounders (see **eTable 2** for study-specific effect estimates used in the meta-analysis).

Dose-response meta-analysis

To determine whether the data support an exposure-response relationship, we conducted a *dose-response mean-effects meta-analysis.* This analysis included studies from the *mean-effects meta-analysis* that reported fluoride exposure levels; we excluded studies for which there was evidence that co-exposures to arsenic or iodine might be differential (see **eTable 2**).

The *dose-response meta-analysis* was conducted using a one-step approach developed in the protocol (https://ntp.niehs.nih.gov/go/78500.76).[5, 6] The approach uses linear mixed models to analyze all available mean effect estimates for the reference group and one or more of the non-reference exposure groups. For each study, the median or mean fluoride level for each exposure group was assigned to its corresponding effect estimate. If median or mean levels by exposure group were not provided, the midpoint of the upper and lower boundaries in every exposure category was assigned as the average level. If the upper boundary for the highest exposure group was not reported, the boundary was assumed to have the same amplitude as the nearest exposure category. For each study, the SMDs and corresponding SEs were used to compare the differences in mean IQ between the exposed and reference groups. The corresponding SMD for the reference group was set to zero for this analysis. The SMDs and corresponding variances were used to estimate a pooled dose-response curve using a restricted maximum likelihood estimation method. To examine a potential nonlinear relationship between exposure to fluoride and children's IQ levels, quadratic terms and restricted cubic splines were created, and a potential departure from a linear trend was assessed by testing the coefficient of the quadratic term and a second spline equal to zero. Models were compared and the best model fit was determined based on the maximum likelihood Akaike information criterion (AIC).[7] The AIC is a goodness-of-fit measure that adjusts for the number of parameters in the model, and lower AIC values indicate better fitting models. Models using a pooled dose-response curve using a restricted maximum likelihood estimation method and a maximum likelihood method were also reported (**eTable4** and **eTable 5**, respectively).

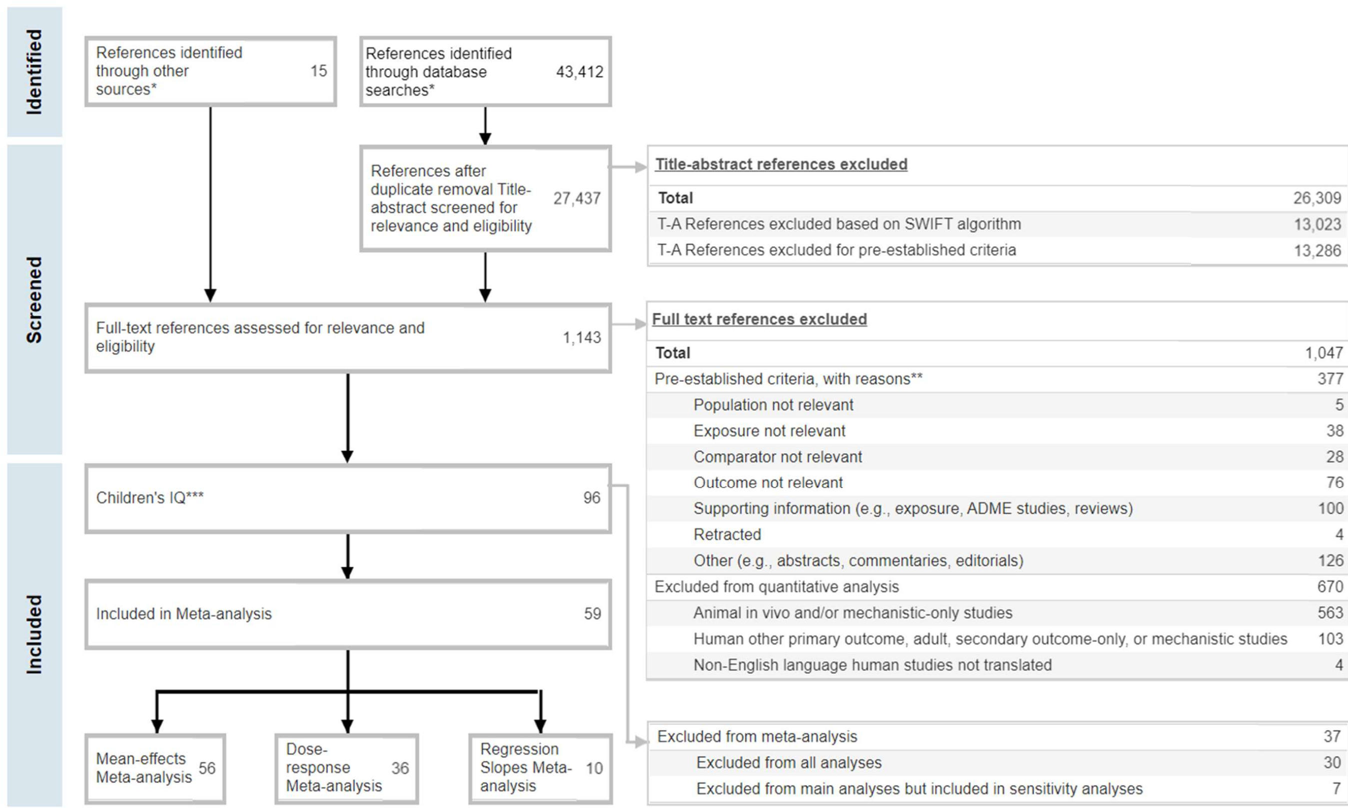
Commented [I2]: See Doc06a_Meta-analysis, 6a.D., page 6 and 7

To examine whether there were effects at lower levels of exposure, we conducted sub-group analyses for both drinking water and urinary fluoride measures. Analyses were restricted to <4 mg/L, the EPA's current enforceable drinking water standard for fluoride; <2 mg/L, the EPA's non-enforceable secondary standard for fluoride in drinking water;[8] and <1.5 mg/L, the WHO's guideline for fluoride in drinking water.[9]

Results

Study Sample

Results of the study identification process are provided in **eFigure 1**. Characteristics of the 55 studies that compared mean IQ scores between groups of children with different levels of fluoride exposure are shown in **Table 1** of the main publication (see **eTable 1** for list of excluded publications). Study-specific effect estimates used in the meta-analyses are presented in **eTable 2**. One study per country was conducted in New Zealand, Mexico, Pakistan, and Canada; 4 studies were conducted in Iran, 8 studies were conducted in India, and the remaining 39 studies were performed in China (see **Table 1** of the main publication). Nine study populations were exposed to fluoride from coal burning[10 [translated in Guo et al. 2008a], 12 [translated in Li et al. 2008b], 14-16,17-19]; otherwise, it is assumed that study populations were exposed to fluoride primarily through drinking water. Measures of fluoride exposure included water fluoride (n = 32 studies), dental fluorosis (n = 7), and other non-drinking water sources of exposure to fluoride (e.g., fluoride exposure from coal burning [n = 16]). Fourteen studies presented results for boys and 13 studies reported results for girls; children < 10 years old and children ≥ 10 years old were examined in 13 and 16 studies, respectively (**Table 2**). The Combined Raven's Test for Rural China (CRT-RC) was used to measure children's IQ in 29 studies. Other measures of IQ included the Wechsler intelligence tests,[20 [translated in Ren et al. 2008], 22 [translated in Wang et al. 2008b], 24, 25] Binet IQ test[10 [translated in Guo et al. 2008a], 26], Raven's Standard Progressive Matrices test,[27-36] Raymond B Cattell test,[37] Japan IQ test,[38, 39] Index of Mental Capacity,[12 [translated in Li et al. 2008b]] and other tests using a doctor-prepared questionnaire.[40, 41] There were 10 low risk-of-bias studies and 45 high risk-of-bias studies (https://hawcproject.org/summary/visual/assessment/405/Figure-X-Meta-analysis-RoB/).



eFigure 1. Prisma Flow Diagram of Study Inclusion

*This information was part of a larger systematic review effort resulting in many studies in the search strategy and PRISMA that were not considered for meta-analysis.

**Studies may have been excluded for more than one reason. The first one identified by the screener was recorded.

*** For the purpose of this PRISMA figure, the Children's IQ count includes three publications[42-44] based on subsamples (i.e., 50–60 children) of a larger Yu et al.[3] cohort. These three publications are not included in the meta-analysis and are not displayed in Figure 1 in the main publication.

eTable 1. List of Excluded Studies from Mean-effects Meta-analysis

Commented [I3]: See Doc05_Meta-analysis, 5.E. (pages 6 and 7), 5.G. (page 8), and 5.M. (page 11)

Reference, Country	Reason for Exclusion
Qin et al. (1990)[45] [translated in Qin et al. 2008], China	Missing mean or SD of outcome measure
Yang et al. (1994)[47] [translated in Yang et al. 2008], China	Overlapping population with Wang et al. (2001)[49]; Table 2 in Yang et al. (1994)[47] seemed incomplete
Wang et al. (2005b)[50] [translated in Wang et al. 2008a], China	Missing mean or SD of outcome measure
Rocha-Amador et al. (2007)[52], Mexico	Missing mean or SD of outcome measure
Liu et al. (2000)[53] [translated in Liu et al. 2008] , China	Overlapping population with Lu et al. (2000)[55]
Sudhir et al. (2009)[56], India	Missing mean or SD of outcome measure
He and Zhang (2010)[57], China	Missing mean or SD of outcome measure
Xiang et al. (2011)[58], China	Overlapping population with Xiang et al. (2003a)[59]
Saxena et al. (2012)[60], India	Missing mean or SD of outcome measure
Wang et al. (2012)[61], China	Overlapping population with Xiang et al. (2003a)[59]
Nagarajappa et al. (2013)[62], India	Seguin Foam Board test; due to the test measuring eye-hand coordination and cognitive-perceptual abilities
Pratap et al.(2013)[63], India	Missing mean or SD of outcome measure
Asawa et al. (2014)[64], India	Seguin Foam Board test; due to the test measuring eye-hand coordination and cognitive-perceptual abilities
Wei et al. (2014)[65], China	Missing mean or SD of outcome measure
Choi et al. (2015)[66], China	Cognitive functions other than IQ
Kundu et al. (2015)[67], India	Unusual IQ scores based on Raven's Standardized Progressive Matrices Test; used only for sensitivity analysis for the *mean-effects meta-analysis*
Aravind et al. (2016)[68], India	Unusually low IQ scores Raven's Standardized Progressive Matrices Test; used only for sensitivity analysis for the *mean-effects meta-analysis*
Jin et al.(2016)[69], China	Cognitive functions other than IQ; potential overlap with Zhang et al. (2015c)[70]
Kumar et al. (2016)[71], India	Seguin Foam Board test; due to the test measuring eye-hand coordination and cognitive-perceptual abilities
Jin et al.(2017)[72], China	Overlap with Jin et al. (2016)[69]; unusual IQ scores reported as percentiles
Razdan et al. (2017)[73], India	Unusually low IQ scores based on Raven's Standardized Progressive Matrices Test; used only for sensitivity analysis for the *mean-effects meta-analysis*
Valdez Jiménez et al. (2017)[74], Mexico	Bayley tests; used only for sensitivity analysis for the *regression slopes meta-analysis*
Wang et al. (2017)[75], China	Overlapping population with Xiang et al. (2003a)[59]

Reference, Country	Reason for Exclusion
Cui et al. (2018)[76], China	Missing mean or SD of outcome measure; used in *regression slopes meta-analysis*
Luo et al. (2018)[77], China	Overlapping population with Lou et al. (2021)[19]
Naik et al. (2018)[78], India	Missing sample sizes by exposure groups. Missing mean and SD for IQ scores
Sharma et al.(2018)[79], India	Missing mean and SD for IQ scores
Soto-Barreras et al. (2019)[80], Mexico	Missing mean or SD of outcome measure
Zhao et al. (2019)[43], China	Overlapping population with Yu et al. (2018)[3], but smaller sample size
Zhou et al. (2019)[44], China	Overlapping population with Yu et al. (2018)[3], but smaller sample size
Till et al.(2020)[81], Canada	Missing mean or SD of outcome measure; used in *regression slopes meta-analysis*
Wang et al. (2020b)[4], China	Missing mean or SD of outcome measure; used in sensitivity analysis for the *regression slopes meta-analysis*
Zhao et al. (2020)[42], China	Overlapping population with Yu et al. (2018)[3], but smaller sample size
Aggeborn and Öhman (2021)[82], Sweden	Cognitive functions other than IQ; cognitive test not specified
Cantoral et al. (2021)[83], Mexico	Bayley tests; used only for sensitivity analysis for the *regression slopes meta-analysis*
Farmus et al. (2021)[84], Canada	Same data as Till et al.(2020)[81]
Guo et al. (2021)[85], China	Overlapping population with Zhao et al. (2018),[86] but smaller sample size; excluded from overall *mean-effects meta-analysis* but used in mean-effects subgroup meta-analysis by age group
Ibarluzea et al. (2021)[87], Spain	Bayley and McCarthy tests; used only for sensitivity analysis for the *mean-effects meta-analysis*, *dose-response meta-analysis*, and *regression slopes meta-analysis*
Wang et al. (2021b)[88], China	Overlapping population with Wang et al. (2021)[89]; cognitive functions other than IQ
Yu et al. (2021)[90], China	Overlapping population with Yu et al. (2018)[3], but smaller sample size
Zhao et al. (2021)[91], China	Missing mean or SD of outcome measure; used in *regression slopes meta-analysis*
Zhou et al. (2021)[92], China	Overlapping population with Yu et al. (2018)[3], but smaller sample size

eTable 2. Study Characteristics and Study-specific Effect Estimates Included in the Meta-analyses and Sensitivity Analyses

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Ren et al. (1989)[20] [translated in Ren et al. 2008][me, o] *Cross-sectional*	China	8–14	No fluoride measurement Low iodine village/high fluoride and low iodine village	Not specified	169, 85.00 (22.30) 160, 64.80 (20.40)			Subjects, Methods, Results section
Chen et al. (1991)[93] [translated in Chen et al. 2008][me, w] *Cross-sectional*	China	7–14	Drinking water Nonendemic/endemic fluorosis village	0.89 mg/L (nonendemic) 4.55 mg/L (endemic)	320, 104.03 (14.96) 320, 100.24 (14.52)	320, 104.03 (14.96) 320, 100.24 (14.52)		Results section, Table 1
Guo et al. (1991)[10] [translated in Guo et al. 2008a][me, o] *Cross-sectional*	China	7–13	Serum Reference area using wood/coal burning-related fluoride endemic area	0.1044 ± 0.0652 mg/L (reference) 0.1483 ± 0.0473 mg/L (endemic)	61, 81.39 (10.26) 60, 76.71 (10.85)			Calculated by ICF
Lin et al. (1991)[95me, o] *Cross-sectional*	China	7–14	Urine, drinking water Reference area with iodine supplementation/high fluoride and low iodine village	Urine: 1.6 mg/L (reference area with iodine supplementation) 2.56 mg/L (high fluoride, low iodine village) Water: 0.34 mg/L (low iodine village) 0.88 mg/L (high fluoride, low iodine village)	256, 78.00 (40.07) 250, 71.00 (40.07)			Calculated by ICF
Sun et al. (1991)[38me, o] *Cross-sectional*	China	6.5–12	No fluoride measurement Nonendemic area/endemic (aluminum-fluoride endemic toxicosis)	Fluorosis: 98.36% (endemic)	224, 82.68 (10.91) 196, 72.35 (11.36)			Calculated by ICF
An et al. (1992)[24me, w] *Cross-sectional*	China	7–16	Drinking water Nonhigh/high fluoride area	0.6−1.0 mg/L (nonhigh) 2.1−3.2 mg/L (secondary high) 5.2−7.6 mg/L (high) 2.1−7.6 mg/L (combined high)	121, 84.00 (12.10) 121, 75.90 (13.60)	121, 84.00 (12.10) 56, 76.10 (13.90) 65, 75.60 (13.30)		Table 1, Table 2

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Li et al. (1994)[12] [translated in Li et al. 2008b][me, o] *Cross-sectional*	China	12–13	Grain (cooked by burning high-fluoride coal) Reference group (no dental fluorosis)/high fluoride group I (no dental fluorosis)/high fluoride group II (dental fluorosis present)/high fluoride group III (dental fluorosis present)	0.5 mg/kg (reference group) 4.7 mg/kg (group I) 5.2 mg/kg (group II) 31.6 mg/kg (group III)	49, 267.20 (39.50) 36, 240.00 (30.80)			Table 1
Xu et al. (1994)[26me, w] *Cross-sectional*	China	8–14	Drinking water Reference region/low- and high-fluoride regions[b]	0.8 mg/L (reference region) 0.38 mg/L (low fluoride) 1.8 mg/L (high fluoride)	32, 83.83 (9.10) 97, 79.25 (2.25)	32, 83.83 (9.10) 21, 80.21 (8.27) 97, 79.25 (2.25)		Chart 1
Li et al. (1995)[14me, o, u] *Cross-sectional*	China	8–13	Urine, dental fluorosis index (DFI) Nonfluorosis/fluorosis area due to soot from coal burning	1.02 mg/L; DFI: <0.4 (nonfluorosis) 1.81 mg/L; DFI: 0.8 (slight fluorosis) 2.01 mg/L; DFI: 2.5 (medium fluorosis) 2.69 mg/L; DFI: 3.2 (severe fluorosis)	226, 89.90 (10.40) 230, 80.30 (12.90)	226, 89.90 (10.40) 227, 89.70 (12.70) 224, 79.70 (12.70) 230, 80.30 (12.90)		Table 2
Wang et al. (1996)[22] [translated in Wang et al. 2008b][me, o, w] *Cross-sectional*	China	4–7	Drinking water (well) Low/high fluoride regions Fluoride exposure from drinking water, contaminated food, and coal burning	0.58−1.0 mg/L (low) >1.0−8.6 mg/L (high)	83, 101.23 (15.84) 147, 95.64 (14.34)	83, 101.23 (15.84) 147, 95.64 (14.34)		Table 1
Yao et al. (1996)[28me, w] *Cross-sectional*	China	8–12	Drinking water Nonendemic/endemic fluorosis areas	1 mg/L (nonendemic) 2 mg/L (slightly endemic) 11 mg/L (severely endemic)	270, 98.46 (13.21) 78, 92.53 (12.34)	270, 98.46 (13.21) 188, 94.89 (11.15) 78, 92.53 (12.34)		Table 2
Zhao et al. (1996)[96me, w] *Cross-sectional*	China	7–14	Drinking water Low fluoride village (Xinghua)/high fluoride village (Sima)	0.91 mg/L (low) 4.12 mg/L (high)	160, 105.21 (14.99) 160, 97.69 (13.00)	160, 105.21 (14.99) 160, 97.69 (13.00)		Table 1

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Yao (1997)[27me, w*] *Cross-sectional*	China	7–12	Drinking water Nonfluorosis/fluorosis area with water improvements/fluorosis area without water improvements	0.4 mg/L (nonfluorosis area) 0.33 mg/L (fluorosis area with water improvement) 2 mg/L (fluorosis area without water improvement)	314, 99.98 (12.21) 183, 94.89 (11.15)	314, 99.98 (12.21) 326, 97.83 (11.27) 183, 94.89 (11.15)		Section 2.1 Intelligence Tests, page 2
Zhang et al. (1998)[39me, o] *Cross-sectional*	China	4–10	Drinking water Reference/high fluoride group (all observation groups included arsenic exposure)	0.58 mg/L (reference) 0.8 mg/L (high fluoride)	52, 87.69 (11.04) 51, 85.62 (13.23)			Table 1
Lu et al. (2000)[55me, w, u] *Cross-sectional*	China	10–12	Urine, drinking water Low/high fluoride area	Urine: 1.43 ± 0.64 mg/L (low) 4.99 ± 2.57 mg/L (high) Water: 0.37 ± 0.04 mg/L (low) 3.15 ± 0.61 mg/L (high)	58, 103.05 (13.86) 60, 92.27 (20.45)	58, 103.05 (13.86) 60, 92.27 (20.45)		Table 1
Hong et al. (2001)[97] [translated in Hong et al. 2008] [me, w] *Cross-sectional*	China	8–14	Drinking water Reference/high fluoride[b]	0.75 mg/L (reference) 2.90 mg/L (high fluoride)	32, 82.79 (8.98) 85, 80.58 (2.28)	32, 82.79 (8.98) 85, 80.58 (2.28)		Table 2
Hong et al. (2001b)[99me, o] *Cross-sectional*	China	8–14	Urine, drinking water Nonendemic/endemic fluorosis areas (high fluoride, high iodine)	Urine: 0.796 ± 0.53 mg/L (nonendemic) 2.09 ± 1.03 mg/L (endemic) Water: 0.48 mg/L (nonendemic) 2.81 mg/L (endemic)	30, 80.66 (11.93) 31, 75.89 (7.74)			Table 3, Table 4
Wang et al. (2001)[49,me, o] *Cross-sectional*	China	8–12	Urine, drinking water Reference point (low fluoride, low iodine)/investigative point (high fluoride, high iodine)	Urine: 0.82 mg/L (low fluoride, low iodine) 3.08 mg/L (high fluoride, high iodine) Water: 0.5 mg/L (low fluoride, low iodine) 2.97 mg/L (high fluoride, high iodine)	30, 81.67 (11.97) 30, 76.67 (7.75)			Table 2

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Li et al. (2003)[100] [translated in Li et al. 2008c][me] *Cross-sectional*	China	6–13	No fluoride measurement Reference/endemic fluorosis areas	Not specified	236, 93.78 (14.30) 720, 92.07 (17.12)			Table 1
Xiang et al. (2003a)[59,me, w*, u] *Cross-sectional*	China	8–13	Urine, drinking water Nonendemic/endemic fluorosis areas	Urine: 1.11 ± 0.39 mg/L (reference) 3.47 ± 1.95 mg/L (high fluoride) Water: 0.36 ± 0.15 mg/L (nonendemic) 0.75 ± 0.14 mg/L (endemic fluorosis area group A) 1.53 ± 0.27 mg/L (endemic fluorosis area group B) 2.46 ± 0.3 mg/L (endemic fluorosis area group C) 3.28 ± 0.25 mg/L (endemic fluorosis area group D) 4.16 ± 0.22 mg/L (endemic fluorosis area group E) 2.47 ± 0.79 mg/L (high fluoride)	290, 100.41 (13.21) 222, 92.02 (13.00)	290, 100.41 (13.21) 9, 99.56 (14.13) 42, 95.21 (12.22) 111, 92.19 (12.98) 52, 89.88 (11.98) 8, 78.38 (12.68)		Table 6, Table 8
Wang et al. (2005)[102,me, w, u] *Cross-sectional*	China	8–12	Urine, drinking water Reference/high fluoride group[c]	Urine: 1.51 mg/L(reference) 5.09 mg/L (high fluoride group) Water: 0.48 mg/L (reference) 8.31 mg/L (high fluoride group)	196, 112.36 (14.87) 253, 107.83 (15.45)	196, 112.36 (14.87) 253, 107.83 (15.45)		Table 1
Seraj et al. (2006)[29,me, w] *Cross-sectional*	Iran	7–11	Drinking water Low/high fluoride area	0.4 ppm (low) 2.5 ppm (high)	85, 98.90 (12.90) 41, 87.90 (11.00)	85, 98.90 (12.90) 41, 87.90 (11.00)		Methodology, Findings section (Text under Table 2)
Wang et al. (2006)[103,me, w, u] *Cross-sectional*	China	8–12	Urine, drinking water Reference/high (area severely affected by fluorosis)	Urine: 1.51 ± 1.66 mg/L (reference) 5.50 ± 2.40 mg/L (high) Water: 0.73 ± 0.28 mg/L (reference) 5.54 ± 3.88 mg/L (high)	166, 111.55 (15.19) 202, 107.46 (15.38)	166, 111.55 (15.19) 202, 107.46 (15.38)		Table 2

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Fan et al. (2007)[104,me, w, u] *Cross-sectional*	China	7–14	Urine, drinking water Low/high fluoride area	Urine: 1.78 ± 0.46 mg/L (low) 2.89 ± 1.97 mg/L (high) Water: 1.03 mg/L (low) 3.15 mg/L (high)	37, 98.41 (14.75) 42, 96.11 (12.00)	37, 98.41 (14.75) 42, 96.11 (12.00)		Table 1
Trivedi et al. (2007)[41,me, w, u] *Cross-sectional*	India	12–13	Urine, drinking water Low/high fluoride area	Urine: 2.30 ± 0.28 mg/L (low) 6.13 ± 0.67 mg/L (high) Water: 2.01 ± 0.009 mg/L (low) 5.55 ± 0.41 mg/L (high)	101, 104.44 (12.36) 89, 91.72 (10.66)	101, 104.44 (12.36) 89, 91.72 (10.66)		Table 2
Wang et al. (2007)[105,me, o, u, w] *Cross-sectional*	China	8–12	Urine, drinking water Low fluoride, low arsenic/high fluoride, low arsenic area	Urine: 1.5 ± 1.6 mg/L (low fluoride, low arsenic) 5.1 ± 2.0 mg/L (high fluoride, low arsenic) Water: 0.5 ± 0.2 mg/L (low fluoride, low arsenic) 8.3 ± 1.9 mg/L (high fluoride, low arsenic)	196, 104.80 (14.70) 253, 100.50 (15.80)	196, 104.80 (14.70) 253, 100.50 (15.80)		Table 2, Table 3
Li et al. (2009)[15,me, o, u*] *Cross-sectional*	China	8–12	Urine Endemic fluorosis region caused by coal burning (reference/mild/medium /severe) Degree of dental fluorosis (normal/suspected/ very mild/mild/medium/ severe)	0.962 ± 0.517 mg/L (reference) 1.235 ± 0.426 mg/L (mild) 1.670 ± 0.663 mg/L (medium) 2.336 ± 1.128 mg/L (severe) 0.867 ± 0.233 mg/L (normal) 1.094 ± 0.355 mg/L (suspected) 1.173 ± 0.480 mg/L (very mild) 1.637 ± 0.682 mg/L (mild) 2.005 ± 0.796 mg/L (medium) 2.662 ± 1.093 mg/L (severe)	20, 102.70 (17.61) 20, 93.85 (18.11)	20, 102.70 (17.61) 20, 97.30 (18.56) 20, 93.90 (17.60) 20, 93.85 (18.11)		Table 1
Li et al. (2010)[106,me] *Cross-sectional*	China	7–10	No fluoride measurement Nondental fluorosis children/dental fluorosis children	Not specified	329, 97.36 (18.24) 347, 98.73 (21.07)			Table 3

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Ding et al. (2011)[107,me, u*, rs] *Cross-sectional*	China	7–14	Dental fluorosis (normal/ questionable/very mild/mild/ moderate) Urine Mean urinary fluoride levels (10 groups)	0.80 ± 0.55 mg/L (normal) 1.13 ± 0.73 mg/L (questionable) 1.11 ± 0.74 mg/L (very mild) 1.31 ± 0.78 mg/L (mild) 1.46 ± 0.79 mg/L (moderate) 0.26 mg/L (group 1) 0.45 mg/L (group 2) 0.56 mg/L (group 3) 0.66 mg/L (group 4) 0.75 mg/L (group 5) 0.89 mg/L (group 6) 1.08 mg/L (group 7) 1.33 mg/L (group 8) 1.74 mg/L (group 9) 2.96 mg/L (group 10) Range: 0.10−3.55 mg/L	136, 104.07 (12.30) 28, 103.54 (13.59)	136, 104.07 (12.30) 54, 103.00 (16.10) 74, 102.11 (15.05) 39, 106.03 (12.33) 28, 103.54 (13.59)	−0.59 (−1.09, −0.08) per 1 mg/L urinary F	Table 2, Section 3 Results and discussion (under Fig. 2)
Eswar et al. (2011)[31,me, w] *Cross-sectional*	India	12–14	Drinking water Low/high fluoride villages	0.29 mg/L (low) 2.45 mg/L (high)	65, 88.80 (15.30) 68, 86.30 (12.80)	65, 88.80 (15.30) 68, 86.30 (12.80)		Table 1
Kang et al. (2011)[108me, o] *Cross-sectional*	China	6–12	Drinking water Reference/high fluoride areas (both areas high arsenic exposure)	1.24 ± 0.74 mg/L (all children) <1.2 mg/L (reference) ≥1.2 mg/L (high fluoride)	90, 96.8 (12.7) 178, 96.8 (16.3)			Table 1. Section 2.1
Poureslami et al. (2011)[32,me, w] *Cross-sectional*	Iran	7–9	Drinking water Reference/endemic dental fluorosis city	0.41 mg/L (reference) 2.38 mg/L (endemic)	60, 97.80 (15.95) 59, 91.37 (16.63)	60, 97.80 (15.95) 59, 91.37 (16.63)		Table 3, Results section (under Table 3)
Shivaprakash et al. (2011)[33,me, w] *Cross-sectional*	India	7–11	Drinking water No fluorosis/fluorosis severity groups (mild/moderate/ severe)/all fluorosis	<0.5 ppm (no fluorosis) 2.5–3.5 ppm (mild) 2.5–3.5 ppm (moderate) 2.5–3.5 ppm (severe) 2.5–3.5 ppm (all)	80, 76.36 (20.84) 80, 66.63 (18.09)	80, 76.36 (20.84) 80, 66.63 (18.09)		Table 1

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Seraj et al. (2012)[30,me, w] *Cross-sectional*	Iran	6–11	Drinking water Normal/medium/high fluoride levels	0.8 ± 0.3 mg/L (normal) 3.1 ± 0.9 mg/L (medium) 5.2 ± 1.1 mg/L (high)	91, 97.77 (18.91) 96, 88.58 (16.01)	91, 97.77 (18.91) 106, 89.03 (12.99) 96, 88.58 (16.01)		Table 2
Trivedi et al. (2012)[40,me, w, u] *Cross-sectional*	India	12–13	Urine, ground water Low/high fluoride area	Urine: 0.42 ± 0.23 mg/L (low) 2.69 ± 0.92 mg/L (high) Water: 0.84 ± 0.38 mg/L (low) 2.3 ± 0.87 mg/L (high)	50, 97.17 (17.96) 34, 92.58 (18.25)	50, 97.17 (17.96) 34, 92.58 (18.25)		Table 3, Results section (above Table 3)
Wang et al. (2012b)[109me] *Cross-sectional*	China	Primary school age	No fluoride measurement Reference/high fluoride areas	Not specified	455, 98.36 (14.56) 800, 92.21 (18.45)			Table 1
Bai et al. (2014)[16,me, o] *Cross-sectional*	China	8–12	Urine Coal-burning-borne fluorosis areas (reference/lightly-affected/seriously-affected)	0.54 mg/L (reference) 0.81 mg/L (lightly-affected area) 1.96 mg/L (seriously-affected area)	164, 107.92 (13.62) 162, 101.22 (15.97)			Table 2
Karimzade et al. (2014)[37,me, w] *Cross-sectional*	Iran	9–12	Drinking water Low/high fluoride area	0.25 mg/L (low) 3.94 mg/L (high)	20, 104.25 (20.75) 19, 81.21 (16.17)	20, 104.25 (20.75) 19, 81.21 (16.17)		Table 1

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Broadbent *et al.* (2015)[25,me, w*] *Prospective Cohort*	New Zealand	7–13	Drinking water Area without community water fluoridation (low)/area with community water fluoridation (high) Fluoride tablet use (never/ever) Fluoride toothpaste use (never/sometimes/always)	Water: 0.0–0.3 mg/L (low) 0.7–1.0 mg/L (high) Tablet use: 0 mg (never used) 0.5 mg (ever used) Range not specified for fluoride toothpaste use (always/sometimes/never)	99, 99.80 (14.50) 891, 100.00 (15.10)	99, 99.80 (14.50) 891, 100.00 (15.10)		Table 1
Khan et al. (2015)[34,me] *Cross-sectional*	India	6–11	Drinking water Low fluoride areas (Tiwariganj)/high fluoride areas (Unnao) Fluorosis grades (normal/very mild/mild/moderate/severe)	0.19 mg/L (Tiwariganj) 2.41 mg/L (Unnao) Ranges not specified by fluorosis grades	241, 110.10 (9.00) 5, 62.40 (2.40)			Table/Fig-5
Kundu et al. (2015)[67,sa] *Cross-sectional*	India	8–12	Drinking water Low fluoride areas/high fluoride areas	Not specified	100, 85.80 (18.85) 100, 76.20 (19.10)			Table 2
Sebastian and Sunitha (2015)[35,me, w*] *Cross-sectional*	India	10–12	Drinking water Low/normal/high fluoride villages	0.40 mg/L (low) 1.2 mg/L (normal) 2.0 mg/L (high)	135, 86.37 (13.58) 135, 80.49 (12.67)	135, 86.37 (13.58) 135, 88.60 (14.01) 135, 80.49 (12.67)		Table 1, Table 2
Zhang et al. (2015b)[110,me, w*, u, rs] *Cross-sectional*	China	10–12	Urine, drinking water, serum Reference/high fluoride areas	Urine: 1.10 ± 0.67 mg/L (reference) 2.40 ± 1.01 mg/L (high) Water: 0.63 (0.58–0.68) mg/L (reference) 1.40 (1.23–1.57) mg/L (high) Serum: 0.06 ± 0.03 (reference) 0.18 ± 0.11 serum (high)	96, 109.42 (13.30) 84, 102.33 (13.46)	96, 109.42 (13.30) 84, 102.33 (13.46)	−2.42 (−4.59, −0.24) per 1 mg/L urinary F	Table 1, Table 3

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Zhang et al. (2015c)[70me, o] *Cross-sectional*	China	7−13	Urine Coal-burning endemic fluorosis area Reference (no dental fluorosis)/mild dental fluorosis/middle dental fluorosis/critically ill dental fluorosis	0.83 ± 0.71 mg/L (reference) 1.54 ± 0.57 mg/L (mildly ill) 2.41 ± 0.76 mg/L (moderately ill) 3.32 ± 1.02 mg/L (critically ill)	30, 110.34 (11.52) (reference) 30, 90.52 (10.37) (critically ill)			Table 1, Table 3
Aravind et al. (2016)[68,sa] *Cross-sectional*	India	10−12	Drinking water Low/high fluoride levels	<1.2 ppm (low) >2 ppm (high)	96, 41.03 (16.36) 96, 31.59 (16.81)			Table 1
Das and Mondal (2016)[111,me, u] *Cross-sectional*	India	6–18	Urine, drinking water intake Dental fluorosis (normal/questionable/very mild/ mild/ moderate/severe)	Urine: 2.91 ± 1.76 mg/L (normal) 2.50 ± 2.39 mg/L (questionable) 2.58 ± 1.31 mg/L (very mild) 2.95 ± 1.44 mg/L (mild) 4.82 ± 3.57 mg/L (moderate) 3.81 ± 2.51 mg/L (severe) Water: 0.069 ± 0.021 mg/kg-d (normal) 0.064 ± 0.004 mg/kg-d (questionable) 0.060 ± 0.036 mg/kg-d (very mild) 0.060 ± 0.030 mg/kg-d (mild) 0.099 ± 0.063 mg/kg-d (moderate) 0.093 ± 0.040 mg/kg-d (severe)	4, 108.30 (53.20) 23, 85.91 (37.68)	4, 108.30 (53.20) 17, 103.18 (33.35) 27, 107.70 (27.92) 35, 92.83 (26.90) 43, 84.51 (35.16) 23, 85.91 (37.68)		Table 3
Mondal et al. (2016)[36,me, w] *Cross-sectional*	India	10–14	Drinking water Low/high fluoride areas	Not reported (low) 0.33–18.08 mg/L (high)	22, 26.41(10.46) 18, 21.17 (6.77)	22, 26.41 (10.46) 18, 21.17 (6.77)		Table 9

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Bashash et al. (2017)[112,me, u, rs] *Prospective Cohort*	Mexico	6–12	Maternal urine Reference/high fluoride levels (based on children urinary fluoride)	<0.80 mg/L (reference) ≥0.80 mg/L (high)	77, 95.37 (10.31) 112, 96.80 (11.16)	77, 95.37 (10.31) 112, 96.80 (11.16)	−2.50 (−4.12, −0.59) per 0.5 mg/L maternal urinary F	Abstract, Table 3
Razdan et al. (2017)[73,sa] *Cross-sectional*	India	12–14	Drinking water Low/high fluoride levels	0.6 ppm (low) 4.99 ppm (high)	69, 38.61 (6.34) 75, 13.95 (5.14)			Table 2
Valdez Jiménez et al. (2017)[74sa] *Prospective Cohort*	Mexico	Infancy	Maternal urine, drinking water	Urine: 1.9 ± 1.0 mg/L (1st trimester) 2.0 ± 1.1 mg/L (2nd trimester) 2.7 ± 1.1 mg/L (3rd trimester) Water: 2.6 ± 1.1 mg/L (1st trimester) 3.1 ± 1.1 mg/L (2nd trimester) 3.7 ± 1.0 mg/L (3rd trimester)			Bayley MDI: −19.05 (8.9) per 1 log10 mg/L maternal urinary F (1st trimester) −19.34 (7.46) per 1 log10 mg/L maternal urinary F (2nd trimester)	Table 2, Table 4
Cui et al. (2018)[76,rs] *Cross-sectional*	China	7–12	Urine	Boys: 1.3 (0.9−1.7)[d] mg/L Girls: 1.2 (0.9−1.6)[d] mg/L			−2.47 (−4.93, −0.01) per 1 log urinary F	Table 2
Yu et al. (2018)[3,me, w, u*, rs] *Cross-sectional*	China	7–13	Maternal urine Low/medium/high fluoride ranges Drinking water Normal/high fluoride	Urine: 0.01–1.60 mg/L (low) 1.60–2.50 mg/L (medium) 2.50–5.54 mg/L (high) Water: ≤1 mg/L (normal) >1 mg/L (high) Overall: 0.01−5.54 mg/L (urine) 0.20−3.90 mg/L (water)	1636, 107.40 (13.00) 1250, 106.40 (12.30)	1636, 107.40 (13.00) 1250, 106.40 (12.30)	0.36 (−0.29, 1.01) per 0.5 mg/L maternal urinary F	Table 1, Table 3
Zhao et al. (2018)[86me, o] *Cross-sectional*	China	7–12	Urine Reference/exposed areas All areas with iodine exposure	≤2.16 mg/L (reference) >2.16 mg/L (exposed)	199, 114.52 (12.72) 100, 109.59 (14.24)			Table 4

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Green et al. (2019)[113,me, w*, u*, rs] *Prospective Cohort*	Canada	3−4	Maternal urine, drinking water, maternal fluoride intake Nonfluoridated/ fluoridated area	Urine: 0.40 ± 0.27 mg/L (nonfluoridated) 0.69 ± 0.42 mg/L (fluoridated) Water: 0.13 ± 0.06 mg/L (nonfluoridated) 0.59 ± 0.08 mg/L (fluoridated) Intake: 0.30 ± 0.26 mg/day (nonfluoridated) 0.93 ± 0.43 mg/day (fluoridated) Overall: 0.51 ± 0.36 mg/L (urine) 0.54 ± 0.44 mg/day (intake) 0.31 ± 0.23 mg/L (water)	238, 108.07 (13.31) 162, 108.21 (13.72)	238, 108.07 (13.31) 162, 108.21 (13.72)	−1.95 (−5.19, 1.28) per 1 mg/L maternal urinary F −5.29 (−10.39, −0.19) per 1 mg/L water F −3.66 (−7.16, 0.15) per 1 mg maternal F intake	Table 2, text page 945, eTable 4
Cui et al. (2020)[114,me, u] *Cross-sectional*	China	7–12	Urine Low/medium/high fluoride levels	<1.6 mg/L (low) 1.6–2.5 mg/L (medium) >=2.5 mg/L (high)	396, 112.16 (11.50) 36, 110.00 (14.92)	396, 112.16 (11.50) 66, 112.05 (12.01) 36, 110.00 (14.92)		Table 1

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Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Till et al. (2020)[81,rs] *Prospective Cohort*	Canada	3−4	Residence, maternal urine, drinking water, infant fluoride intake from formula Nonfluoridated areas/fluoridated	Urine: 0.38−0.42 mg/L (nonfluoridated) 0.64−0.70 mg/L (fluoridated) Water: 0.13 mg/L (nonfluoridated) 0.58 mg/L (fluoridated) Intake: 0.02−0.08 mg/day (nonfluoridated) 0.12−0.34 mg/day (fluoridated)			−2.69 (−7.38, 2.01) per 0.5 mg/day infant F intake (formula)	Table 2
Wang et al. (2020b)[4,sa] *Cross-sectional*	China	7−13	Urine, drinking water	Urine: 0.01−5.54 mg/L Water: 0.20−3.90 mg/L			−1.214 (−1.987, −0.442) per 1 mg/L urinary F −1.037 (−2.040, −0.035) per 1 mg/L urinary F (males) −1.379 (−2.628, −0.129) per 1 mg/L urinary F (females); −1.587 (−2.607, −0.568) per 1 mg/L water F −1.422 (−2.792, −0.053) per 1 mg/L water F (males) −1.649 (−3.201, −0.097) per 1 mg/L water F (females)	Table 4
Wang et al. (2020c)[18me, o] *Cross-sectional*	China	7−12	Urine Coal-burning endemic fluorosis area Nonendemic/endemic fluorosis regions	0.461 ± 0.210 mg/L (nonendemic) 0.689 ± 0.502 mg/L (endemic)	100, 97 (20.3) 170, 82.5 (21.7)			Section 2.1, Table 2

Reference[a] ***Study Design***	**Study Location**	**Age Range (Years)**	**Assessment (Metric, Exposure Groups)**	**Fluoride Exposure Levels**	**Mean-effects Meta-analysis** **N, Mean (SD) [Reference] [Exposed]**	**Dose-response Mean-effects Meta-analysis** **N, Mean (SD) [Reference] [Exposed]**	**Regression Slopes Meta-analysis** **Slope (SE) or 95% CI per Unit Change Fluoride**	**Source**
Xu et al. (2020)[115] [me, u*, rs] *Cross-sectional*	China	7−13	Urine Reference/high prenatal exposure only/high childhood exposure only/both prenatal and childhood exposure group	0.82 ± 0.30 mg/L (reference) 0.98 ± 0.29 mg/L (high prenatal exposure only) 2.05 ± 0.58 mg/L (high childhood exposure only) 2.13 ± 0.59 mg/L (both prenatal and childhood exposure group)	228, 123.92 (12.50) 141, 123.04 (11.24)	228, 123.92 (12.50) 107, 119.76 (11.28) 157, 124.65 (10.88) 141, 123.04 (11.24)	−0.055 (−1.626, 1.517) per 1 mg/L urinary F 2.785 (−0.832, 6.403) per 1 mg/L urinary F (<1.7 mg/L) −4.965 (−9.198, −0.732) per 1 mg/L urinary F (≥1.7 mg/L) 4.054 (−3.169, 11.277) per 1 mg/L prenatal urinary F (<1.7 mg/L) −3.929 (−9.396, 1.538) per 1 mg/L prenatal urinary F (≥1.7 mg/L) 3.146 (−1.138, 7.430) per 1 mg/L postnatal urinary F (<1.7 mg/L) −6.595 (−13.323, 0.133) per 1 mg/L postnatal urinary F (≥1.7 mg/L)	Table 1, Table 3, author correspondence
Cantoral et al. (2021)[83sa] *Prospective Cohort*	Mexico	1−2	Maternal fluoride intake	1.12 ± 0.54 mg/day			Bayley III cognitive scores: −1.14 (−3.26, 0.99) per 0.5 mg/L maternal F intake 0.07 (−2.37, 2.51) per 0.5 mg/L maternal F intake (females) −3.50 (−6.58, −0.42) per 0.5 mg/L maternal F intake (males)	Table 3, Table 4

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Guo et al., (2021)[85me] *Cross-sectional*	China	7−12	Urine Reference/exposed areas (all areas with iodine exposure)	1.16 mg/L (reference) 1.29 mg/L (iodine area 1) 2.01 mg/L (iodine area 2)	7−9 years: 71, 116.71 (12.16) 35, 118.11 (12.8) 22, 113.95 (12.26) 10−12 years: 79, 109.86 (12.05) 48, 110.83 (10.58) 44, 105.39 (13.6)			Table 2, Table 3
Ibarluzea et al. (2021)[87sa] *Prospective Cohort*	Spain	1, 4	Maternal urine Nonfluorinated/ fluoridated communities	Urine: 0.38 ± 0.27 mg/L (nonfluorinated) 0.70 ± 0.41 mg/L (fluoridated) Water: <0.1 mg/L (nonfluorinated) 0.81 ± 0.15 mg/L (fluoridated)	Bayley MDI scores: 153, 97.696 (14.91) 160, 100.395 (15.411) McCarthy GCI scores: 123, 98.666 (15.531) 124, 101.473 (15.423)	Bayley MDI scores: 153, 97.696 (14.91) 160, 100.395 (15.411) McCarthy GCI scores: 123, 98.666 (15.531) 124, 101.473 (15.423)	Bayley MDI scores: 4.67 (−1.78, 11.13) per 1 mg/L maternal urinary F 7.86 (−1.68, 17.40) per 1 mg/L maternal urinary F (males) 1.77 (−7.32, 10.87) per 1 mg/L maternal urinary F (females) McCarthy GCI scores: −2.16 (−8.56, 4.23) per 1 mg/L maternal urinary F −1.79 (−11.85, 8.27) per 1 mg/L maternal urinary F (males) −3.60 (−12.07, 4.86) per 1 mg/L maternal urinary F (females)	Section 2.2, author correspondence
Lou et al. (2021)[19me, o] *Cross-sectional*	China	8−12	Coal-burning endemic fluorosis area No fluoride measurement Nondental fluorosis children/dental fluorosis children	Not specified	44, 96.64 (11.70) 55, 88.51 (12.77)			Table 4

Reference[a] *Study Design*	Study Location	Age Range (Years)	Assessment (Metric, Exposure Groups)	Fluoride Exposure Levels	Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Dose-response Mean-effects Meta-analysis N, Mean (SD) [Reference] [Exposed]	Regression Slopes Meta-analysis Slope (SE) or 95% CI per Unit Change Fluoride	Source
Saeed et al. (2021)[116me, o, rs] *Cross-sectional*	Pakistan	5−16	Urine, drinking water Reference/high fluoride areas Co-exposure with arsenic	Urine: 0.24 ± 0.15 mg/L (reference) 3.27 ± 2.60 mg/L (high fluoride) Water: 0.15 ± 0.13 mg/L (reference) 5.64 ± 3.52 mg/L (high fluoride)	30, 100.93 (13.10) 118, 97.26 (15.39)		−3.54 (0.50) per 1 mg/L urinary F	Table 1, Table 3
Wang et al. (2021)[89me, w] *Cross-sectional*	China	9−11	Drinking water Reference/high fluoride areas	1.0 ± 0.07 mg/L (reference) 2.8 ± 0.06 mg/L (high fluoride)	303, 109.0 (14.4) 275, 102.1 (16.3)	303, 109.0 (14.4) 275, 102.1 (16.3)		Section 2.1, Table 2
Zhao et al. (2021)[91rs] *Cross-sectional*	China	6−11	Urine Nonendemic/endemic fluorosis areas	1.03 (0.72, 1.47) mg/L			−5.957 (−9.712, −2.202) per 1 log urinary F	Section 3.1, Table 3

Notes:

SD = standard deviation; SE = standard error; MDI = Mental Development Index; GCI = General Cognitive Index

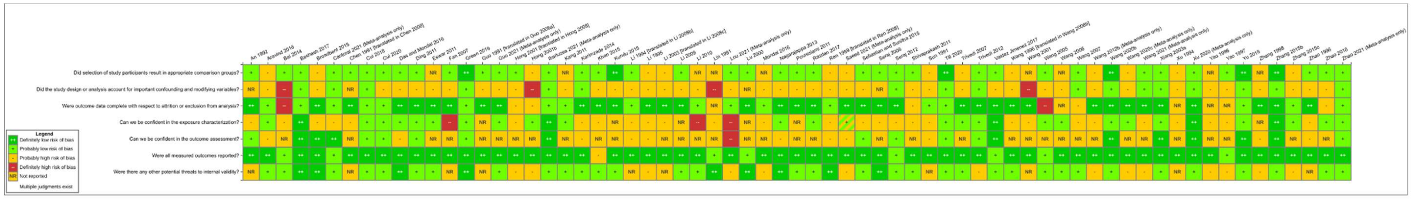
[a]An “me” superscript indicates that the studies included in the *mean-effects meta-analysis*; an “o” superscript indicates a study included in “other” exposures mean-effects analysis (see Table 2 footnote in the main publication); a “w” superscript indicates studies included in the *mean-effects dose-response meta-analysis* using fluoride in water; a “u” superscript indicates studies included in the *mean-effects dose-response meta-analysis* using fluoride in urine; “*” indicates studies included in the *mean-effects dose-response meta-analysis* at levels < 1.5 mg/L; an “rs” superscript indicates studies included in the *regression slopes meta-analysis*.

[b]Additional exposure regions including iodine levels were not included in the analysis.

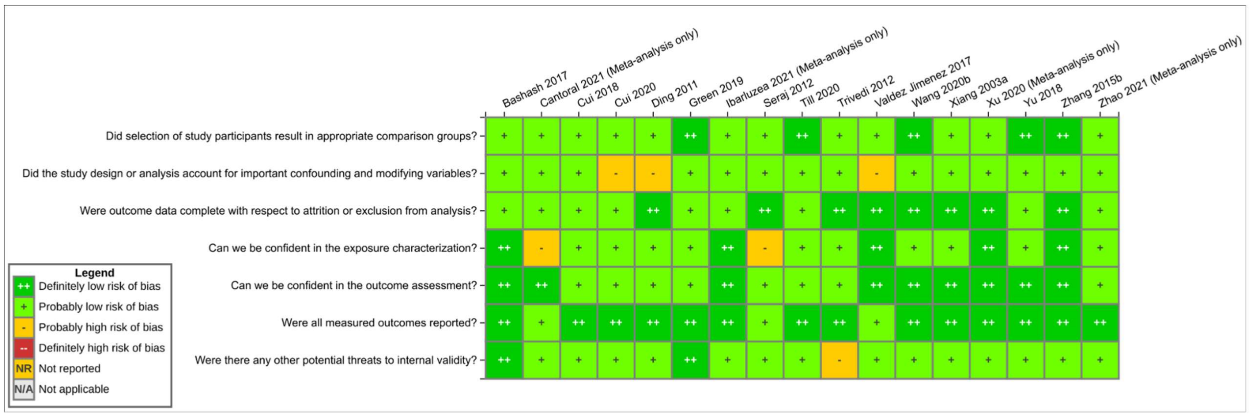
[c]Additional exposure regions including arsenic levels were not included in the analysis.

[d]Median (q1−q3).

(a) All Studies



(b) Low Risk-of-bias Studies



eFigure 2. Results from Risk-of-bias Evaluations for Studies Included in the Meta-analyses and Sensitivity Analyses[a]

Panel (a) presents risk-of-bias results for all studies. An interactive version of eFigure 2(a) is available here: https://hawcproject.org/summary/visual/assessment/405/eFigure-2-Meta-analysis-RoB/. Panel (b) presents risk-of-bias results for low risk-of-bias studies only. An interactive version of eFigure 2(b) is available here: https://hawcproject.org/summary/visual/assessment/405/eFigure-2b-Meta-analysis-RoB-low-RoB-studies/.

The following studies are included in the *mean-effects meta-analysis* and *mean-effects dose-response meta-analysis*: Bashash et al. (2017),[112] Cui et al. (2020),[114] Ding et al. (2011),[107] Green et al. (2019),[113] Seraj et al. (2012),[30] Trivedi et al. (2012),[40] Xiang et al. (2003a),[59] Xu et al. (2020),[115] Yu et al. (2018),[3] and Zhang et al.(2015b).[110]

The following studies are included in the *regression slopes meta-analysis*: Bashash et al. (2017),[112] Cui et al. (2018),[76] Ding et al. (2011),[107] Green et al. (2019),[113] Till et al. (2020),[81] Xu et al. (2020),[115] Yu et al. (2018),[3] Zhang et al.(2015b),[110] and Zhao et al. (2021).[91]

Four studies are only included in sensitivity analyses. All four of these studies are included in sensitivity analyses for the *regression slopes meta-analysis* and include Cantoral et al. (2021),[83] Ibarluzea et al. (2021),[87] Valdez Jiménez et al. (2017),[74] and Wang et al. (2020b).[4] Ibarluzea et al. (2021)[87] is also included in sensitivity analyses for the *mean-effects meta-analysis* and *mean-effects dose-response meta-analysis*.

Mean-effects Meta-analysis

in fluoridated *vs*. non-fluoridated areas in Canada,[113] or in New Zealand.[25] No other studies included in the main *mean-effects meta-analysis* made comparisons between fluoridated *vs*. non-fluoridated areas. In both studies, levels of fluoride in water were low, even in communities with fluoridated drinking water, likely limiting the power to detect an effect.

In Bashash et al.,[112] the SMD compares mean IQ scores in children with urinary fluoride levels below *vs*. above 0.80 mg/L in Mexico.[112] Unlike other studies in the *mean-effects meta-analysis* which compared mean IQ scores between fluoridated *vs*. non-fluoridated areas, or areas with high *vs.* low fluoride exposures (see **eTable 2**), the Bashash et al.[112] study was not designed to measure fluoride exposure by geographical area. However, since the mean IQ scores were provided in the manuscript for children with urinary fluoride levels below *vs*. above 0.80 mg/L, we included them in this analysis. It's worth noting that there was no significant difference when comparing MUF levels between the groups of children with urinary fluoride levels above or below 0.80 mg/L, however when children's IQs were regressed against MUF, a statistically significant inverse association was found.

Commented [I5]: See Doc06a_Meta-analysis, 6a.M., page 8 and 9

Commented [I6]: See Doc06b_Meta-analysis, 6b.C., page 2 and 3

Meta-regression results

The results of the meta-regression models indicate that year of publication and mean age of study children did not explain a large degree of heterogeneity as neither were significant predictors of the relationship between fluoride and children's intelligence, and the residual I^2 remained high (85% and 87%, respectively). Year of publication (SMD = 0.01, 95% CI: -0.01, 0.02) and mean age (SMD = -0.04, 95% CI: -0.13, 0.04) explained relatively little between-study variance (adjusted R^2 of 12% and 5%, respectively). When both year of publication and mean age were included in the model, there were no notable improvements to the amount of between-study variance explained (adjusted R^2 = 13%) or percent residual variation due to heterogeneity (residual I^2 = 85%).

Excluding the outlier study[34] resulted in a slightly lower heterogeneity for the overall effect estimate (I^2=84%) and for the India-specific effect estimate (I^2=69%). The meta-regression indicates that mean age is a significant predictor of the effect (SMD = -0.06, 95% CI: −0.12, −0.01, p-value =0.025), explaining 9% of the between-study variance. Year of publication (SMD = 0.01, 95% CI: 0.001, 0.02, p-value=0.028) explained a larger degree of between-study variance (R^2 = 19 %).

Commented [I7]: See Doc06b_Meta-analysis, 6b.G., page 7 and 8

Commented [I8]: See Doc08_Meta-analysis, 8.E., page 4 and 5

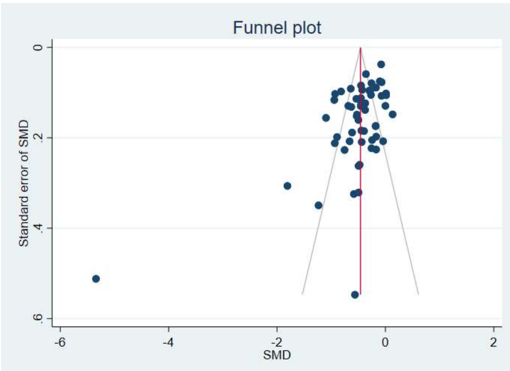
Mean-effects meta-analysis sensitivity analyses

eTable 3. Sensitivity Analyses for Mean-effects Meta-analysis: Pooled SMDs and 95% CIs for Children's IQ Score and Exposures to Fluoride

Commented [I9]: See Doc05_Meta-analysis, 5.D., page 4 and 5

Analysis	Number of Studies	SMD (95% CI)	Heterogeneity p-value	Heterogeneity I²
Excluding Khan et al. (2015)[34]				
	54	−0.43 (−0.51, −0.34)	<0.001	84%
Excluding Lin et al. (1991)[95]				
	54	−0.47 (−0.56, −0.37)	<0.001	87%
Excluding Li et al. (1994)[12] [translated in Li et al. 2008b]				
	54	−0.46 (−0.55, −0.36)	<0.001	87%
Excluding Trivedi et al. (2012)[40]				
	54	−0.46 (−0.56, −0.37)	<0.001	87%
Low risk of bias studies, excluding Trivedi et al. (2012)[40]				
	9	−0.22 (−0.40, −0.04)	<0.001	85%
Including Ibarluzea et al. (2021),[87] Bayley MDI score				
	56	−0.45 (−0.54, −0.36)	<0.001	88%
Including Ibarluzea et al. (2021),[87] McCarthy GCI score				
	56	−0.45 (−0.54, −0.36)	<0.001	87%
Including Aravind et al. (2016),[68] Kundu et al. (2015),[67] Razdan et al. (2017)[73]				
	58	−0.52 (−0.62, −0.42)	<0.001	93%
Including Aravind et al. (2016),[68] Kundu et al. (2015),[67] Razdan et al. (2017)[73], Ibarluzea et al. (2021),[87] Bayley MDI score				
	59	−0.51 (−0.61, −0.40)	<0.001	91%
Including Aravind et al. (2016),[68] Kundu et al. (2015),[67] Razdan et al. (2017)[73], Ibarluzea et al. (2021),[87] McCarthy GCI score				
	59	−0.51 (−0.61, −0.40)	<0.001	91%
Any exposure group				
	55	−0.44 (−0.54, −0.34)	<0.001	91%

Notes:
CI = confidence interval; SMD = standardized weighted mean difference; MDI = Mental Development Index; GCI = General Cognitive Index.



eFigure 3. Funnel Plot of Included Studies

This funnel plot shows individual studies included in the analysis according to random-effect standardized weighted mean difference (SMD) estimates (x-axis) and the standard error (SE) of each study-specific SMD (y-axis). The solid vertical line indicates the pooled SMD estimate for all studies combined and the dashed lines indicated pseudo 95% confidence limits around the pooled SMD estimate.

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
            beta1 =     -3.20
      SE of beta1 =     0.576
                z =     -5.55
       Prob > |z| =    0.0000

Begg's test for small-study effects

Kendall's score =   -299.00
    SE of score =   137.750
              z =     -2.18
     Prob > |z| =    0.0305
```

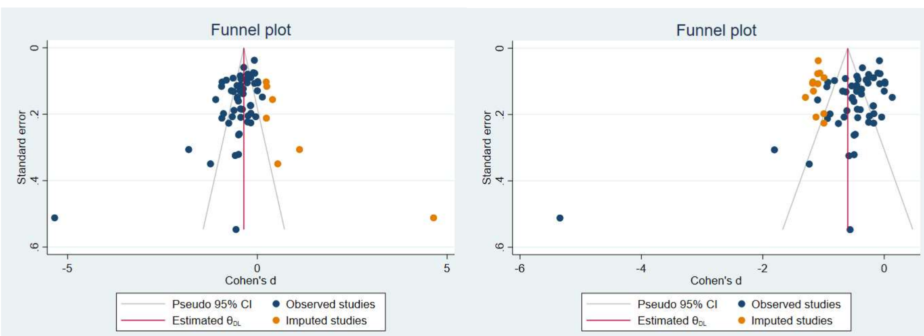
eFigure 4. Test for Publication Bias

```
Nonparametric trim-and-fill analysis of publication bias
Run estimator, imputing on the right

Iteration                        Number of studies =     62
  Model: Random-effects                   observed =     55
 Method: DerSimonian-Laird                imputed =       7

Pooling
  Model: Random-effects
 Method: DerSimonian-Laird

--------------------------------------------------------------
             Studies |      Cohen's d    [95% conf. interval]
---------------------+----------------------------------------
            Observed |         -0.461      -0.554      -0.368
  Observed + Imputed |         -0.357      -0.459      -0.255
--------------------------------------------------------------
```

```
Nonparametric trim-and-fill analysis of publication bias
Linear estimator, imputing on the left

Iteration                        Number of studies =     67
  Model: Random-effects                   observed =     55
 Method: DerSimonian-Laird                imputed =      12

Pooling
  Model: Random-effects
 Method: DerSimonian-Laird

--------------------------------------------------------------
             Studies |      Cohen's d    [95% conf. interval]
---------------------+----------------------------------------
            Observed |         -0.461      -0.554      -0.368
  Observed + Imputed |         -0.601      -0.713      -0.489
--------------------------------------------------------------
```

eFigure 5. Trim-and-fill Analysis

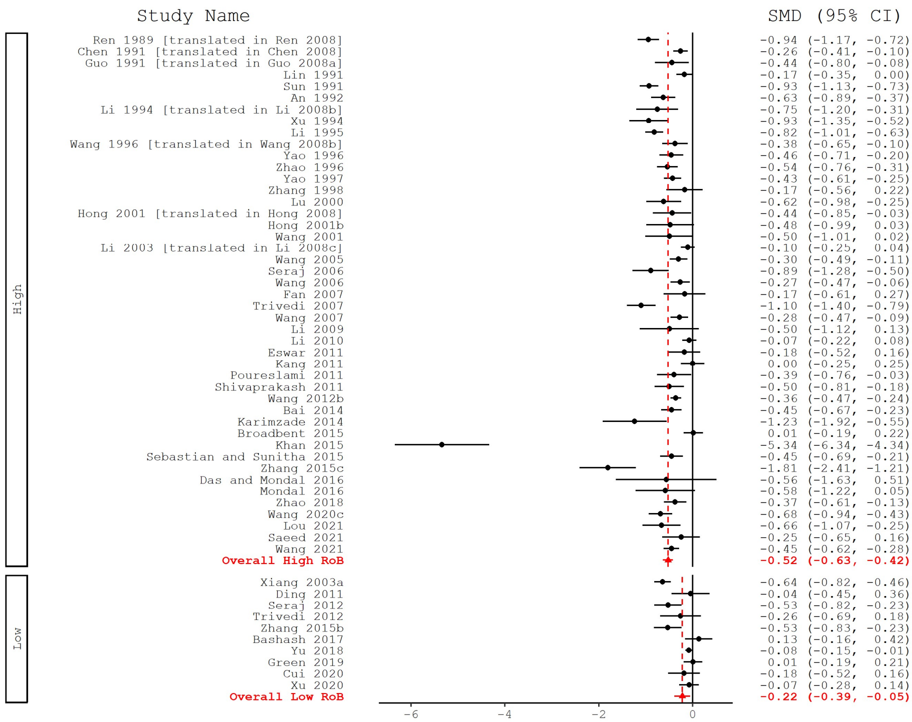
Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator (the linear estimator to the right showed no change in pooled SMD); right panel shows random-effects pooled SMD after filling in to the left using a linear estimator (the run estimator to the left showed no change in pooled SMD).



eFigure 6. Filled-in Funnel Plots to Eliminate Publication Bias

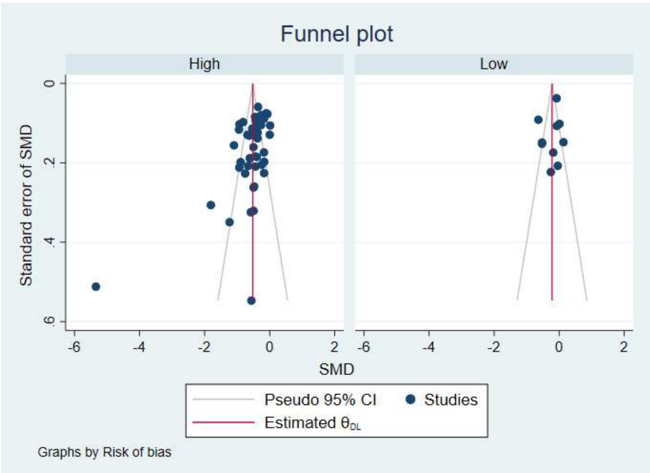
Left panel shows the funnel plot filled in to the right using a run estimator (the linear estimator to the right showed no change in pooled SMD); right panel shows the funnel plot filled in to the left using a linear estimator (the run estimator to the left showed no change in pooled SMD).

Risk-of-bias Subgroup Analysis



eFigure 7. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Risk of Bias

Commented [EAM10]: See Doc06b_Meta-analysis, 6b.W., page 19 through 21.



eFigure 8. Funnel Plot by Risk-of-bias Evaluation

Commented [EAM11]: See Doc06b_Meta-analysis, 6b.W., page 19 through 21.

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird                          High RoB

H0: beta1 = 0; no small-study effects
            beta1 =     -3.41
      SE of beta1 =     0.618
                z =     -5.52
       Prob > |z| =    0.0000

. *meta bias if rob==1, begg rob==1
. meta bias if rob==2, egger random(dl) nometashow

Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird                          Low RoB

H0: beta1 = 0; no small-study effects
            beta1 =     -0.17
      SE of beta1 =     1.835
                z =     -0.09
       Prob > |z| =    0.9275
```

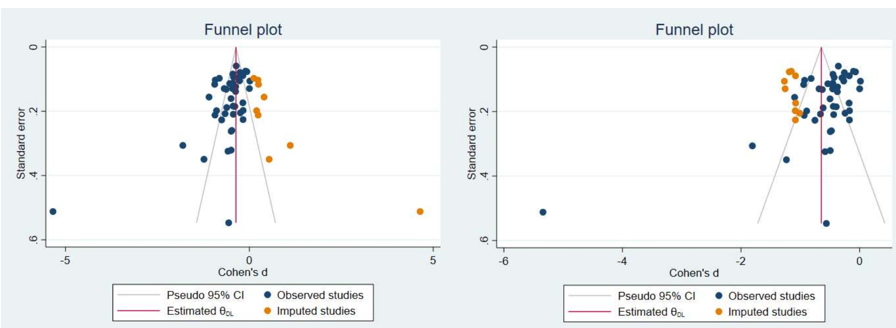
eFigure 9. Test for Publication Bias by Risk of Bias

```
Nonparametric trim-and-fill analysis of publication bias
Run estimator, imputing on the right

Iteration                          Number of studies =     54
  Model: Random-effects                     observed =     45
 Method: DerSimonian-Laird                  imputed  =      9

Pooling
  Model: Random-effects
 Method: DerSimonian-Laird

--------------------------------------------------------------
            Studies |       Cohen's d   [95% conf. interval]
--------------------+-----------------------------------------
           Observed |         -0.521      -0.625      -0.416
  Observed + Imputed |         -0.365      -0.484      -0.246
--------------------------------------------------------------
```

```
Nonparametric trim-and-fill analysis of publication bias
Linear estimator, imputing on the left

Iteration                          Number of studies =     54
  Model: Random-effects                     observed =     45
 Method: DerSimonian-Laird                  imputed  =      9

Pooling
  Model: Random-effects
 Method: DerSimonian-Laird

--------------------------------------------------------------
            Studies |       Cohen's d   [95% conf. interval]
--------------------+-----------------------------------------
           Observed |         -0.521      -0.625      -0.416
  Observed + Imputed |         -0.646      -0.765      -0.526
--------------------------------------------------------------
```

eFigure 10. Trim-and-fill Analysis for High Risk-of-bias Studies

Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

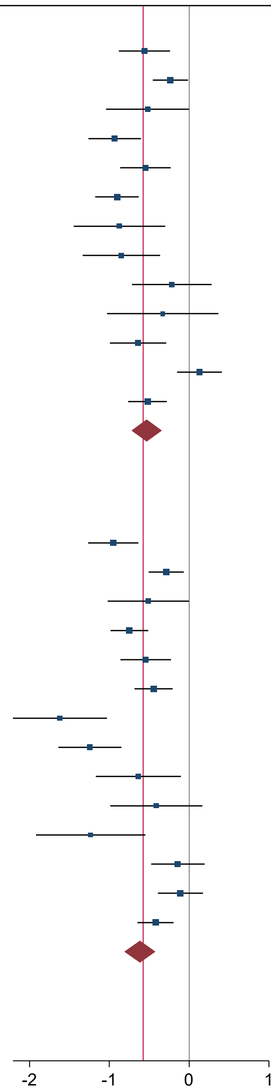


eFigure 11. Filled-in Funnel Plots for High Risk-of-bias Studies

Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator (the linear estimator to the right showed no change in the pooled SMD); right panel shows random-effects pooled SMD after filling in to the left using a linear estimator (the run estimator to the left showed no change in the pooled SMD).

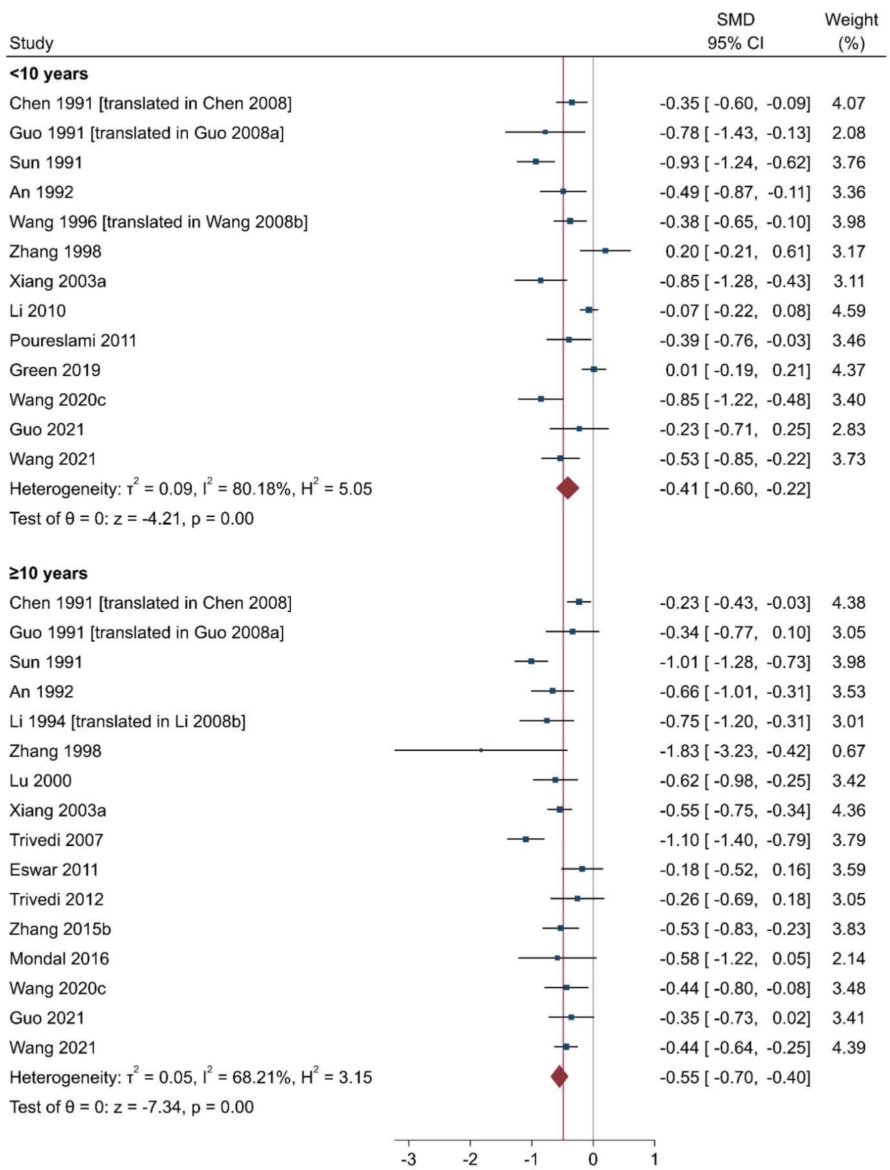
Sex Subgroup Analysis

Study	SMD 95% CI	Weight (%)
Female		
Ren 1989 [translated in Ren 2008]	-0.56 [-0.88, -0.24]	4.09
Chen 1991 [translated in Chen 2008]	-0.24 [-0.46, -0.02]	4.67
Guo 1991 [translated in Guo 2008a]	-0.52 [-1.04, -0.00]	2.95
Li 1995	-0.93 [-1.26, -0.60]	4.03
Zhao 1996	-0.55 [-0.86, -0.23]	4.11
Xiang 2003a	-0.90 [-1.18, -0.63]	4.37
Seraj 2006	-0.87 [-1.45, -0.30]	2.68
Trivedi 2007	-0.85 [-1.33, -0.37]	3.13
Poureslami 2011	-0.22 [-0.72, 0.28]	3.05
Trivedi 2012	-0.33 [-1.03, 0.37]	2.16
Zhao 2018	-0.64 [-1.00, -0.29]	3.88
Green 2019	0.13 [-0.15, 0.41]	4.32
Wang 2021	-0.52 [-0.77, -0.28]	4.55
Heterogeneity: τ^2 = 0.08, I^2 = 73.80%, H^2 = 3.82	-0.53 [-0.72, -0.34]	
Test of θ = 0: z = -5.50, p = 0.00		
Male		
Ren 1989 [translated in Ren 2008]	-0.95 [-1.27, -0.64]	4.12
Chen 1991 [translated in Chen 2008]	-0.29 [-0.51, -0.07]	4.67
Guo 1991 [translated in Guo 2008a]	-0.51 [-1.02, -0.00]	2.99
Li 1995	-0.75 [-0.98, -0.51]	4.59
Zhao 1996	-0.54 [-0.86, -0.23]	4.11
Xiang 2003a	-0.45 [-0.69, -0.21]	4.57
Seraj 2006	-1.62 [-2.21, -1.03]	2.61
Trivedi 2007	-1.25 [-1.64, -0.85]	3.64
Poureslami 2011	-0.64 [-1.17, -0.11]	2.88
Trivedi 2012	-0.41 [-0.99, 0.16]	2.66
Karimzade 2014	-1.23 [-1.92, -0.55]	2.21
Zhao 2018	-0.14 [-0.48, 0.19]	4.00
Green 2019	-0.11 [-0.39, 0.18]	4.30
Wang 2021	-0.42 [-0.65, -0.20]	4.64
Heterogeneity: τ^2 = 0.10, I^2 = 78.33%, H^2 = 4.61	-0.62 [-0.81, -0.42]	
Test of θ = 0: z = -6.26, p = 0.00		



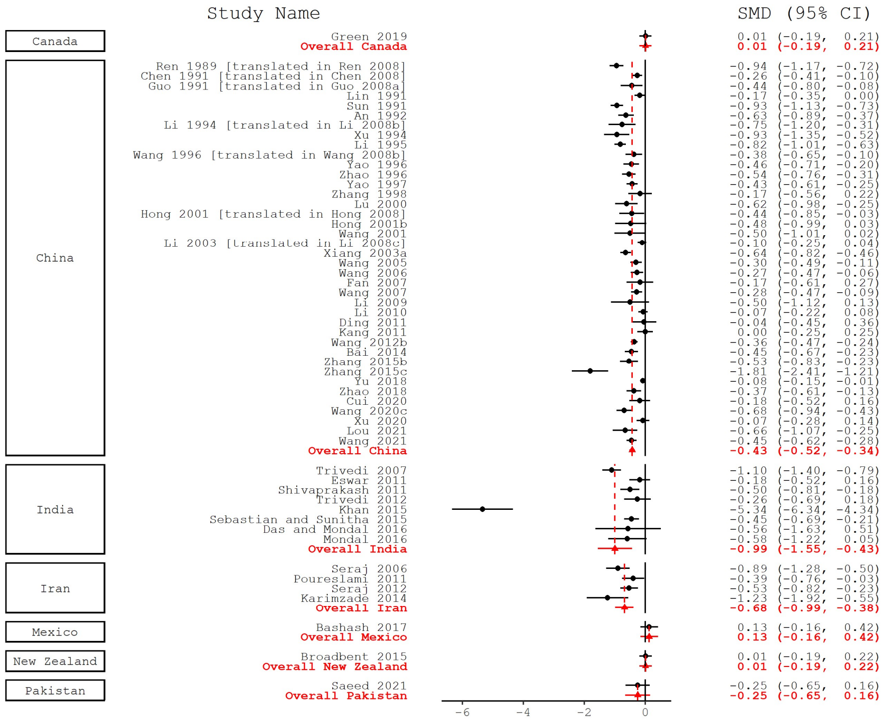
eFigure 12. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Sex

Age Group Subgroup Analysis



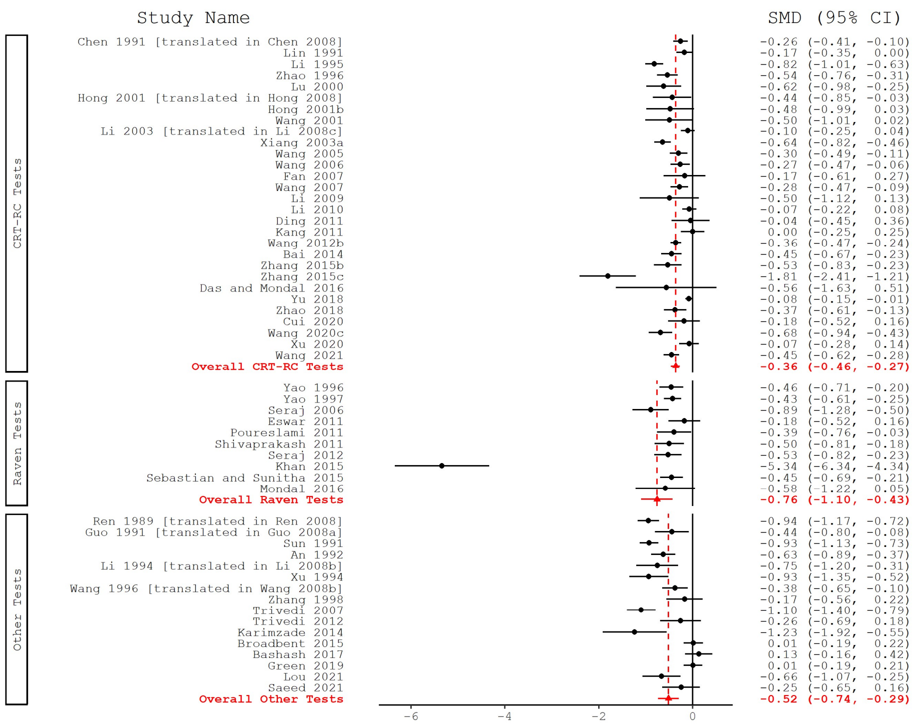
eFigure 13. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Age Group

Country Subgroup Analysis



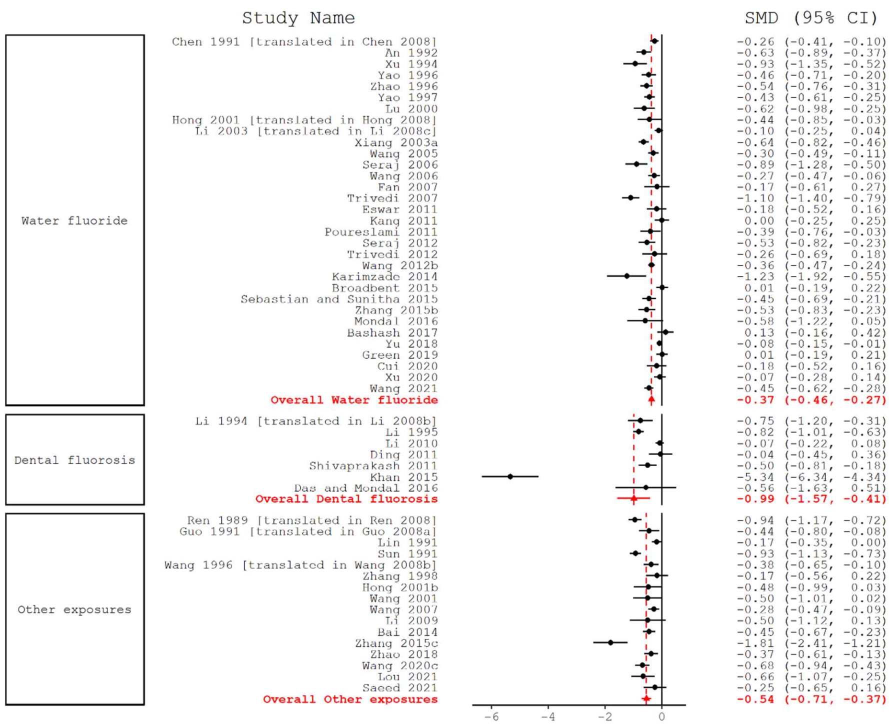
eFigure 14. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Country

Assessment Type Subgroup Analysis



eFigure 15. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Assessment Type

Exposure Type Subgroup Analysis



eFigure 16. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Exposure Type

Exposure types include water, dental fluorosis, and other exposures (iodine, arsenic, aluminum, and fluoride from coal burning).

Dose-Response Meta-analysis Using Mean Effect Estimates

When analyses were restricted to exposed groups with <4 mg/L (i.e., 0 to <4 mg/L) fluoride in drinking water (n = 21 publications [6 low and 15 high risk-of-bias studies]), there was a statistically significant inverse association between fluoride exposure and children's IQ (SMD: −0.22; 95% CI: −0.27, −0.17; p-value < 0.001) (**eTable 4**). When restricted to <2 mg/L (i.e., 0 to <2 mg/L) in drinking water (n = 7 publications [3 low and 4 high risk-of-bias studies]), the magnitude of the effect estimate did not substantially change (SMD: −0.15; 95% CI: −0.41, 0.12; p-value = 0.274). However, when restricted to exposed groups with <1.5 mg/L (i.e., 0 to <1.5 mg/L) in drinking water (n = 7 publications [3 low and 4 high risk-of-bias studies]), there was no longer an association between fluoride in drinking water and children's IQ (SMD: 0.05; 95% CI: −0.36, 0.45; p-value = 0.816). When analyses were further restricted to low risk-of-bias publications at <4 mg/L, <2 mg/L, and <1.5 mg/L, the associations remained in the same direction and were larger in magnitude compared to when data from both low and high risk-of-bias studies were combined (**eTable 4** and **eTable 5**).

When analyses were restricted to exposed groups with <4 mg/L urinary fluoride (n = 13 publications [9 low and 4 high risk-of-bias studies]), there was a statistically significant inverse association between children's urinary fluoride exposure and IQ (SMD: −0.17; 95% CI: −0.30, −0.05; p-value = 0.005) (**eTable 4**). When restricted to <2 mg/L urinary fluoride (n = 7 publications [5 low and 2 high risk-of-bias studies]), there was an inverse association (SMD: −0.06; 95% CI: −0.14, 0.01; p-value = 0.094). When restricted to exposed groups with <1.5 mg/L urinary fluoride (n = 5 publications [4 low and 1 high risk-of-bias studies]), there was an inverse association (SMD: −0.09; 95% CI: −0.16, −0.01; p-value = 0.026). When analyses were further restricted to low risk-of-bias publications, the associations at <2 mg/L and <1.5 mg/L became smaller in magnitude and were statistically significant at <1.5 mg/L (p-value = 0.472 and p-value = 0.028, respectively) (**eTable 4**). Similar results were observed when the maximum likelihood estimation method was used (**eTable 5**).

Commented [I12]: See Doc06a_Meta-analysis, 6a.L., page 7 and 8

Commented [I13]: See Doc06a_Meta-analysis, 6a.L., page 7 and 8

Commented [I14]: See Doc06a_Meta-analysis, 6a.L., page 7 and 8

Commented [I15]: See Doc01_Meta-analysis, 1.P. (page 8) and Doc06b_Meta-analysis, 6b.EE. (page 24 and 25)

eTable 4. Dose-Response Meta-analysis Using Mean Effects—Model Selection[a]

Commented [I16]: See Doc01_Meta-analysis, 1.K., Page 4 and 5

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Water Fluoride – All Studies					
No. Studies/No. Observations Number of Children		29/39 11,656	21/27 8,723	7/9 2,971	7/7 2,832
Linear Model[b]	Beta (95% CI) p-value AIC	−0.15 (−0.20, −0.11) p < 0.001 AIC = 53.8	−0.22 (−0.27, −0.17) p < 0.001 AIC = 16.1	−0.15 (−0.41, 0.12) p = 0.274 AIC = 11.8	0.05 (−0.36, 0.45) p = 0.816 AIC = 8.2
Quadratic Model[c]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.27 (−0.34, −0.21); p < 0.001 0.02 (0.01, 0.03); p < 0.001 AIC = 48.8 p* < 0.001	−0.12 (−0.35, 0.11); p = 0.318 −0.04 (−0.10, 0.03); p = 0.280 AIC = 21.2 p* = 0.012	0.79 (−0.01, 1.58); p = 0.052 −0.56 (−0.97, −0.16); p = 0.006 AIC = 12.5 p* = 0.007	0.30 (−0.53, 1.14); p = 0.477 −0.23 (−1.01, 0.55); p = 0.561 AIC = 11.3 p* = 0.04
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.29 (−0.39, −0.20); p < 0.001 0.48 (0.18, 0.78); p = 0.002 AIC = 42.3 p* < 0.001	−0.14 (−0.34, 0.06), p = 0.162 −0.23 (−0.66, 0.20), p = 0.295 AIC = 16.9 p* = 0.009	1.15 (0.07, 2.22) p = 0.037 −1.20 (−2.03, −0.36) p = 0.005 AIC = 10.5 p* = 0.010	0.49 (−0.50, 1.47) p = 0.334 −0.69 (−2.40, 1.02) p = 0.428 AIC = 10.2 p* = 0.05
Water Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations Number of Children		6/11 4,355	6/9 4,251	3/4 921	3/3 879
Linear model	Beta (95% CI) p-value AIC	−0.19 (−0.34, −0.05) p = 0.009 AIC = 10.3	−0.22 (−0.36, −0.07) p = 0.003 AIC = 3.9	−0.34 (−0.72, 0.03) p = 0.070 AIC = 4.5	−0.32 (−0.91, 0.26) p = 0.276 AIC = 4.1

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	**<4 mg/L**	**<2 mg/L**	**<1.5 mg/L**
Urinary Fluoride – All Studies					
No. Studies/No. Observations Number of Children		18/32 8,502	13/26 6,885	7/11 4,654	5/8 3,992
Linear Model[b]	Beta (95% CI) p-value AIC	−0.16 (−0.24, −0.08) p < 0.001 AIC = 73.8	−0.17 (−0.30, −0.05) p = 0.005 AIC = 68.0	−0.06 (−0.14, 0.01) p = 0.094 AIC = 1.2	−0.09 (−0.16, −0.01) p = 0.026 AIC= 2.8
Quadratic Model[c]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.10 (−0.31, 0.11); p = 0.360 −0.01 (−0.05, 0.02); p = 0.496 AIC = 84.3 p* = 0.14	0.07 (−0.23, 0.38); p = 0.645 −0.07 (−0.16, 0.01); p = 0.071 AIC = 75.8 p* = 0.08	−0.22 (−0.65, 0.20); p = 0.303 0.08 (−0.13, 0.30); p = 0.456 AIC = 9.2 p* = 0.42	0.65 (−1.46, 2.76); p = 0.548 −0.66 (−2.11, 0.80); p = 0.379 AIC = 8.3 p* = 0.10
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.12 (−0.28, 0.04); p = 0.150 −0.10 (−0.43, 0.23); p = 0.545 AIC = 79.6 p* = 0.13	−0.03 (−0.22, 0.16); p = 0.741 −0.24 (−0.47, −0.002); p = 0.048 AIC = 73.3 p* = 0.07	−0.14 (−0.32, 0.04); p = 0.130 0.13 (−0.17, 0.43); p = 0.395 AIC = 8.5 p* = 0.37	−0.52 (−1.65, 0.62); p = 0.371 0.63 (−1.32, 2.59); p = 0.524 AIC = 6.7 p* = 0.07
Urinary Fluoride – Sensitivity analysis including Ibarluzea et al. **(2021)[87] Bayley MDI scores**					
No. Studies/No. Observations Number of Children		19/33 8,815	14/27 7,445	8/12 4,967	6/9 4,305
Linear model	Beta (95% CI) p-value AIC	−0.15 (−0.23, −0.07) p < 0.001 AIC = 75.0	−0.15 (−0.28, −0.03) p = 0.015 AIC = 69.0	−0.04 (−0.14, 0.05) p = 0.371 AIC = 1.7	−0.08 (−0.15, −0.003) p = 0.043 AIC = 3.6
Urinary Fluoride – Sensitivity analysis including Ibarluzea et al. **(2021)[87] McCarthy GCI scores**					
No. Studies/No. Observations Number of Children		19/33 8,749	14/27 7,445	8/12 4,901	6/9 4,239

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Linear model	Beta (95% CI) p-value AIC	−0.15 (−0.23, −0.07) p < 0.001 AIC = 74.5	−0.16 (−0.28, −0.04) p = 0.011 AIC = 68.6	−0.05 (−0.14, 0.04) p = 0.259 AIC = 1.3	−0.08 (−0.16, −0.01) p = 0.036 AIC = 3.0
Urinary Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations Number of Children		9/15 5,713	9/15 5,713	5/8 4,141	4/7 3,952
Linear model	Beta (95% CI) p-value AIC	−0.10 (−0.21, 0.01) p = 0.082 AIC = 5.9	−0.10 (−0.21, −0.01) p = 0.082 AIC = 5.9	−0.05 (−0.17, 0.08) p = 0.472 AIC = 2.8	−0.08 (−0.16, −0.01) p = 0.028 AIC = 2.5

Notes:
AIC = Akaike information criterion; SMD = standardized mean difference; p = p-value for effect estimate; p* = p-value for likelihood ratio tests; MDI = Mental Development Index; GCI = General Cognitive Index

[a]Parameter estimates are changes in SMDs (beta [95% CI]) based on the restricted maximum likelihood models; model fit is represented by the maximum likelihood AIC.

[b]The estimates represent change in SMD for the linear model and AIC, respectively.

[c]The estimates represent change in SMD for the linear term, change in SMD for quadratic term, AIC, and p-values for likelihood ratio test versus linear model, respectively. Potential departure from a linear trend was assessed by testing the coefficient of the quadratic term equal to zero.

[d]The estimates represent change in SMD for the first spline term, change in SMD for the second spline term, AIC, and p-value for likelihood ratio test vs linear model, respectively. Potential departure from a linear trend was assessed by testing the coefficient of the second spline equal to zero.

eTable 5. Dose-response Meta-analysis Using Mean Effects: Maximum Likelihood Models[a]

Commented [I17]: See Doc01_Meta-analysis, 1.K., page 4 and 5

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	**<4 mg/L**	**<2 mg/L**	**<1.5 mg/L**
Water Fluoride – All Studies					
No. Studies/No. Observations Number of Children		29/39 11,656	21/27 8,723	7/9 2,971	7/7 2,832
Linear Model[b]	Beta (95% CI) p-value AIC	−0.15 (−0.20, −0.11) p < 0.001 AIC = 47.9	−0.22 (−0.27, −0.17) p < 0.001 AIC = 10.5	−0.15 (−0.39, 0.08) p = 0.202 AIC = 9.6	0.02 (−0.33, 0.36) p = 0.928 AIC = 6.7
Quadratic Model[c]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.26 (−0.32, −0.20); p < 0.001 0.02 (0.01, 0.03); p < 0.001 AIC = 33.0 p* < 0.001	−0.11 (−0.33, 0.11); p = 0.332 −0.04 (−0.10, 0.02); p = 0.229 AIC= 10.2 p* = 0.012	0.64 (0.04, 1.24); p = 0.036 −0.49 (−0.81, −0.16); p = 0.003 AIC = 8.2 p* = 0.007	0.34 (−0.37, 1.04); p = 0.349 −0.26 (−0.88, 0.35); p = 0.405 AIC = 8.5 p* = 0.04
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.29 (−0.38, −0.21); p < 0.001 0.48 (0.20, 0.78); p = 0.001 AIC = 33.9 p* < 0.001	−0.13 (−0.32, 0.05); p = 0.162 −0.24 (−0.65, 0.16); p = 0.233 AIC= 9.7 p* = 0.009	0.27 (−0.09, 0.62); p = 0.140 −0.44 (−0.83, −0.04); p = 0.029 AIC = 8.9 p* = 0.010	0.26 (−0.26, 0.79); p = 0.321 −0.49 (−1.54, 0.56); p = 0.363 AIC = 8.7 p*= 0.05
Water Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations Number of Children		6/11 4,355	6/9 4,251	3/4 921	3/3 879
Linear model	Beta (95% CI) p-value AIC	−0.19 (−0.31, −0.06) p = 0.003 AIC = 6.7	−0.21 (−0.33, −0.09) p = 0.001 AIC = 0.3	−0.35 (−0.63, −0.07) p = 0.015 AIC = 2.7	−0.34 (−0.80, 0.12) p = 0.153 AIC = 3.3

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Urinary Fluoride – All Studies					
No. Studies/No. Observations Number of Children		18/32 8,502	13/26 6,885	7/11 4,654	5/8 3,992
Linear Model[b]	Beta (95% CI) p-value AIC	−0.16 (−0.23, −0.08) p < 0.001 AIC = 69.2	−0.17 (−0.29, −0.06) p = 0.004 AIC = 64.2	−0.07 (−0.13, 0.003) p = 0.060 AIC = −3.7	−0.12 (−0.36, 0.12) p = 0.325 AIC = 0.8
Quadratic Model[c]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.19 (−0.44, 0.06); p = 0.131 0.01 (−0.02, 0.05); p = 0.462 AIC = 73.0 p*= 0.14	0.08 (−0.21, 0.37); p = 0.587 −0.08 (−0.16, 0.0004); p = 0.051 AIC = 67.2 p* = 0.08	−0.23 (−0.62, 0.17); p = 0.267 0.08 (−0.12, 0.29); p = 0.423 AIC = 1.7 p* = 0.42	−0.11 (−1.45, 1.23); p = 0.868 0.02 (−0.74, 0.77); p = 0.967 AIC = 4.1 p* = 0.10
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.12 (−0.28, 0.04); p = 0.138 −0.10 (−0.41, 0.21); p = 0.524 AIC = 72.9 p*= 0.13	−0.03 (−0.21, 0.15); p = 0.775 −0.24 (−0.47, −0.02); p = 0.034 AIC = 66.8 p* = 0.07	−0.13 (−0.29, 0.03); p = 0.107 0.12 (−0.14, 0.38); p = 0.366 AIC = 1.5 p* = 0.37	−0.26 (−0.72, 0.20); p = 0.270 0.36 (−0.58, 1.29); p = 0.453 AIC = 3.5 p* = 0.07
Urinary Fluoride – Sensitivity analysis including Ibarluzea et al. **(2021)[87] Bayley MDI scores**					
No. Studies/No. Observations Number of Children		19/33 8,815	14/27 7,445	8/12 4,967	6/9 4,305
Linear model	Beta (95% CI) p-value AIC	−0.15 (−0.23, −0.07) p < 0.001 AIC = 70.3	−0.16 (−0.28, −0.04) p = 0.010 AIC = 65.2	−0.06 (−0.13, 0.01) p = 0.086 AIC = −3.2	−0.08 (−0.15 −0.003) p = 0.043 AIC = −1.2
Urinary Fluoride – Sensitivity analysis including Ibarluzea et al. **(2021)[87] GCI scores**					
No. Studies/No. Observations Number of Children		19/33 8,749	14/27 7,445	8/12 4,901	6/9 4,239

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Linear model	Beta (95% CI) p-value AIC	−0.15 (−0.23, −0.07) p < 0.001 AIC = 69.8	−0.16 (−0.28, −0.04) p = 0.008 AIC = 64.9	−0.04 (−0.20, 0.13) p = 0.653 AIC = −0.9	−0.08 (−0.16, −0.01) p = 0.036 AIC = −1.7
Urinary Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations Number of Children		9/15 5,713	9/15 5,713	5/8 4,141	4/7 3,952
Linear model	Beta (95% CI) p-value AIC	−0.10 (−0.20, 0.004) p = 0.059 AIC = 2.0	−0.10 (−0.20, 0.004) p = 0.059 AIC = 2.0	−0.07 (−0.14, 0.01) p = 0.073 AIC = −1.8	−0.08 (−0.16, −0.01) p = 0.028 AIC = −2.2

Notes:
AIC = Akaike information criterion; SMD = standardized mean difference; p = p-value for effect estimate; p* = p-value for likelihood ratio tests; MDI = Mental Development Index; GCI = General Cognitive Index

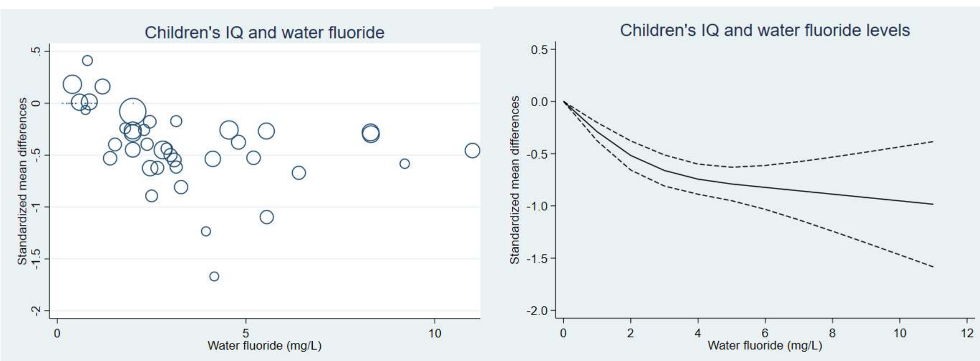
[a]Parameter estimates are changes in SMDs (beta [95% CI]) based on the maximum likelihood models; model fit is represented by the maximum likelihood AIC.

[b]The estimates represent change in SMD for the linear model and AIC, respectively.

[c]The estimates represent change in SMD for the linear term, change in SMD for quadratic term, AIC, and p-values for likelihood ratio test versus linear model, respectively. Potential departure from a linear trend was assessed by testing the coefficient of the quadratic term equal to zero

[d]The estimates represent change in SMD for the first spline term, change in SMD for the second spline term, AIC, and p-value for likelihood ratio test vs linear model, respectively. Potential departure from a linear trend was assessed by testing the coefficient of the second spline equal to zero.

Water Fluoride Exposure



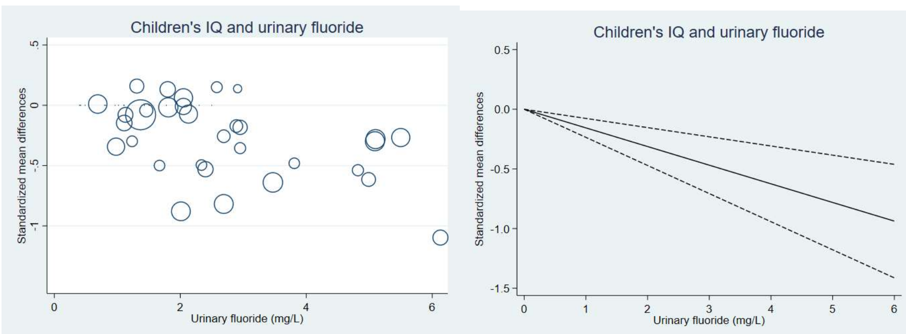
eFigure 17. Pooled Dose-Response Association Between Fluoride in Water and Standardized Mean Differences in Children's IQ

Left panel: circles indicate standardized weighted mean differences (SMDs) in individual studies; size of bubbles is proportional to precision (inverse of variance) of the standardized mean differences. Right panel: Water fluoride levels were modeled with restricted cubic splines terms in a random-effects model (solid line). Dashed lines represent the 95 % confidence intervals for the spline model. Please see eTable 2 for characteristics of the studies included in the *dose-response meta-analysis* (studies with water fluoride exposure and at least two exposure levels).

Commented [I18]: See Doc08_Meta-analysis., 8.R., page 10 and 11

Commented [I19]: See Doc03_Meta-analysis, 3.F., page 4

Urinary Fluoride Exposure



eFigure 18. Pooled Dose-Response Association Between Fluoride in Urine and Standardized Mean Differences in Children's IQ

Commented [I20]: See Doc03_Meta-analysis, 3.F., page 4

Left panel: Circles indicate standardized weighted mean differences in individual studies; size of bubbles is proportional to precision (inverse of variance) of the standardized mean differences. Right panel: Urinary fluoride levels were modeled with a linear random-effects model (solid line). Dashed lines represent the 95 % confidence intervals for the linear model. Please see **eTable 2** for characteristics of the studies included in the *dose-response meta-analysis* (studies with urinary fluoride exposure and at least two exposure levels).

Regression Slopes Meta-analysis

Studies with overlapping populations

Yu et al.[3] and Wang et al.[4] used the same study cohort of children recruited in 2015 from the rural areas of Tianjin City, China. Since Wang et al.[4] (n = 571) used a subset of the original study sample from Yu et al.[3] (n = 2,886), only results from Yu et al.[3] were included in the meta-analysis. A sensitivity analysis was performed to evaluate the impact of using the effect estimate from Wang et al.[4] rather than the pooled effect estimate from Yu et al.[3]. Green et al.[113] and Till et al.[81] used the same Maternal-Infant Research on Environmental Chemicals (MIREC) cohort that reported drinking tap water in 10 Canadian cities, with the studies overlapping for 398 mother-child pairs. Both studies reported effect estimates for maternal urinary fluoride (MUF) and water fluoride concentrations. In the Green et al.[113] study, 512 mother-child pairs had MUF data compared to 398 pairs in Till et al.[81]. Water fluoride levels were available for 420 pairs in Green et al.[113] compared to 398 pairs in Till et al.[81]. Both studies reported effect estimates adjusted for maternal education, maternal race, child's sex, HOME total score, and secondhand smoke status in the child's home. In addition, Till et al.[81] adjusted for child's age at IQ testing (the age range for all children was 3–4 years old). Because of the larger sample size and because covariate adjustments were similar, results from Green et al.[113] were included in the main analysis. However, because of the more adjusted estimates from Till et al.[81] compared to Green et al.[113], a sensitivity analysis was performed using the water fluoride result for formula-fed children and the MUF result from Till et al.[81]. For fluoride from intake, the estimates from both studies were used since they represent total fluoride intake from Green et al.[113] and infant fluoride intake from formula Till et al.[81].

Three studies were excluded with reported slopes because the exposure was measured at the community level.[25, 30, 35] Only one study[116] included in this meta-analysis was considered high risk of bias. For Bashash et al.[112], Yu et al.[3] and Till et al.[81], units of exposure were transformed from 0.5 mg/L to 1 mg/L. Cui et al.[76], and Zhao et al. (2021)[91] reported associations between IQ and log-transformed exposure, and units of exposure were transformed from 1 log mg/L to 1 mg/L[117]. Yu et al.[3] reported estimates from piecewise linear regression models and provided three ranges for urinary fluoride exposure (low 0.01–1.60 mg/L, medium 1.60–2.50 mg/L, high 2.50–5.54 mg/L) and two ranges for water fluoride (low 0.20–3.40 mg/L and high 3.40–3.90 mg/L). Since these piecewise effect estimates are likely correlated, the study-specific pooled effect estimates were used for urine and water fluoride exposures for the overall effect meta-analysis. A sensitivity analysis was performed to evaluate the impact of using pooled estimates rather than piecewise estimates from Yu et al.[3].

For studies reporting multiple measures of fluoride exposure, the results associated with measured or estimated individual-level exposures, biomarker levels (such as urinary fluoride), or fluoride intake levels were prioritized over water fluoride concentrations (see protocol; https://ntp.niehs.nih.gov/go/785076); however, subgroup analyses by exposure metric (urinary fluoride, fluoride intake, and water fluoride) were also performed.

Regression slopes meta-analysis sensitivity analyses

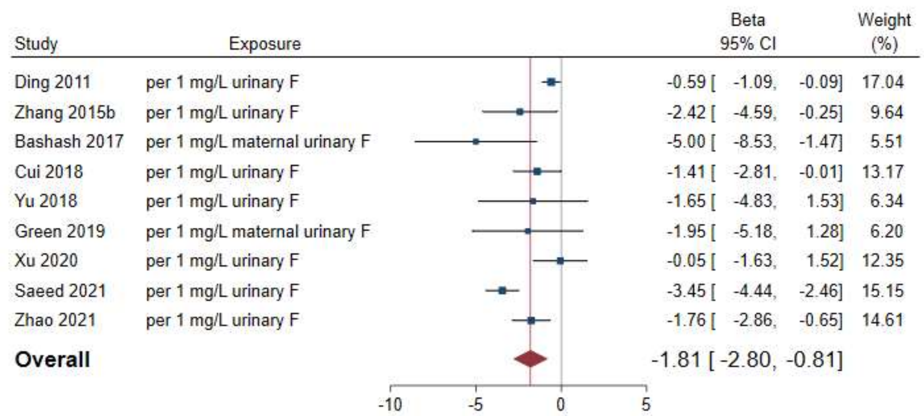
Information about demographic variables was not always accessible, making it difficult to study the impact of potential confounders on effect estimates. Sensitivity analyses for the regression slopes explored the impact of using unadjusted estimates, and results were not significantly impacted (**eTable 6**). Also, most of the estimates used in the *mean-effects meta-analyses* come from studies that used fluoride concentrations at the community level to represent exposure. Therefore, unless community-level clustering is accounted for in the analysis, the standard errors of the difference in means between exposed and reference groups are likely to be biased. This is less of an issue in studies using individual-level exposures (e.g., the *regression slopes meta-analysis*). However, most studies lacked adjustment for clustering,[3, 76, 110] or for complex sampling strategies.[3, 110] Therefore, we performed sensitivity analyses to assess the impact of such issues and there were minimal changes in the pooled slopes (**eTable 6**). In the *regression slopes meta-analysis*, from the Green et al.[113] and Bashash et al.[112] studies, we used the estimates reported from the models using the clustering variable (city or cohort, respectively) as a fixed effect. However, the sensitivity analysis using the regression slopes from the corresponding models with random effects from the Green et al.[113] and Bashash et al.[112] studies,[118, 119] showed that a 1-mg/L increase in urinary fluoride was associated with a statistically significant lower IQ score of 1.80 points (95% CI: −2.80, −0.81). This suggests that clustering is not a significant issue in the results of our *regression slopes meta-analysis*.

eTable 6. Regression Slopes Meta-analysis

Commented [l21]: See Doc05_Meta-analysis, 5.C. (page 3 and 4), 5.D. (page 4 through 6) and 5.F. (page 7 and 8). See Doc06b_Meta-analysis, 6b.W., page 19 through 21.

Analysis	Number of Studies	Beta (95% CI)	Heterogeneity	
			p-value	I^2
Overall Estimate				
Full-scale IQ	9	−1.81 (−2.80, −0.81)	<0.001	77%
Sensitivity Analyses				
Using the piecewise estimates from Yu et al. (2018)[3]				
Full-scale IQ	11	−1.68 (−2.65, −0.71)	<0.001	79%
Using effect estimates from Wang et al. (2020b)[4] rather than Yu et al. (2018)[3]				
Full-scale IQ	9	−1.70 (−2.55, −0.85)	<0.001	77%
Using Till et al. *(2020)[81] rather than Green et al. (2019)[113] estimates*				
Full-scale IQ	9	−1.83 (−2.80, −0.86)	<0.001	77%
Using estimates from random effect models for Green et al. (2019)[113] and Bashash et al. (2017)[112]				
Full-scale IQ	9	−1.80 (−2.80, −0.80)	<0.001	76%
Males	2	−2.39 (−5.89, 1.10)	0.070	69%
Females	2	−0.53 (−3.43, 2.37)	0.186	43%
Excluding Cui et al.[76]				
Full-scale IQ	8	−1.89 (−3.03, −0.74)	<0.001	80%
Excluding Yu et al. (2018)[3] and Zhang et al. (2015b)[110]				
Full-scale IQ	7	−1.76 (−2.90, −0.62)	<0.001	82%
Using unadjusted estimates from Bashash et al. (2017),[112] Cui et al. (2018),[76] Green et al. (2019)[113], Yu et al. (2018)[3]				
Full-scale IQ	9	−1.82 (−2.81, −0.83)	<0.001	76%
Using Verbal or Performance IQ scores from Green et al. (2019)[113]				
Verbal IQ	9	−1.78 (−2.78, −0.79)	<0.001	77%
Performance IQ	9	−1.77 (−2.77, −0.77)	<0.001	77%
Using Bashash et al. (2017)[112] McCarthy GCI scores, Valdez Jimenez et al. (2017)[74] (Bayley MDI scores), Cantoral et al. (2021)[83] (Bayley III cognitive scores), Ibarluzea et al. (2021)[87] (Bayley MDI scores).				
Urinary fluoride	11	−1.78 (−2.78, −0.78)	<0.001	75%
Intake	3	−3.28 (−5.87, −0.68)	0.799	0%
Water fluoride	2	−4.77 (−9.09, −0.45)	0.707	0%
Using Bashash et al. (2017)[112] McCarthy GCI scores, Valdez Jimenez et al. (2017)[74] (Bayley MDI scores), Cantoral et al. (2021)[83] (Bayley III cognitive scores), Ibarluzea et al. (2021)[87] (McCarthy GCI scores).				
Urinary fluoride	11	−1.90 (−2.86, −0.94)	<0.001	73%
Intake	3	−3.28 (−5.87, −0.68)	0.799	0%
Water fluoride	2	−4.77 (−9.09, −0.45)	0.707	0%

Notes:
CI = confidence interval; GCI = General Cognitive Index; MDI = Mental Development Index.

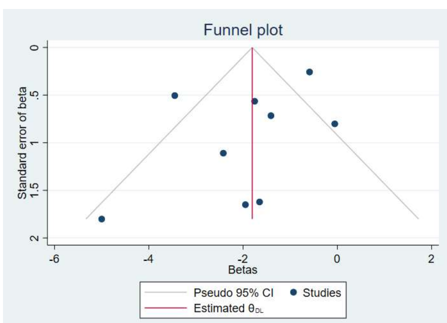


eFigure 19. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Overall Analysis

Estimates (betas) for individual studies are shown with solid boxes representing the weight, and the pooled estimate is shown as a solid diamond. Horizontal lines represent 95% Cis for the study-specific betas.

Commented [I22]: See Doc06b_Meta-analysis, 6b.C., page 2 and 3

Commented [I23]: See Doc06a_Meta-analysis, 6a.M., page 8 and 9



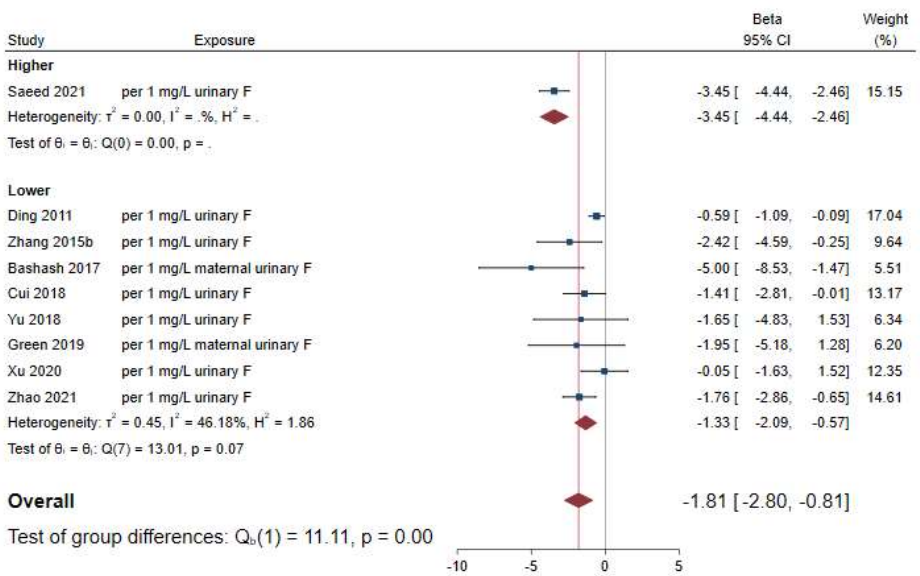
eFigure 20. Funnel Plot for Studies with Individual-level Exposures

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
            beta1 =     -1.06
      SE of beta1 =     1.066
                z =     -1.00
       Prob > |z| =    0.3192
```

eFigure 21. Test for Publication Bias for Studies with Individual-level Exposures

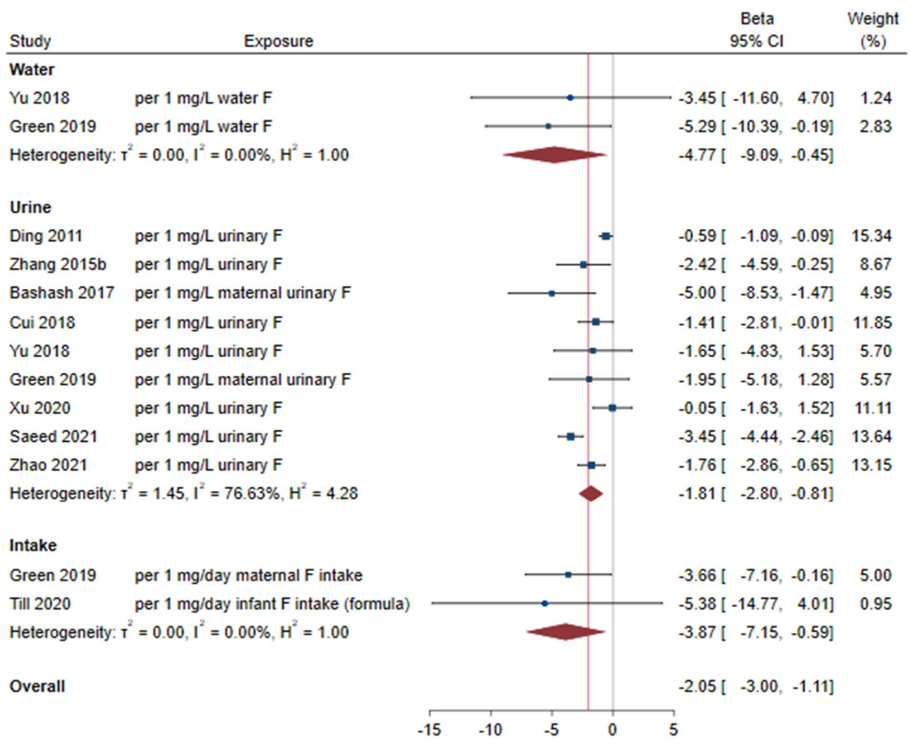
Subgroup Analyses

Risk-of-bias Subgroup Analysis



eFigure 22. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Risk of Bias

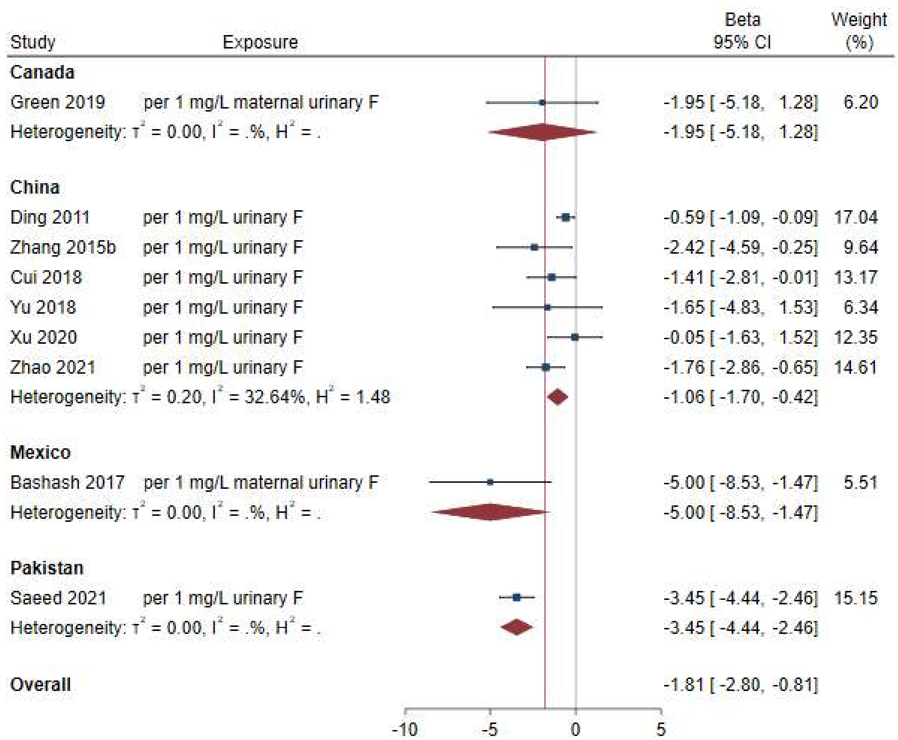
Exposure Type Subgroup Analysis



eFigure 23. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Exposure Type

Commented [I24]: See Doc06b_Meta-analysis, 6b.C., page 2 and 3

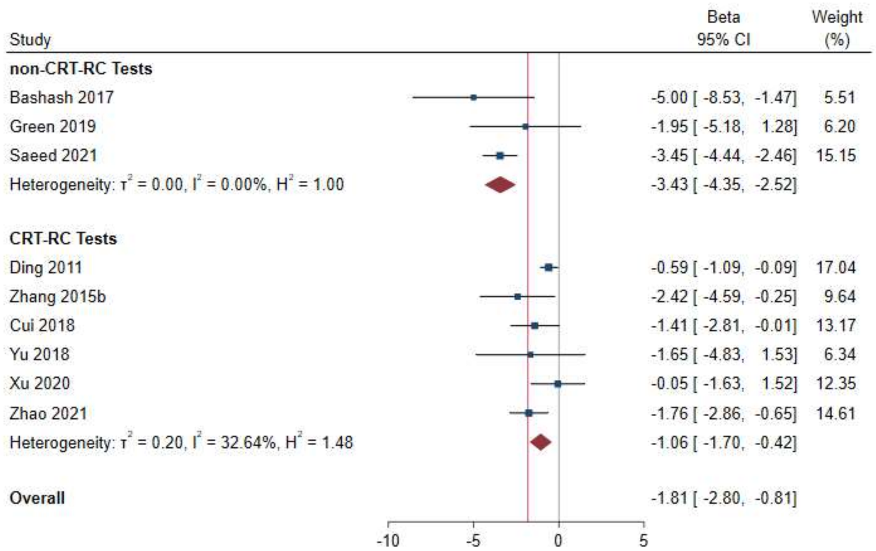
Country Subgroup Analysis



eFigure 24. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Country

Note: The analyses for publication bias for studies from China, Canada, and Mexico rely on a very small number of studies each and are not shown.

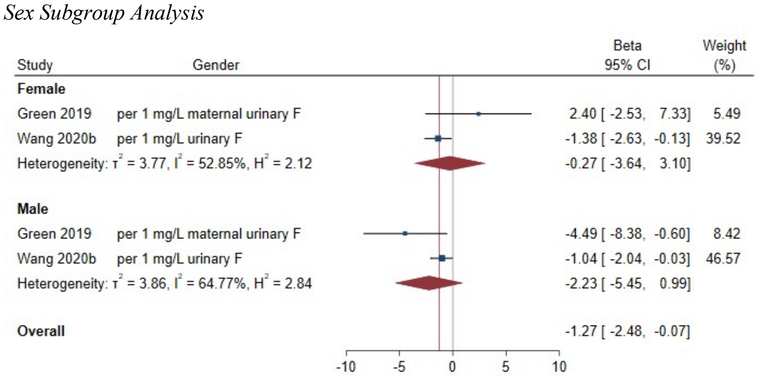
Assessment Type Subgroup Analysis



eFigure 25. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Assessment Type

Note: The analyses for publication bias for CRT-RC studies and non-CRT-RC studies include only six and three studies, respectively, and are not shown.

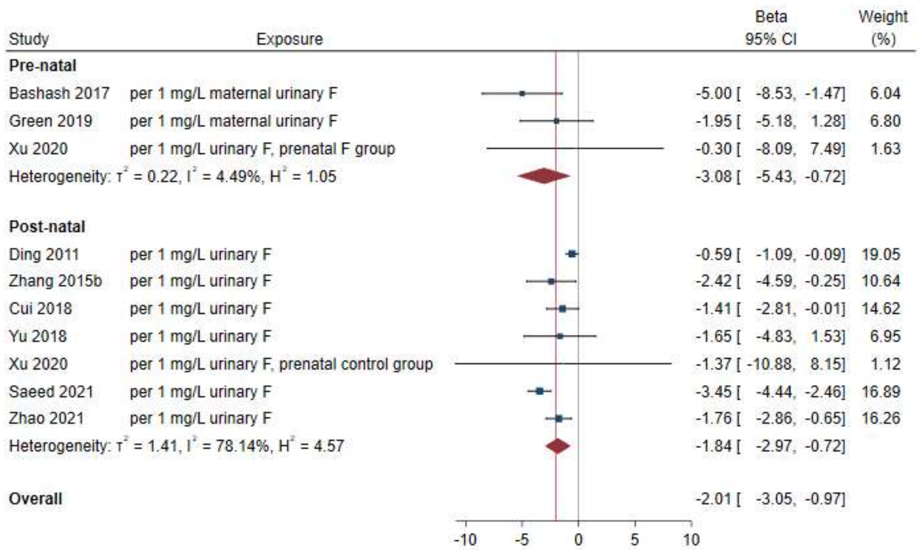
Sex Subgroup Analysis



eFigure 26. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Sex

Note: The analysis for publication bias by gender relies on two studies each and are not shown.

Pre-natal vs post-natal exposure Subgroup Analysis



eFigure 27. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Prenatal vs. Postnatal Exposure

References

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