ADA American Dental Association®

1111 14th Street, N.W.
Suite 1200
Washington, DC 20005

T 202.898.2400
F 202.898.2437
www.ada.org

April 28, 2023

Kathleen M. Gray, Ph.D.
Chair, NTP Board of Scientific Counselors
c/o Office of Policy, Review, and Outreach
Division of Translational Toxicology
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709

Re: NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review

Dear Dr. Gray:

On behalf of our 159,000 members, we would like to share our recommendations for improving the scientific integrity, clarity, transparency, and timeliness of the National Toxicology Program's third (and purportedly final) draft report, titled *Draft NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review*.[1] We offer these comments in response to your Federal Register notice of March 31, 2023 (88 FR 19315).

This systematic review, which has been underway for several years, is intended to summarize the literature about a relationship (if any) between fluoride exposure and neurodevelopmental and cognitive health. The original report has been revised several times, which is a common practice for peer-reviewed papers.

NTP Director Rick Woychik has tasked the NTP Board of Scientific Counselors to determine whether NTP adequately addressed outside questions and criticisms of its methods, conclusions, clarity, and transparency, including those raised by the National Academies of Sciences, Engineering and Medicine.[2,3] NASEM is the acknowledged gold standard for providing independent and objective advice on complex scientific issues.

On May 4, the BSC will hold a virtual meeting to discuss whether and how the draft report should move forward, based on the findings of a BSC Working Group[4] and comments from the public.

We urge the BSC to adopt the following recommendations to improve the report's scientific integrity, clarity, transparency, and timeliness—and to support the lay public's scientific literacy and that of local elected officials who determine community water fluoridation policies. Our reasons, which are detailed in several attachments, are consistent with those expressed by the NASEM peer review committee.[*]

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[*] NTP took the unusual step of abandoning its course of peer review with NASEM after the acknowledged gold standard peer panel twice reported that major revisions were needed for the report to survive scientific scrutiny. Instead, NTP hand-picked its own panel to peer review the third (and purportedly final) draft now being discussed. Changing peer reviewers is not a standard practice.

1. NTP should complete the full course of peer review with its original independent peer review panel, NASEM. (NASEM is the acknowledged gold standard for peer review.)

2. NTP should update and publish its meta-analysis of epidemiological studies, but only after it survives peer review by NASEM or been accepted for publication in a reputable journal, as the BSC Working Group recommended.

3. NTP should provide clear context for statements about low-level fluoride exposures, as NASEM recommended.[2,3]

4. NTP should include a stand-alone disclaimer indicating that the report should not be construed as an indictment of low-level fluoride exposures, as NASEM recommended.[2,3]

5. NTP should revise its risk of bias rating for several studies, based on NASEM's concerns[2,3] and the enclosed analysis.

We call special attention to NTP's apparent aversion to adding a clear, strongly worded disclaimer about the report's treatment of low-level fluoride exposures (<1.5 mg/L), including concentrations recommended for community water fluoridation (0.7 mg/L).

On two occasions, the NASEM committee urged NTP to "state clearly", "[reiterate] at the end", and "make it clear that the monograph cannot be used to draw any conclusions regarding low fluoride exposure concentrations…" The acknowledged gold standard peer review panel also made clear that statements about low-level fluoride exposures were "outside its scope" and that "comments or inferences that are not based on rigorous analyses should be avoided…"[2,3]

NTP ignored that recommendation. Instead, the latest version is full of non-contextualized statements about "potential associations"[1] and the evidence being "unclear." [1] In one area, NTP even states, "[L]ower concentrations of fluoride may support reduced IQ in humans" without offering any data or context to support its claim.

Statements suggesting "more studies are needed"[1] are technically accurate. But without context, the lay reader might conclude the lack of evidence justifies a precautionary approach to community water fluoridation, which the report does not validate.

These non-contextualized statements can easily be misconstrued. In fact, they may be indicative of a desire to retain in some form the blanket hazard assessment that appeared in the first two drafts and was eventually removed after the NASEM committee (2021) determined, "[T]he monograph falls short of providing a clear and convincing argument that supports its assessment."[3]

We strongly urge that all references to "hazard conclusions found in previous draft monographs"[1] be accompanied by a clear follow-up statement indicating why NASEM recommended that those hazard conclusions be withdrawn.

The BSC is now in the fortunate position of knowing how current version of this report will be used. For example, on March 15—the day the current draft was made public—anti-fluoridation activists[5] issued a press release claiming that NTP "could not detect any safe exposure, including at levels common from drinking artificially fluoridated water."[6] The press release further claimed, "There is now little question that a large body of scientific evidence supports a conclusion that fluoride can lower child's IQ, including at exposure levels from fluoridated water."

The non-contextualized language that inspired this rhetoric is exactly why the NASEM committee (2021) urged NTP to "make it clear that the monograph cannot be used to draw any conclusions regarding low fluoride exposure concentrations…"[3]

In the interest of supporting the scientific literacy of both the lay public and local elected officials who determine community water fluoridation policies, **it is critical that the state of the science report, the meta-analysis, and any corresponding press releases or public statements heed NASEM's recommendation to include a disclaimer about low-level fluoride concentrations (<1.5 mg/L).** A disclaimer akin to the following would provide context for the report and help prevent the findings from being misconstrued or mischaracterized.

> *This state of the science report should not be construed as an indictment of consistent low-level fluoride exposures (<1.5 mg/L), including concentrations recommended for community water fluoridation (0.7 mg/L). Community water fluoridation is the purposeful upward adjustment of the naturally occurring fluoride content in water to levels recommended by the United States Public Health Service (0.7 mg/L) to prevent tooth decay.*[7]
>
> *The report should also not be used to draw conclusions about the fluoride content of toothpaste, fluoride supplements, or any other dental treatments.*
>
> *An examination of the literature on low-level fluoride exposures did not validate the hypothesis that consistent exposure to low levels of fluoride (<1.5 mg/L) poses a risk to neurodevelopmental and cognitive health. Additional research may inform that point.*

We strongly urge that a disclaimer of this kind be included in the science report, the meta-analysis, and any corresponding press releases or public statements.

A clear, strongly worded disclaimer of this kind would address the NASEM committee's criticism about the report's lack of context[2,3] and "lack of details in several places and the lack of clarity on several substantive issues."[3] It would also comport with the recommendations of the White House Task Force on Scientific Integrity, which called for federal agencies to adopt better methods of communicating scientific findings to ensure lay audiences have an accurate understanding of science.[8,9]

At a time when the public's trust in federal research is declining,[10] failing to include a disclaimer about low-level fluoride concentrations (and address other shortcomings) could determine whether the public's health will be driven by science…or by unanswered rhetoric.

The Centers for Disease Control and Prevention hailed community water fluoridation as one of ten great public health achievements of the 20th century.[11,12] It is a safe and inexpensive way to reduce tooth decay by at least 25 percent in the population.[13] It would be a shame to distract from over 75 years of public health success over a simple matter of communicating the science, which is often more nuanced than a sound bite can convey.

Thank you for providing us the opportunity to comment. If you have any questions, please contact Mr. Robert J. Burns at 202-789-5176 or burnsr@ada.org.

Sincerely,

/s/ /s/

George R. Shepley, D.D.S.
President

Raymond A. Cohlmia, D.D.S.
Executive Director

GRS:RAC:rjb
Enclosures (5)

References

[1] National Toxicology Program. May 2022. *[Third] Draft NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review*. Office of Health Assessment and Translation, Division of the NTP, National Institute of Environmental Health Sciences, National Institutes of Health, U.S. Department of Health and Human Services. doi:10.22427/NTP-MGRAPH-8

[2] National Academies of Sciences, Engineering, and Medicine. 2020. *Review of the Draft NTP Monograph: Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*. Washington, DC: The National Academies Press. doi:10.17226/25715

[3] National Academies of Sciences, Engineering, and Medicine. 2021. *Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*: A Letter Report. Washington, DC: The National Academies Press. doi:10.17226/26030

[4] National Toxicology Program. April 2023. *NTP Board of Scientific Counselors Working Group Report on the Draft State of the Science Monograph and the Draft Meta-Analysis Manuscript on Fluoride*. Office of Health Assessment and Translation, National Institute of Environmental Health Sciences, National Institutes of Health, U.S. Department of Health and Human Services. Available at: https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2023/may/wgrptbsc20230400.pdf (accessed April 28, 2023)

[5] Quackwatch. A Critical Look at Paul Connett and his Fluoride Action Network [Blog]. April 9, 2013. Available at: https://quackwatch.org/11ind/connett (accessed April 28, 2023)

[6] Fluoride Action Network. Suppressed Government Report Finding Fluoride Can Reduce Children’s IQ Made Public Under EPS Lawsuit. Press Release, March 15, 2023. Available at: https://fluoridealert.org/articles/suppressed-government-report-finding-fluoride-can-reduce-childrens-iq-made-public-under-epa-lawsuit (accessed April 28, 2023)

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

[8] Scientific Integrity Fast-Track Action Committee of the National Science and Technology Council, Protecting the integrity of Government Science, (January 2022). Available at: https://www.whitehouse.gov/ostp/news-updates/2022/01/11/white-house-office-of-science-technology-policy-releases-scientific-integrity-task-force-report (accessed April 28, 2023)

[9] White House Office of Science and Technology Policy. OSTP Releases Framework for Strengthening Federal Scientific Integrity Policies and Practices. Press Release, January 12, 2023. Available at: https://www.whitehouse.gov/ostp/news-updates/2023/01/12/ostp-releases-framework-for-strengthening-federal-scientific-integrity-policies-and-practices (accessed April 28, 2023)

[10] Pew Research Center, Americans’ Trust in Scientists, Other Groups Declines. Report, February 2022. Available at: https://www.pewresearch.org/science/2022/02/15/americans-trust-in-scientists-other-groups-declines (accessed April 28, 2023)

[11] Centers for Disease Control and Prevention. Ten Great Public Health Achievements – United States, 1900-1999. MMWR 1999; 48 (12): 241-243. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/00056796.htm (accessed April 28, 2023)

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[12] Murthy VH, Surgeon General's Perspectives: Community Water Fluoridation—One of CDC's 10 Great Public Health Achievements of the 20th Century, *Public Health Rep* 2015; 130(4): 296-298. doi:10.1177/003335491513000402

[13] American Dental Association, *Fluoridation Facts*, 2018. Available at https://www.ada.org/resources/community-initiatives/fluoride-in-water/fluoridation-facts (accessed April 28, 2023)

ATTACHMENT A
ANALYSIS AND RECOMMENDATIONS

NTP MONOGRAPH ON THE STATE OF THE SCIENCE CONCERNING FLUORIDE EXPOSURE AND NEURODEVELOPMENTAL AND COGNITIVE HEALTH EFFECTS: A SYSTEMATIC REVIEW

NTP MONOGRAPH 08

April 28, 2023

In its third (and purportedly final) draft state-of-the-science report, NTP states, "This review finds, with moderate confidence, that higher fluoride exposure (e.g., represented by populations whose total fluoride exposure approximates or exceeds the World Health Organization Guidelines for Drinking-water Quality of 1.5 mg/L of fluoride) is consistently associated with lower IQ in children."[1]

NTP's claim for a potential association is based on 19 publications it judged to have a low risk-of-bias. The National Academies of Sciences, Engineering and Medicine peer review committee (2021) expressed serious concerns about whether NTP's risk-of-bias methodology was sound and had been consistently applied. There is no indication that those concerns have been resolved to NASEM's satisfaction.[*]

At a time when the public's trust in federal research is declining,[2] the BSC might consider whether the evaluation methods, clarity, transparency, and timeliness of NTP's report—and the piecemeal way NTP plans to release it—will support the lay public's scientific literacy and that of local elected officials who determine community water fluoridation policies. The answer could determine whether public policy will be driven by science…or by unanswered rhetoric.

We therefore ask the BSC to issue the following recommendations to improve the report's scientific integrity, clarity, transparency, and timeliness.

1. NTP should complete the full course of peer review with its original independent peer review panel, NASEM. (NASEM is the acknowledged gold standard for peer review.)

2. NTP should update and publish its meta-analysis of epidemiological studies, but only after it survives peer review by NASEM or been accepted for publication in a reputable journal, as the BSG Working Group recommended.

3. NTP should provide clear context for statements about low-level fluoride exposures, as NASEM recommended.

4. NTP should include a stand-alone disclaimer indicating that the report should not be construed as an indictment of low-level fluoride exposures, as NASEM recommended.

[*] NTP took the unusual step of abandoning its course of peer review with the NASEM committee after the acknowledged gold standard peer reviewer twice reported that major revisions were needed for the report to survive scientific scrutiny. Instead, NTP hand-picked its own panel to peer review the third (and purportedly final) draft now being discussed. Changing peer reviewers is not a standard practice.

5. NTP should revise its risk-of-bias ratings for several studies, based on NASEM's concerns and the enclosed analysis.

1. NTP should complete the full course of peer review with its original independent peer review panel, NASEM. (NASEM is the acknowledged gold standard for peer review.)

At a time when the public's trust in federal research is declining,[2] the public deserves to know that its research agencies are not arbitrarily changing peer reviewers when the results are not to their liking.

NTP began its work by asking NASEM to serve as the report's independent peer reviewer. NASEM is the acknowledged gold standard for providing independent and objective advice on complex scientific issues.

NTP then took the unusual step of abandoning its course of peer review with NASEM after the acknowledged gold standard peer review organization twice reported that major revisions were needed for the report to survive scientific scrutiny.[3,4] Instead, NTP hand-picked its own panel to peer review the third (and purportedly final) draft now being discussed. Arbitrarily changing peer reviewers when the results are not to the authors' liking is not a standard practice.

In the third (and purportedly final) draft, NTP implies it has resolved NASEM's major concerns by stating, "NTP has responded to the NASEM committee's comments on the revised draft (September 16, 2020) in a separate document (placeholder for URL) and revised relevant sections of this monograph."[1] We question NTP's credibility to presume its response to the NASEM committee is adequate.

Replacing a gold standard peer review committee with a hand-picked group of reviewers is not a standard practice. It is not consistent with the spirit of an independent peer review and the action has not been adequately explained in the report. It raises legitimate questions about the report's scientific integrity, as well as NTP's motivations.

NTP should complete the full course of peer review with its original peer review panel, NASEM.

If NTP is intent on proceeding without the full course of peer review without NASEM, NTP needs to immediately release or include a summary of its "separate document"[1] to NASEM in the report itself, which would include an explanation for the "revised relevant sections of this monograph".[1] It is a relatively simple task that would prevent the reader from having to go back and forth between documents to determine what was done and why. Moreover, it would add a level of transparency that is lacking.

Again, the public deserves to know that its research agencies are not arbitrarily changing peer reviewers when the results are not to their liking. The key question is whether an agency's desire to publish an outdated report quickly outweighs the public's need for a report whose evaluation methods, clarity, transparency, and timeliness are beyond reproach.

2. NTP should update and publish its meta-analysis of epidemiological studies, but only after it survives peer review by NASEM or been accepted for publication in a reputable journal.

At a time when the public's trust in federal research is declining,[2] are we simply to take NTP's word that its meta-analysis—which has yet to survive peer review or even be accepted for publication—shows "there was no need to downgrade for publication bias"?[1]

NTP has provided no context for its proposal to publish its meta-analysis separately, or explained why the data are not already compiled in a statistically meaningful manner.

A meta-analysis, which is used to detect publication bias, is essential to a report of this kind. In its first peer review, the NASEM committee (2020) criticized NTP for not performing a meta-analysis, stating, "Given that meta-analysis is a useful tool for aggregating and summarizing data and analyzing comparable studies, the committee strongly recommends that NTP reconsider its decision not to perform one."[3]

In its second peer review, the NASEM committee (2021) expressed serious concerns about the meta-analysis that NTP eventually performed, questioning whether its risk-of-bias methodology was sound and had been consistently applied. The gold standard peer review organization used the term "worrisome remaining inconsistencies"[4] to describe NTP's meta-analysis, noting in its second peer review:[4]

> [I]nconsistencies remain in the application of risk-of-bias criteria to individual studies, particularly in NTP's evaluation of how various studies handled major confounders, co-exposures, and outcomes…For example, Broadbent et al. 2015 and Cui et al. 2020 were deemed high risk for bias for confounding, whereas Trivedi et al. 2012 and others were not…The committee also identified several studies whose classification changed in revisions in the draft monograph without any justification provided (Sudhir et al. 2009; Trivedi et al. 2012; Das and Modal 2016).

The NASEM committee (2021) further reported the need for major revision before NTP's meta-analysis would survive scientific scrutiny, noting:[4]

> The committee had difficulty in following various aspects of the reported methods, identified a few worrisome remaining inconsistencies, was not able to find some key data used in the meta-analysis, and had concern about the wording of some conclusions.
>
> The revised monograph states that it addressed the independence issue, but the exact process used for selection of a single publication remains unclear, and in the meta-analysis, two reports on the same population are inappropriately included…It would be useful for the monograph to identify clearly which publications were derived from which study to minimize concerns about potential selection bias; doing so would also help to define the publications selected for the meta-analysis.
>
> NTP should examine the studies included in the meta-analysis in greater depth to determine whether each study properly accounted for its design because not doing so could invalidate the meta-analysis results.

> It would be useful for the monograph to identify clearly which publications were derived from which study to minimize concerns about potential selection bias; doing so would also help to define the publications selected for the meta-analysis.
>
> NTP should review all its analyses to ensure that overlapping publications are not included in any single meta-analysis. That exercise is especially important given that the issue of "double counting" was a substantive concern of the committee in its first review.
>
> NTP should… [provide] more information on each study result, including the actual result used from each study (SMDs, regression coefficients, and CIs), any data that NTP might have used to calculate the results (for example, means, standard deviations, and sample sizes), and other key information (for example, exposure concentrations of the high- and low-fluoride groups, the method used to assess exposure and outcome, which populations overlap, and information obtained from study authors).
>
> NTP should also include subgroup or sensitivity analyses that respond to the committee's concerns about blinding, complex sampling designs, and statistical analyses that account for clustered study designs.
>
> Information on the meta-analysis protocols and information on the meta-analysis results are presented in several places. That approach forces the reader to go back and forth between sections and between documents to determine what was done or to obtain a clear picture of the meta-analysis findings.

It is unclear whether these issues were resolved to NASEM's satisfaction because NTP removed the meta-analysis from its third draft. Instead, NTP stated, "[The] meta-analysis conducted in association with this systematic review further informs this issue and will be published separately."[1] No context was given for its decision to publish the meta-analysis separately, or why the data were not already compiled in a statistically meaningful manner. NTP also did not give a timeline to ensure the dates of the literature search would be consistent with the state of the science report.

Considering NTP's initial decision to forgo a meta-analysis, we question whether NTP is bound to pursue its publication. We also question whether a journal will accept it for publication and whether it would survive peer review. (It is already rumored that one journal, *JAMA Pediatrics*, did not accept it for publication.)

NTP should be required to publish its meta-analysis, but only after it survives peer review by NASEM or been accepted for publication in a reputable journal. That approach would help satisfy the concerns of those who question why NTP abandoned its peer review with NASEM, which was highly critical of NTP's meta-analysis. It would also add a level of transparency that is lacking.

NTP also needs to update its literature search. This would be consistent with NTP's already stated intent to add at least one more study to the meta-analysis that was not available during the original study period.[†] As the BSC Working Group noted, "[A] journal would likely ask the

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[†] The NTP report states, "NTP is aware that this study was published after April 2021 (Ibarluzea et al. 2021) and, therefore, is not included in this monograph because it is beyond the dates of the literature search…The study will be examined as part of the NTP meta-analysis, which is being prepared as a separate report for publication."

NTP authors to update the literature search."[5]

NTP's finding is based on 19 studies. At least eight more have been published since the study period ended in 2020. One—a meta-analysis by Veneri et al. 2023—was published just four months ago in the journal *Environmental Research*.[6]

Unlike NTP's meta-analysis, Veneri et al. 2023 survived the full course of peer review by its original peer review panel. Veneri et al. found:[6]

> [T]he limitations of most studies…with particular reference to the risk of residual confounding, raise uncertainties about both the causal nature of such relation and the exact thresholds of exposure involved. Such key issues can only be confirmed by additional, high-quality longitudinal studies.

Kumar et al. 2023, another meta-analysis published just this month, reached similar conclusions:[7]

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

In other words, the current state of the science does not validate the hypothesis that fluoride exposure is consistently associated with lower IQ in children. **We therefore support the BSC Working Group's recommendation[5] for NTP to update the study period and publish the report and meta-analysis separately and proximate to one another.**

For clarification purposes, the revised report should survive the full course of peer review with NASEM, and the meta-analysis should survive the full course of peer review with either NASEM or a reputable peer reviewed journal.

In addition to Veneri et al. 2023 and Kumar et al. 2023, NTP should include the following studies:

Aggeborn L, Öhman M. The effects of fluoride in drinking water. *J of Political Economy* 2021;129(2):465-491. doi:10.1086/711915

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

Farmus L, Till C, Green R, et al. Critical windows of fluoride neurotoxicity in Canadian children. *Environmental Res*. 2021;200: 11153. doi.org/10.1016/j.envres.2021.111315

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

Guth, S., Hüser, S., Roth, A. et al. Contribution to the ongoing discussion on fluoride toxicity. *Arch Toxicol* 95, 2571–2587 (2021). doi.org/10.1007/s00204-021-03072-6

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

Xu K, An N, Huang H, et al. Fluoride exposure and intelligence in school-age children: evidence from different windows of exposure susceptibility. *BMC Public Health* 2020;20(1):1657-1664.

Again, at a time when the public's trust in federal research is declining,[2] are we simply to take NTP's word that its meta-analysis—which has yet to survive peer review or even be accepted for publication—shows "there was no need to downgrade for publication bias"? We question whether an agency's desire to publish an outdated report quickly should outweigh the public's need for a report whose methods, conclusions, clarity, transparency, and timeliness are beyond reproach.

3. NTP should provide clear context for statements about low-level fluoride exposures, as NASEM recommended.

The third (and purportedly final) draft report is full of non-contextualized statements about "potential associations"[1] between fluoride exposure and IQ, and the evidence being "unclear."[1] In one area, NTP even states, "[L]ower concentrations of fluoride may support reduced IQ in humans" without offering any data or context to support its claim.[1]

Statements suggesting "more studies are needed"[1] are technically accurate. Without context, however, the lay reader might conclude the lack of evidence justifies a precautionary approach to community water fluoridation.

For example:

> <u>Associations</u> between lower total fluoride exposure [e.g., represented by populations whose total fluoride exposure was lower than the WHO Guidelines for Drinking-water Quality of 1.5 mg/L of fluoride (WHO 2017)] and children's IQ <u>remain unclear</u>.
>
> <u>More studies are needed to fully understand the potential</u> for lower fluoride exposure to affect children's IQ.
>
> <u>More studies at lower exposure levels are needed to fully understand potential associations</u> in ranges typically found in the United States (i.e., <1.5 mg/L in water). However, it should be noted that, as of April 2020, CWS supplying water with ≥1.5 mg/L naturally occurring fluoride served 0.59% of the U.S. population (~1.9 million people) (CDC Division of Oral Health 2020).
>
> Although any effects in the brain or neurological tissue at <u>lower concentrations of fluoride may support reduced IQ in humans</u>, it may be difficult to distinguish the potential effects of

fluoride on learning and memory functions from other neurological or general health outcomes.

These non-contextualized statements can easily be misconstrued. In fact, they may be indicative of a desire to retain in some form the blanket hazard assessment that was removed from the third (and purportedly final) draft after the NASEM committee (2021) determined, "[T]he monograph falls short of providing a clear and convincing argument that supports its assessment."[4]

We strongly urge that all references to "hazard conclusions found in previous draft monographs"[1] be accompanied by a clear follow-up statement indicating why NASEM recommended that those hazard conclusions be withdrawn.

Further, the NASEM committee (2021) made clear that statements about low level fluoride exposures were outside the monograph's purview and inferences about "potential associations"[1]—alongside claims suggesting the evidence is "unclear"[1] or "may support"[1] associations—should be avoided. In its second peer review, the NASEM committee wrote:[4]

> Little or no conclusive information can be garnered from the revised monograph about the effects of fluoride at low exposure concentrations (less than 1.5 mg/L). *NTP therefore should make it clear that the monograph cannot be used to draw any conclusions regarding low fluoride exposure concentrations, including those typically associated with drinking-water fluoridation.* Drawing conclusions about the effects of low fluoride exposures (less than 1.5 mg/L) would require a full dose-response assessment, which would include at a minimum more detailed analyses of dose-response patterns, models, and model fit; full evaluations of the evidence for supporting or refuting threshold effects; assessment of the differences in exposure metrics and intake rates; more detailed analyses of statistical power and uncertainty; evaluation of differences in susceptibility; and detailed quantitative analyses of effects of bias and confounding of small effect sizes. Those analyses fall outside the scope of the NTP monograph, which focuses on hazard identification and not dose-response assessment. *Given the substantial concern regarding health implications of various fluoride exposures, comments or inferences that are not based on rigorous analyses should be avoided…*

NTP needs to provide context for or otherwise remove comments and inferences about low-level fluoride exposures, as the NASEM committee recommended. Doing so would help prevent the lay reader from misconstruing the state of the literature on low-level fluoride exposures, particularly given the most recent studies identified in Recommendation #2.

4. NTP should include a stand-alone disclaimer indicating that the report should not be construed as an indictment of low-level fluoride exposures, as NASEM recommended.

We question why NTP has been so averse to adding a disclaimer clarifying that its literature review did not validate the hypothesis that consistent exposure to low levels of fluoride impact neurodevelopment and cognition. The lay reader would have trouble knowing the report's findings are limited to fluoride exposures that are more than double what the USPHS recommends for community water fluoridation. A disclaimer would help prevent the findings from being mischaracterized in debates about fluoridating local water systems.

Community water fluoridation is an inexpensive way to reduce tooth decay by at least 25 percent in the population.[8] The CDC hailed it as one of ten great public health achievements of the 20th century.[9-10]

Passions run deep about the population-based public health practice of adjusting the fluoride concentration of public water supplies to the levels recommended[11] by the U.S. Public Health Service to prevent tooth decay (0.7 mg/L). In fact, opposition to community water fluoridation has been the driving force for this report.[12,13,14,15]

For over the last 75 years, opponents have argued that fluoride is toxic and causes numerous harmful health effects, fluoride does not prevent tooth decay, fluoridation is costly, and fluoridation interferes with freedom of choice and infringes on individual rights. It was even called a Communist plot in the 1950s and a conspiracy between the U.S. government, the dental-medical establishment, and industry in the 1970s.[8]

NASEM understood the public health ramifications of the report's limited findings being mischaracterized in debates about whether to fluoridate community water systems. In its first peer review, the NASEM committee (2020) wrote:[3]

> The committee found some issues associated with data presentation and communication of various aspects of the process that are discussed further in the context of the evaluation of the animal and human evidence. <u>One particular aspect of communication needs to be emphasized here</u>. Many people are interested in whether water fluoridation to prevent tooth decay poses a threat to human neurodevelopment and cognition. Although the monograph provides some discussion of dose–response relationships, NTP did not conduct a formal dose–response assessment and <u>needs to state clearly that the monograph is not designed to be informative regarding decisions about fluoride concentrations for water fluoridation</u>.
>
> NTP did not conduct a formal dose-response assessment that could inform a discussion on water fluoridation. <u>NTP needs to state clearly that the monograph is not designed to be informative with respect to decisions about the concentrations of fluoride that are used for water fluoridation.</u> That point should be reiterated at the end of the monograph with some indication that its evaluation of the literature is focused on hazard identification of fluoride and that it <u>does not draw any conclusions regarding drinking-water fluoridation or other fluoride sources</u>, such as toothpaste or other dental treatments. Although NTP does not explicitly claim that it has done something other than hazard identification, <u>the context into which the monograph falls calls for much more carefully developed and articulated communication on this issue.</u>

The NASEM committee (2021) reiterated in its second review:[4]

> The report must present its methods clearly, document the results transparently, and <u>provide the rationale for conclusions in such a way that even those who disagree with them will appreciate that the process by which they were derived is clear and was implemented without error</u>. The question is not whether this committee or the multiple audiences come to the same conclusions but rather whether the methods and analysis documented in the monograph support NTP's conclusions…
>
> Little or no conclusive information can be garnered from the revised monograph about the effects of fluoride at low exposure concentrations (less than 1.5 mg/L). *<u>NTP therefore should make it clear that the monograph cannot be used to draw any conclusions regarding low</u>*

> *<u>fluoride exposure concentrations, including those typically associated with drinking-water fluoridation</u>.* Drawing conclusions about the effects of low fluoride exposures (less than 1.5 mg/L) would require a full dose-response assessment, which would include at a minimum more detailed analyses of dose-response patterns, models, and model fit; full evaluations of the evidence for supporting or refuting threshold effects; assessment of the differences in exposure metrics and intake rates; more detailed analyses of statistical power and uncertainty; evaluation of differences in susceptibility; and detailed quantitative analyses of effects of bias and confounding of small effect sizes. Those analyses fall outside the scope of the NTP monograph, which focuses on hazard identification and not dose-response assessment. *Given the substantial concern regarding health implications of various fluoride exposures, <u>comments or inferences that are not based on rigorous analyses should be avoided</u>…*
>
> [I]t is extremely important for it to be able to withstand scientific scrutiny by those who have vastly different opinions on the risks and benefits associated with fluoride exposure. *The committee strongly recommends that NTP improve the revised monograph by seriously considering the suggestions that are provided in this letter report to <u>improve its clarity and transparency</u>.*

NTP ignored NASEM's recommendation. Instead, the report is full of non-contextualized statements about "potential associations"[1] between fluoride exposure and IQ, and the evidence being "unclear."[1] In one area, NTP even states, "[L]ower concentrations of fluoride may support reduced IQ in humans"[1] without offering any data or context to support its claim.

Statements suggesting "more studies are needed"[1] are technically accurate. Without context, however, the lay reader might conclude the lack of evidence justifies a precautionary approach to community water fluoridation.

These non-contextualized statements can easily be misconstrued. In fact, they may be indicative of a desire to retain in some form the blanket hazard assessment that appeared in the first two drafts and was eventually removed after the NASEM committee (2021) determined, "[T]he monograph falls short of providing a clear and convincing argument that supports its assessment."[4]

We strongly urge that all references to "hazard conclusions found in previous draft monographs"[1] be accompanied by a clear follow-up statement indicating why NASEM recommended that those hazard conclusions be withdrawn.

NTP's poorly worded language has already had consequences. For example, on March 15—the day the third (and purportedly final) draft was made public—anti-fluoridation activists[16] issued a press release claiming NTP "could not detect any safe exposure, including at levels common from drinking artificially fluoridated water."[17] The press release further claimed, "There is now little question that a large body of scientific evidence supports a conclusion that fluoride can lower child's IQ, including at exposure levels from fluoridated water."

The press release is consistent with a 2020 editorial from <u>the NTP director who commissioned the report</u>, suggesting that the unpublished, non-peer reviewed second draft was justification enough to end community water fluoridation nationwide.[18,19] It is highly unusual for a researcher to comment on work that has not survived peer review.

The BSC is now in the fortunate position of knowing how the current version of this report will be used. ***NTP should therefore adopt NASEM's recommendation to add a disclaimer about low-level fluoride concentrations to the final report.*** A disclaimer akin to the following would address legitimate concerns about the findings being misconstrued or mischaracterized in debates about fluoridating community water systems.

DISCLAIMER

> ***This state-of-the-science report should not be construed as an indictment of consistent low-level fluoride exposures (<1.5 mg/L), including concentrations recommended for community water fluoridation (0.7 mg/L). Community water fluoridation is the purposeful upward adjustment of the naturally occurring fluoride content in water to levels recommended by the United States Public Health Service (0.7 mg/L) to prevent tooth decay.***
>
> ***The report should also not be used to draw conclusions about fluoride content of toothpaste, fluoride supplements, or any other dental treatments.***
>
> ***An examination of the literature on low-level fluoride exposures did not validate the hypothesis that consistent exposure to low levels of fluoride (<1.5 mg/L) poses a risk to neurodevelopmental and cognitive health. Additional research may inform that point.***

A clear, strongly worded disclaimer of this kind would address the NASEM committee's criticism about the report's lack of context[3,4] and "lack of details in several places and the lack of clarity on several substantive issues."[4] It would also comport with the recommendations of the White House Task Force on Scientific Integrity, which called for better methods of communicating scientific findings to ensure lay audiences have an accurate understanding of science.[20,21]

As the NASEM committee (2021) observed, "[I]t is extremely important for [the monograph] to be able to withstand scientific scrutiny by those who have vastly different opinions on the risks and benefits associated with fluoride exposure."[4] The gold standard peer reviewer therefore urged NTP to "make it clear that the monograph cannot be used to draw any conclusions regarding low fluoride exposure concentrations…"[4]

Crafty language, the former NTP director's editorial, and other actions—such as abandoning the course of peer review with NASEM, removing the criticized meta-analysis (which NTP initially declined to perform), and asking the public to take on faith that there is no need to downgrade a number of risk-of-bias determinations—is consistent with a pattern of behavior that suggests the line between research and activism may have been blurred. We question whether this is typical of how NTP carries-out its work and whether further oversight is needed.

At a time when the public's trust in federal research is declining,[2] the BSC might consider whether the lack of clarity in NTP's report—and the piecemeal way that NTP plans to release it—will contribute to (or detract from) the lay public's understanding of science and that of local elected officials who determine community water fluoridation policies. The answer could determine whether the public's health will be driven by science…or by unanswered rhetoric.

5. NTP should revise its risk of bias rating for several studies, based on NASEM's concerns and the enclosed analysis.

At a time when the public's trust in federal research is declining,[2] are we simply to take NTP's word that its risk-of-bias ratings—which have yet to survive peer review—show "there was no need to downgrade for publication bias"?[1]

The NASEM committee twice expressed serious concerns about the methodology NTP used to determine study bias and questioned whether it had been consistently applied. The gold standard peer review organization used the term "worrisome remaining inconsistencies", noting in its second peer review:[4]

> [I]nconsistencies remain in the application of risk-of-bias criteria to individual studies, particularly in NTP's evaluation of how various studies handled major confounders, co-exposures, and outcomes…For example, Broadbent et al. 2015 and Cui et al. 2020 were deemed high risk for bias for confounding, whereas Trivedi et al. 2012 and others were not…The committee also identified several studies whose classification changed in revisions in the draft monograph without any justification provided (Sudhir et al. 2009; Trivedi et al. 2012; Das and Modal 2016).

A more recent meta-analysis, Veneri et al. 2023, found "noticeable differences of the estimates across categories of overall study quality, with a general trend towards weaker or null associations in the most carefully conducted studies."[6] The authors further noted:[6]

> [T]he serious adverse effect found in lower quality studies according to [risk-of-bias], could be at least in part due to the methodological limitations of those studies, thus increasing the uncertainty about the actual association between fluoride exposure and children's cognitive neurodevelopment and reaffirming the strong need for properly designed and higher quality research on this topic.

Kumar et al. 2023, another meta-analysis published just this month, reached similar conclusions:[7]

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

In terms of NTP's low and moderate risk-of-bias ratings, we note that in a pilot study of 51 children Choi et. al 2015—the <u>sample size is too small</u> to warrant a low risk-of-bias rating.

Two prospective secondary analysis studies—Bashash et al. 2017 and Green et al. 2019—rely on an <u>invalid biomarker</u> (spot maternal urinary fluoride) as a proxy for measuring fetal fluoride exposure. Thomas et al. 2016 reported lack of association between spot maternal urinary fluoride and maternal plasma fluoride in their multiple regression analysis. The Spearman coefficient was 0.29 in first trimester and -0.24 in third trimester. In fact, Thomas et al. 2016 found maternal plasma fluoride levels to be some 40 times lower than urinary fluoride levels.

Using an invalid biomarker alone warrants a high risk-of-bias rating.

Eight papers (based on 11 separate publications) are cross-sectional evaluations of endemic fluorosis areas. Cross-sectional study design cannot rule out reverse causality in endemic fluorosis areas. As stated in Guth et al. 2021:

> It is possible that parents with higher IQ read or inform themselves about the possible health hazards to children, and therefore avoid fluoride exposure. In this case, high maternal/parental intelligence [which is correlated with children's IQ] would be causally linked to lower fluoride exposure rather than high fluoride exposure causing lower intelligence in children.

Except for Yu et al. 2018, these papers also rely on questionable methods, such as non-probability convenience (or purposive) sampling of endemic fluorosis areas and statistical operations that rely on randomness for their validity (e.g., hypothesis testing or linear regression).

Additionally, the authors of the eight papers made no effort to validate the data in the 11 foundational publications, or to scrutinize the analytical methods used for the findings.

For example, the initial confidence is based on comparison of the groups used. Many studies from high fluoride areas do not provide sufficient data to support this key criterion. Notwithstanding other limitations, these eight publications are too sufficiently flawed to warrant a moderate confidence in the body of evidence.

Risk-of-bias. NTP graded a number of studies as having a low risk-of-bias despite acknowledging individual critical elements had a high risk-of-bias. Examples are Ding et al. 2011 (high risk-of-bias for confounding); Rocha-Amador et al. 2007 (high risk-of-bias for selective reporting); Seraj et al. 2012 (high risk-of-bias for exposure assessment); Trivedi et al. 2012 (high risk-of-bias for statistical analysis), etc.

Out of ten publications, nine used a non-probability convenience sample. Only one study (Yu et al. 2018) sampled more than ten villages/towns/cities, which should decrease confidence in the body of evidence. The community-level effect was not adequately addressed in any of the studies. Often, the exposure measure is one or two samples of spot urinary fluoride with or without adjustment for urinary dilution. This is not a valid measure of long-term fluoride exposure. Only one study (Bashash et al. 2017) adjusted for maternal IQ.

Unexplained inconsistencies. Previous meta-analyses have shown substantial unexplained heterogeneity. Duan et al. 2018 conducted a meta-analysis of standardized mean difference in IQ scores between higher water fluoride communities (Mean F=3.7 mg/L) and normal fluoride communities (Mean F=0.6 mg/L). The summary results indicated high water fluoride exposure was associated with lower intelligence levels (standardized mean difference: -0.52; 95% CI: -0.62 to -0.42; $P < 0.001$). However, there was substantial heterogeneity (I^2 =69.1%; $P < 0.001$). The authors were unable to explain the source of heterogeneity. Studies conducted after 2014 show that the effect sizes are smaller and not statistically significant, including Green et al. 2019 and Bashash et al. 2017.

There are also inconsistencies within the same study. For example, Green et al. 2019 (the Maternal-Infant Research on Environmental Chemicals study, or MIREC) reported a differential effect such that the association between maternal urinary fluoride (MUF) and IQ was found only in boys. However, Till et al. 2020 stated that MUF was not statistically significant either in boys or girls once postnatal fluoride was added to the model. Farmus et al. 2021 reported that fluoride exposures (during any trimester, average across all trimesters, infancy, and childhood) was not significantly associated with IQ outcomes after city was controlled and correction for multiple testing was applied. While Bashash et al. 2017 reported a threshold at 0.8 mg/L MUF (ages 6-12 years), Thomas et al. 2014 found no evidence of a detectable adverse outcome on offspring (ages 1-3 years) neurobehavioral development associated with maternal fluoride exposure during pregnancy.

Imprecision. As NASEM observed in its second review, standard errors are underestimated.

> Of most concern are the studies that used fluoride concentration measured at the community level as the exposure—see, for example, Seraj et al. 2012, Till et al. 2020, Trivedi et al. 2012, and Wang et al. 2012. When everyone in a community is subject to the same exposure, the standard error of the difference in means between high-exposure and low-exposure groups increases multiplicatively by the square root of a variance inflation factor (VIF) equal to [1 + (n - 1)r], where n is the number of persons in each community and r is the correlation in outcomes (such as IQ score) between members of the same community (Murray 1998; Donner and Klar 2000; Feng et al. 2001). The same phenomenon occurs in randomized control trials that assign treatment to groups of persons. Thus, unless within-community clustering is accounted for in the analysis—for example, through a random effects model—standard-error estimates will be too small and confidence intervals (CIs) too narrow…For individual-level exposures, such as urinary fluoride concentration, the VIF is probably smaller than one would see for community level exposures because some communities might contain people in multiple exposure groups. However, it is still important to account for clustering in the analysis because one would expect most people in a community to be in the same exposure group.

Note that when the average cluster size is large (e.g., n=66 in Green et al. 2019), even an interclass correlation coefficient of 0.2 will greatly impact VIF.

Publication bias. There is also evidence of publication bias. For example, the Thomas et al. 2014 thesis that showed a beneficial effect of fluoride exposure in the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) was not published. Another example is that Green et al. 2019 do not discuss the lack of effect of MUF on FSIQ in their paper. There was also the sudden removal of a critical sentence from the final pre-print version of Farmus et al. 2021: “However, exposures do not significantly associate with IQ outcomes once city is controlled and FDR is applied.”[22]

Again, at a time when the public’s trust in federal research is declining,[2] are we simply to take NTP’s word that its risk-of-bias ratings—which have yet to survive peer review—show “there was no need to downgrade for publication bias”? We question is whether an agency’s desire to publish an outdated report quickly should outweigh the public’s need for a report whose evaluation methods, clarity, transparency, and timeliness are beyond reproach.

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ATTACHMENT B
RISK-OF-BIAS ASSESSMENT

NTP MONOGRAPH ON THE STATE OF THE SCIENCE CONCERNING FLUORIDE EXPOSURE AND NEURODEVELOPMENTAL AND COGNITIVE HEALTH EFFECTS: A SYSTEMATIC REVIEW
NTP MONOGRAPH 08

A meta-analysis, which is used to detect publication bias, is essential to a report of this kind. The NASEM peer review committee (2021) expressed serious concerns about NTP's meta-analysis, questioning whether its risk-of-bias methodology was sound and had been consistently applied. The gold standard peer review organization used the term "worrisome remaining inconsistencies" to describe NTP's meta-analysis, noting in its second peer review:[1]

> [I]nconsistencies remain in the application of risk-of-bias criteria to individual studies, particularly in NTP's evaluation of how various studies handled major confounders, co-exposures, and outcomes…For example, Broadbent et al. 2015 and Cui et al. 2020 were deemed high risk for bias for confounding, whereas Trivedi et al. 2012 and others were not…The committee also identified several studies whose classification changed in revisions in the draft monograph without any justification provided (Sudhir et al. 2009; Trivedi et al. 2012; Das and Modal 2016).

We urge you to recommend that NTP revisit its meta-analysis to account for more recent literature. This would be consistent with NTP's stated intent to add at least one more study to the meta-analysis that was not available during the original study period, [2] and the BSC Working Group's observation that "[A] journal would likely ask the NTP authors to update the literature search."[3] It would also allow for a more recent meta-analysis, published earlier this year, to be included:

> Veneri F, Vinceti M, Generali L, et al. Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis. *Environmental Res*. 2023 Mar 15;221:115239. doi: 10.1016/j.envres.2023.115239. Epub 2023 Jan 10.

We also urge you to recommend that NTP revisit its risk-of-bias ratings for the studies herein to account for the mitigating factors identified below. These mitigating factors warrant an adjustment to NTP's risk-of-bias determinations.

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[2] The NTP report of May 2022 states, "NTP is aware that this study was published after April 2021 (Ibarluzea et al. 2021) and, therefore, is not included in this monograph because it is beyond the dates of the literature search…The study will be examined as part of the NTP meta-analysis, which is being prepared as a separate report for publication."

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Study	Rationale
Bashash (2017)	NTP rated Bashash et al. (2017) as having a low risk-of-bias. However, the study relies on convenience sampling of spot maternal urinary fluoride—an invalid biomarker—as a proxy for measuring fetal fluoride exposure. Using an invalid biomarker alone warrants a definitely high risk-of-bias rating. This cohort study is based on a convenience sample drawn from multiple hospitals (clusters) in Mexico. Study results based on convenience sampling cannot be used to draw inferences. Spot maternal urinary fluoride is the proxy for fetal exposure. However, Thomas et al. (2016) showed a weak correlation between urinary F and plasma F. There was no association between urinary fluoride and plasma fluoride in a multiple regression analysis. Not a valid biomarker. The source of F is salt. Therefore, the higher fluoride exposure is confounded by higher salt intake, which is associated unhealthy diet and poor pregnancy outcomes. The authors did not assess whether the lower IQ is due to an unhealthy diet. Cantoral et al. (2021) cited this as a limitation in their analysis of the ELEMENT data. The authors did not account for clustering resulting from samples drawn from hospitals. The study is not compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) research methodology, which is a best practice for studies of this kind. To avoid bias, or even the perception of bias, an independent, STROBE-compliant analysis of the MIREC and ELEMENT data is warranted. <u>Selective reporting</u>: This study should receive a definitely high risk-of-bias rating for selective reporting because it excluded the positive findings associated with fluoride exposure from the Thomas et al. (2014) dissertation that analyzed the same ELEMENT cohorts.
Choi (2015)	NTP rated this study as having a low risk-of-bias. However, not only is the sample size too small, but the study also relies on unrelated exposure variables. A high risk-of-bias rating is warranted. This is a pilot study of 51 students in China. The authors also used dental fluorosis as an exposure variable, which is a *postnatal* phenomenon. Dental fluorosis of primary teeth is extremely rare, even in endemic fluorosis areas.

Study	Rationale
Cui (2018) Cui (2020) Wang (2020) Yu (2018) Zhang (2015)	NTP rated Cui et al. (2018), Cui et al. (2020), Wang et al. (2020), Yu et al. (2018), and Zhang et al. (2015) as having a low risk-of-bias. However, the study designs (cross-sectional) do not account for reverse causality, which is likely in these cases. A high risk-of-bias determination is warranted. These publications are from a more extensive study of 2886 resident children, aged 7 to 13 years, randomly from endemic and non-endemic fluorosis areas in Tianjin, China (Yu et al. (2018)). Used a complex survey design (stratified sampling of clusters from endemic and non-endemic fluorosis areas). Cui et al. (2018), Cui et al. (2020), and Zhang et al. (2015) selected a subset of schools based on IQ scores and F levels, leading to selection bias. However, the authors did not account for the complex survey design and the standard errors are therefore underestimated. There is a possibility of Type 1 error. Exposure measure is a spot urinary fluoride of unproven validity. NTP highlighted only the statistically significant results but left out the results that did not show statistically significant results. Yu et al. (2018) showed a threshold effect such that there is no effect of fluoride on IQ below 3.4 mg/L fluoride in water (B=−0.04 (−0.33, 0.24)) or below 1.6 mg/L urinary F (B=0.36 (−0.29, 1.01)).
Ding (2011)	NTP rated Ding et al. (2011) as having a low risk-of-bias despite finding a high risk-of-bias for confounding. The cross-sectional study design also does not account for reverse causality, which is likely in this case. A high risk-of-bias rating is therefore warranted. The authors selected schools from 4 sites in Inner Mongolia, China. All four sites were in endemic and nonendemic fluorosis areas. The authors did not account for the cluster sampling design. The standard errors are therefore underestimated. Additionally, the regression equation included only age.
Green (2019) Till (2020)	NTP rated Green et al. (2019) and Till et al. (2020) as having a low risk-of-bias. However, both studies rely on spot maternal urinary fluoride—an invalid biomarker—as a proxy for measuring fetal fluoride exposure. An invalid biomarker alone justifies a high risk-of-bias rating. NTP also lists these as prospective cohort studies; however, there is only one IQ measurement. Had Green et al. (2019) and Till et al. (2020) assessed the validity of this biomarker, they would have found that Thomas et al. (2016) reported lack of association between spot maternal urinary fluoride and maternal plasma

Study	*Rationale*
	fluoride in their multiple regression analysis. The Spearman coefficient was 0.29 in first trimester and -0.24 in third trimester. In fact, Thomas et al. (2016) found maternal plasma fluoride levels to be some 40 times lower than urinary fluoride levels. With respect to Green et al. (2019), the convenience sample was drawn from seven hospitals in six cities (clusters) in Canada, creating a hierarchical data structure. The statistical analysis did not adequately account for the city-level effect. IQ varied by as much as 8 points between the non-fluoridated cities of Vancouver and Kingston (page 30, Green 2018 Master's Thesis). A single staff person from each study site administered in-person IQ assessments. Thus, the assessor was matched to the city. This would be considered a fatal flaw in any RCT or case-control study. Further, Green et al. (2019) is not compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) research methodology, which is a best practice for studies of this kind. To avoid bias, or even the perception of bias, an independent, STROBE-compliant analysis of the MIREC and ELEMENT data is warranted. In its peer review of NTP's second draft, the NASEM (2021) committee reported[1]: In the case of Green et al. (2019), NTP learned from the investigators that accounting for city-level clustering via a random-effects model "showed similar results to the main model." More details should be provided regarding the similarity of results because although overall conclusions might not have changed, the results of the meta-analysis could be affected by incorrect exposure-effect or standard-error estimates. The Canadian Agency for Drug and Technologies in Health also analyzed Green et al. (2019) study and determined a high risk-of-bias in the study[2]: The study by Green et al., 2019 concluded that "maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years." (p. E1) This conclusion was not supported by the data... Between nonfluoridated and fluoridated maternal exposure (assessed by MUF_{SG} or daily fluoride intake), the difference in mean FSIQ in total children (108.07 ± 13.31 versus 108.21 ± 13.72) was minimal. The average FSIQ in boys in the non-fluoridated and fluoridated groups were 106.31 ± 13.60 and 104.78 ± 14.71, respectively, and in girls were 109.86 ± 12.83 and 111.47 ± 11.89, respectively. According to the WPPSI test scoring, these numbers were considered as normal, as a score of 90 to 109 represents average intelligence.

Study	*Rationale*
	Given that these values were available during data collection period, it was unclear about the authors' rationale to further explore the associations between maternal fluoride exposure and children's IQ. Indeed, adjusted estimates with a limited set of covariates showed no statistically significant association between an increase of 1 mg/L in MUFSG and FSIQ, PIQ or VIQ in all children. These were not discussed or considered when formulating the conclusion. Additionally, Health Canada evaluated Green et al. (2019) and concluded[3]: The authors identified limitations in the study and where possible implemented measures to reduce their impact. However, a number of uncertainties remain (e.g., estimation of prenatal fluoride exposure, other unmeasured factors affecting child IQ) which limit this study's ability to confirm a causal relationship between prenatal fluoride and deficits in child IQ. Health Canada and CADTH evaluations are included as Attachments C and D, respectively. With respect to Till et al. (2020), the authors reported that after postnatal exposure was introduced into the model, maternal urinary fluoride was not associated with FSIQ in boys or girls. The authors found two outliers in the same cohort, and the association became non-significant when two outliers were removed. NTP reports correspondence with Till about assessors lack of knowledge of fluoridation status; however, Till neglected to mention that a single staff person from each study site administered in-person IQ assessments of 3 and 4 year-olds. Thus, the assessor was matched to the city with no attempt to assess inter-rater reliability. This would be considered a fatal flaw in any RCT or case-control study.
Rocha-Amador (2007)	NTP rated Rocha-Amador et al. (2007) as having a low risk-of-bias overall despite finding a high risk-of-bias for selective reporting. The cross-sectional study design does not account for reverse causality, which is likely in this case. A high risk-of-bias rating is therefore warranted. This cross-sectional study of 132 children of age 6-10 was conducted in areas of Brazil where mean levels of Arsenic in water were 17 and 19 times higher than WHO limits in Salitral (mean F level in water 5.3 mg/L) and 5 de Febrero (9.4 mg/L F), respectively. However, it was not included in the regression model.

Study	Rationale
	While height for age was included in the model, age was not. Mothers' education levels differed among the three areas with low fluoride community with the highest level of education. This community-level effect was not controlled. Therefore, NTP noted that the results might still be biased.
Saxena (2012)	NTP rated Saxena et al. (2012) as having a low risk-of-bias. However, the cross-sectional study design does not account for reverse causality, which is likely in this case. A high risk-of-bias grading is therefore warranted. This is a cross-sectional study of 120 children in India from 3 endemic areas, and 50 children from 1 non-endemic area were included in the analysis. The mean urinary fluoride level in the non-endemic areas was 2.25 mg F/L which is about three times higher compared to a fluoridated area. NTP correctly noted that the author's use of linear regression for an ordinal IQ outcome with five levels was inappropriate. Similarly, the authors used ANOVA for socioeconomic status and other variables measured with an ordinal scale. This alone should have received a high risk-of-bias rating.
Seraj (2012)	NTP rated Seraj et al. (2012) as having a low risk-of-bias overall despite finding a high risk-of-bias for exposure assessment. However, the cross-sectional study design does not account for reverse causality, which is likely in this case. A high risk-of-bias rating is therefore warranted. This cross-sectional study of 293 6- to 11-year-old children in Iran from five selected rural areas. The authors state that these areas were similar in their general demographic and geographic characteristics, with the inhabitants having a comparable socioeconomic status and similar occupations. However, there is no data to support the comparability of areas. NTP somehow found indirect evidence of comparability. NTP rated probably high risk-of-bias for exposure assessment. The authors did not provide data to indicate that the mean was representative of the fluoride levels over 12 years and throughout the village. The statistical analysis is also difficult to comprehend.
Soto-Barreras (2019)	NTP rated Soto-Barreras et al. (2019) as having a low risk-of-bias despite finding a high risk-of-bias for confounding and water fluoride exposure. Also, the cross-sectional study design does not account for reverse causality, which is likely in this case. A high risk-of-bias rating is therefore warranted.

Study	Rationale
	This is a cross-sectional study of 161 children aged 9 to 10 years of age from Chihuahua, Mexico. There was no adjustment for clustering at the school level or the sampling design; however, the authors report that they did not find a relationship between fluoride exposure and IQ.
Sudhir (2019)	NTP rated Sudhir et al. (2019) as having a low risk-of-bias overall despite finding a high risk-of-bias for lack of blinding and because no information was provided to indicate that the methods to assess IQ outcomes were reliable and valid in this study population. We observe also that the cross-sectional study design does not account for reverse causality, which is likely in this case. A high risk-of-bias rating is therefore warranted. This is a cross-sectional study of exactly 1000 children of 13 to 15 years of age from Nalgonda district (Andhra Pradesh), India. Clustering of children within the four areas was not accounted for in the analysis. About 70% of children in the low exposure group were in the below-average intelligence grade. The authors did not consider a multivariate analysis.
Trivedi (2012)	NTP rated Trivedi et al. (2012) as having a low risk-of-bias overall despite finding a high risk for statistical analysis. However, the cross-sectional study design does not account for reverse causality, which is likely in this case. A high risk-of-bias rating is therefore warranted. This is a cross-sectional study of 84 children from 6 different villages in Gujarat, India. NTP noted insufficient information on the sampling methods to determine whether the populations were similar. Again, NTP noted a probably high risk-of-bias rating for statistical analysis, stating, "Area-level exposures were used. There was no accounting for the clustering of children within the villages, and comparative analyses did not account for covariates. Urinary fluoride was not considered in the comparative analyses. The lack of individual exposure levels and the lack of accounting for clustering are likely to bias the standard error of the difference in mean IQ levels between the high- and low-fluoride villages and make the differences appear stronger than they actually are."
Xiang (2003) Xiang (2011) Wang (2012)	NTP rated Xiang et al. (2003), Xiang et al. (2011), and Wang et al. (2012) as having a low risk-of-bias. However, the cross-sectional study design does not account for reverse causality, which is likely in this case. A high risk-of-bias grading is therefore warranted.

Study	Rationale
	This is a cross-sectional study of 512 children aged 8-13 years from Wamiao (severe endemic fluorosis) and Xinhua (non-endemic) villages in Sihong County, Jiangsu Province, China. According to the authors, these “villages are situated in isolated low-income areas with less economic development and a relative lack of communication with the outside world, resulting in poor living conditions for the majority of the residents, especially the elderly and children.” The two villages are not comparable concerning the education of parents. The proportion of parents with senior high school education was 13.5% in Wamiao and 41.7% in Xinhua. NTP noted that a potential concern raised by the NASEM (2020) committee’s review was the lack of accounting for relationships in exposure between persons from the same village. Given only two villages were included and the analyses consisted of village-level comparisons (no use of individual-level covariate data), it is likely that the standard error of the difference in mean IQ between fluoride in water exposure groups will be biased, making differences appear stronger than they actually are. Without controlling for village effects and given the large differences in fluoride concentrations and IQ levels between villages, the apparent dose-response relationship could be due to a village effect in addition to a fluoride effect.
Broadbent (2015)	NTP rated Broadbent et al. (2015) as having high risk-of-bias, primarily because the authors did not account for other sources of fluoride in non-fluoridated areas. The high risk-of-bias rating is questionable, however, because NTP did not seek clarification from the authors in the same manner they did with the authors of other studies. The study should be given full and fair consideration. In response, the authors filed their own response in a letter to the editor of the *American Journal of Public Health*, noting:[4] > In the Dunedin [New Zealand] Study cohort, the majority of children who took fluoride tablet supplements did so intermittently and for only a short period of time. We have now estimated average total fluoride intake in our cohort up to age five years, including tablets, toothpastes, and dietary sources. We identified no differences in IQ in childhood or adulthood by total fluoride intake, but we did identify significantly fewer dental caries in both childhood and adulthood among those with higher estimated fluoride intake up to age five years.

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Overview of York University Fluoride Study

Prepared by the Water and Air Quality Bureau, Health Canada

(le français suit)

Health Canada's *Guidelines for Drinking Water Quality in Canada* provides parameters to provinces, territories and federal Government Departments for water systems across the country. The Drinking Water Guideline for fluoride establishes a maximum acceptable concentration (MAC) for fluoride at 1.5 mg/L that factors in all sources of exposure to fluoride. The Guideline, published in 2010, was informed by published peer reviewed studies and the recommendations of an expert panel that included the Chief Dental Officer. The expert panel examined both potential adverse health effects of fluoride and the public health benefits of adding fluoride to drinking water through community water fluoridation to prevent dental caries. Since the Drinking Water Guideline for fluoride was established in 2010, Health Canada has regularly reviewed the state of the science on the health effects of fluoride and has concluded the current available science indicates that fluoride at levels below this guideline does not pose a health concern.

A York University study, "Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada", linking maternal fluoridation exposure during pregnancy to lower IQ scores in children aged 3 to 4 was published in JAMA Pediatrics on August 19, 2019. As is the case with all new science, Health Canada has reviewed this study and has considered it in weight of evidence-based decision-making to protect the health and safety of Canadians. It is important to note that when assessing the health risk, Health Canada looks at the available body of science –not one single study— in order to determine whether there is enough evidence to warrant a change in position.

In reviewing this study, Health Canada notes that from analysis of data and banked maternal urine (for fluoride) from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, the authors conclude that "… maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years." The key element of this study is that it is an observational study, which found an association between higher levels of two different measures of fluoride exposure during pregnancy and small decreases in child IQ at 3-4 years of age. This one study is not able to prove that prenatal fluoride exposure causes deficits in child IQ, only that there was an observation of such an association. The study was well designed and analysed. The authors identified limitations in the study and where possible implemented measures to reduce their impact. However, a number of uncertainties remain (e.g., estimation of prenatal fluoride exposure, other unmeasured factors affecting child IQ) which limit this study's ability to confirm a causal relationship between prenatal fluoride and deficits in child IQ.

This study is one of the first linking fluoride and neurological effects, and Health Canada will continue to monitor and evaluate studies as they are published. Based on the current weight of evidence, Health Canada continues to support the existing Drinking Water Guideline for fluoride. As Health Canada continues to keep abreast of scientific developments, the Department will collaborate with the Office of the Chief Dental Officer, provinces and territories and other interested stakeholders.

CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	October 23, 2019
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CADTH

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to Requests@CADTH.ca

CADTH

Abbreviations

CI	Confidence interval
CWF	Community water fluoridation
FSIQ	Full Scale IQ
HOME	Home Observation for Measurement of the Environment
HTA	Health technology assessment
IQ	Intelligence quotient
MA	Meta-analysis
MIREC	Maternal-Infant Research on Environment Chemicals
MUF	Maternal urine fluoride
NR	Not reported
PIQ	Performance IQ
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SD	Standard deviation
SR	Systematic review
VIQ	Verbal IQ

Context and Policy Issues

In Canada, community water fluoridation (CWF) is the process of monitoring and controlling fluoride levels (by adding or removing fluoride) in the public water supply to reach the optimal level of 0.7 part per million (ppm) and not to exceed the maximum concentration of 1.5 ppm, as recommended in the 2010 *Health Canada Guidelines for Drinking Water Quality*.[1] CWF has been identified as a cost-effective method of delivering fluoride to the population and reducing dental caries in children and adults.[2,3] The Centers for Disease Control and Prevention recognized CWF as one of 10 great public health achievements of the 20th century because of its contribution to the prevention of tooth decay and improvement in oral health over the past 70 years.[4] CWF is endorsed by over 90 national and international governments and health organizations around the world.[5,6]

Despite the endorsement of governments and health organizations, and a large body of empirical evidence on the preventive effect of CWF on dental caries, a number of municipalities across Canada have not implemented or have discontinued water fluoridation.[7] In 2017, 38.7% of the Canadian population were exposed to community water systems having recommended optimal fluoride levels to protect their teeth.[7] Different factors contributed to CWF cessation including concerns about the potential harmful side effects of water fluoride to human health, including fluorosis, skeletal fractures, cancer, reproduction and development, thyroid function, and children's intelligence quotient (IQ).[1]

Multiple studies have been published showing that exposure to higher levels of fluoride in drinking water may be associated with lower intelligence among children.[8-11] However, the generalizability of the findings from those studies to the Canadian context is unlikely given they were conducted in rural areas and areas of low socioeconomic status in countries, such as China, India, Iran, or Mexico, which also include other sources of fluoride such as fluoridated salts or naturally occurring water fluoride levels that are many folds higher than the current Canadian levels.[8-11] Multiple methodological limitations were identified in these studies including the lack of control for important confounding variables such as exposure to known neurotoxicants (e.g., lead, arsenic, or iodine), socioeconomic status, nutritional status, and parental education that could be related to fluoride exposure and also potentially affect children's IQ.[12] The CADTH CWF Review of Dental Caries and Other Health Outcomes reviewed studies from countries with comparable water fluoride levels and socioeconomic parameters, and found no evidence for an association between water fluoridation at recommended Canadian levels and IQ or cognitive function.[12] A study published by a group of researchers in Canada and the US after the CADTH HTA concluded that exposure to higher levels of fluoride during pregnancy is associated with lower IQ scores in children aged 3 to 4 years in Canada.[13] The findings of that study prompted a further review on this topic.
The aim of this report is to review recent evidence on the effects of fluoride exposure through CWF at levels that are relevant to the Canadian context on the neurological or cognitive development in children and adolescents less than 18 years of age.

In this report, gender-neutral language has been used where possible in order to be inclusive of all gender identities. When reporting results from the published manuscript, gender-neutral language was not used in order to be consistent with the terms used in the source material.

CADTH

Research Question

What are the neurological or cognitive effects of community water fluoridation, compared with non-fluoridated or different fluoride levels in drinking water, in individuals less than 18 years of age?

Key Findings

This review identified one prospective birth cohort study[13] examining the association between fluoride exposure of mothers during pregnancy and subsequent children's intelligence quotient scores at age 3 to 4 years. Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L in mother urine fluoride and Full Scale intelligence quotient score in the total sample of boys and girls, or in girls. Adjusted estimates also showed no statistically significant association between an increase of 1 mg/L in mother urine fluoride and performance intelligence quotient or verbal intelligence quotient in all children. In boys, every 1 mg/L increased in mothers' urine fluoride levels was associated with a 4.49 point lower intelligence quotient score. Every 1 mg increase in daily fluoride intake of mothers corresponded with 3.66 points lower in total children's intelligence quotient score. The interaction between child sex and maternal fluoride intake was not statistically significant. The evidence is weak due to multiple limitations (e.g., non-homogeneous distribution of data, potential errors and biases in the estimation of maternal fluoride exposure and in IQ measurement, uncontrolled potential important confounding factors); therefore, the findings of this study should be interpreted with caution.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were water fluorination and children (<18 years). No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2017 and September 13, 2019. The search dates were selected to identify information published subsequent to a previous search for the CADTH CWF Review of Dental Caries and Other Health Outcomes.[12]

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Persons less than 18 years of age (including *in utero*)
Intervention	Natural or artificial water fluoridation (range between 0.4 ppm to 1.5 ppm with the optimal level being 0.7 ppm)
Comparator	No water fluoridation, low fluoride level (< 0.4 ppm), or different fluoride levels in drinking water
Outcomes	Neurological (e.g., neurotoxicity) or cognitive outcomes (e.g., Intelligence Quotient)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), randomized controlled trials (RCTs), and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2017. Primary studies were also excluded if they had been included in the recent CADTH HTA report on CWF.[12]

Critical Appraisal of Individual Studies

The methodological quality (i.e., internal and external validity) of the included non-randomized study was assessed using the National Institute for Health and Care Excellence (NICE) checklist.[14] Summary scores were not calculated for the included study; rather, a review of the strengths and weaknesses were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 302 citations were identified in the literature search. Following screening of titles and abstracts, 294 citations were excluded and eight potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of the eight potentially relevant articles, seven publications were excluded for various reasons, while one study met the inclusion criteria and was included in this report. **Appendix 1** presents the PRISMA flowchart[15] of the study selection.

Summary of Study Characteristics

The characteristics of the identified study (Table 2) are presented in Appendix 2.

Study Design

The identified study was a prospective, multicentre birth cohort study,[13] which acquired data and frozen urine samples from the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) program. Maternal urine fluoride (MUF) concentrations were measured in urine spot samples collected at each trimester of gestation and adjusted for specific gravity (MUF_{SG}). Information regarding pregnant persons' consumption of tap water and other beverages such as tea and coffee was obtained using a self-reported questionnaire. The water fluoride concentrations in the areas where persons resided during pregnancy were estimated based on the levels of fluoride in the municipal water reported by waste water treatment plants and persons' postal code. Daily fluoride intake was estimated based on a combination of the above measures. IQ of children was assessed once at ages of three to four years.

Country of Origin

The identified study[13] was conducted by authors in Canada and the US.

Population

The MIREC study recruited 2,001 pregnant persons within the first 14 weeks of pregnancy from 10 Canadian cities. A subset of mother-child pairs (n = 610) from six of 10 cities (Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax) were recruited for the measurement of children's IQ. Of 610 children, 601 had complete IQ data. Of 601 mother-child pairs, 369 had complete exposure and covariate data and drink tap water or live in a water treatment zone and were thus included in an analysis of the association between MUF and children's IQ. Further, 400 mother-child pairs had complete data and drink tap water or live in a water treatment zone and were included in a second analysis of the association between daily fluoride intake and children's IQ. Thus, 39.5% and 34.4% of the initial sample (n = 610) were excluded from the first and second analyses, respectively, due to missing data or ineligible exposure.

The mean age of pregnant persons at the time of recruitment was 32.3 years, and mean age of children at IQ testing was 3.4 years. Fifty two percent of children were female. Other characteristics of mothers and children are shown in Table 2 of Appendix 2.

Interventions and Comparators Mean MUF_{SG} value of the total sample of pregnant persons was 0.51 mg/L. The mean MUF_{SG} values of non-fluoridated and fluoridated groups were 0.40 mg/L and 0.69 mg/L, respectively.

Mean daily fluoride intake value of the total sample of pregnant persons was 0.54 mg. The mean daily fluoride intake values of non-fluoridated and fluoridated groups were 0.30 mg and 0.93 mg, respectively.

The average community fluoride level of areas of total sample of pregnant persons was 0.31 ppm. The mean water fluoride levels in the non-fluoridated and fluoridated areas were 0.13 ppm and 0.59 ppm, respectively.

Outcomes

The primary outcome was full scale IQ (FSIQ), a measure of global intellectual functioning, assessed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III).[16] Verbal IQ (VIQ), a measure of verbal reasoning, and performance IQ (PIQ), a measure of non-verbal reasoning, spatial processing and visual-motor skills, were also assessed. The WPPSI-III contains 14 subtests and two age ranges (from 2 years and 6 months to 3 years and 11 months, and from 4 years and 0 months to 7 years and 3 months). For children in the first age range, FSIQ, VIQ and PIQ scores are obtained from four core subtests. Seven core subtests are for children in the second age range. An overall intelligence score between 90 to 109 with a standard deviation of 15 is considered as average.[16,17] The reliability coefficients for WPPSI-III composite scales range from 0.89 to 0.95[16,17] [Reliability coefficient values range from 0.00 (significant error – no reliability) to 1.00 (no error – perfect reliability), and are used to indicate the amount of error in the scores]. The associations between children's IQ and maternal fluoride exposure (e.g., MUF, daily fluoride intake, water fluoride level) were estimated using linear regression analyses.

Summary of Critical Appraisal

The assessment of the methodological quality of the identified study is presented in Table 3 of Appendix 3.

Strengths

The identified study[13] was conducted in Canada with a well described source population.

The study assessed maternal fluoride exposure using a combination of mother urine fluoride, daily fluoride intake, in areas with or without fluoridation.

The study used linear regression analyses with two main measures of fluoride exposure (i.e., maternal fluoride urine and daily fluoride intake) to estimate the association between maternal fluoride exposure and children's IQ. Test statistics and associated *P* values were reported for all analyses.

The study analyzed mother urine fluoride concentration using established methods that were previously published. Children's' IQ (i.e., full scale IQ, verbal IQ and performance IQ) was assessed using a well-established method (i.e., the Wechsler Preschool and Primary Scale of Intelligence, third Edition).

Weaknesses

The recruitment of participants was not defined. It was unclear how 6 of 10 cities (Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax) were chosen. The authors stated that, due to budgetary restraints, those cities were chosen as most participants fell into the age range required. While there was minimal difference between the MIREC sample, the sample of persons included in the analyses and the sample of persons who had incomplete MUF data, the study did not describe the method of selection of participants from the eligible population. There was no report on the percentage of selected individuals who agreed to participate. Thus, there is a potential risk of bias in selection of participants into the study.

The study did not clearly pre-define the level of fluoride exposure that was considered as low or high at start of the study. As participants were not randomly assigned to level of fluoride exposure at the beginning of the study, mother-child pairs were sorted out based on maternal urine fluoride and fluoride intake after maternal fluoride exposure was determined by a combination of maternal urine fluoride, daily fluoride intake and community water fluoride concentrations. This approach, together with the knowledge of children's IQ, might have affected the classification of exposure status of the mothers. The study did not report the period of fluoride exposure. Some persons might have a lifetime exposure, while others might just have exposure during pregnancy. This strategy may result in classification of intervention bias.

The study tried to link fluoride exposure through drinking tap water and IQ in children. However, fluoride exposure may not specifically come solely from CWF, but rather from other sources, including food and toothpaste. Other sources of fluoride were not accounted and controlled in the analyses.

Although the study used appropriate statistical analyses (e.g., multiple linear regression) to control for some confounding variables, other potential important confounding factors during pregnancy and after birth, as well as those between birth and children's age of 3 or 4 when IQ was assessed, were not fully addressed. Some potential important confounders included parental IQ, father's education, socioeconomic status, duration of breast feeding, postnatal exposure to fluoride, postnatal diet and nutrition, and child's health status.[18,19] There is a potential risk of bias due to confounding.

The outcome measures (i.e. FSIQ, PIQ, and VIQ) could have been influenced by the knowledge of intervention received, or fluoride exposure, as the authors were aware of potential correlation and association between higher maternal fluoride exposure and lower children's' IQ from previous studies. Systematic errors might exist in the measurement IQ, MUF and daily fluoride intake. No information was provided regarding IQ measurement, such as the number of times the test was given per child (as a single measure may not capture all cognitive performance),[20] when and where the test took place (different environments and times may give different results),[18] whether the child was comfortable with the examiner before the test,[17] and whether the outcome assessors were blinded (risk of detection bias). For urine fluoride, although the authors corrected for variations in urine dilution (e.g., samples collected in early morning is more concentrated than those collected in later of the day) by adjusting MUF for specific gravity, the accurate measure of true values of MUF that correctly reflect maternal fluoride exposure remains questionable, given the short half life of fluoride (about 5 hours),[21] and only three urine samples, one at each trimester, during the entire pregnancy. The estimation of the maternal daily fluoride intake may inherit inaccuracies due to the fact that the self-reported questionnaire and the estimation/calculation methods of fluoride intake have not been validated. The estimation was subjected to recall bias as it was based on self-reported estimates of the amount of tap water and types of tea (e.g., black tea has more fluoride than green tea) consumed per day, whose data were collected on only two occasions, first and third trimesters, of pregnancy. The daily fluoride intake did not consider other sources of fluoride such as food or swallowing toothpaste after toothbrushing. The accuracy of the estimated fluoride intake levels is questionable given the discrepancies compared with MUF_{SG} values. For example, the difference in values were lower in the non-fluoridated groups (0.30 mg relative to 0.40 mg/L) and higher in the fluoridated groups (0.93 mg relative to 0.69 mg/L).[21] Given the interrelationship between maternal fluoride exposure and IQ in the estimation of the association, any incorrect assessment of fluoride intake, MUF or IQ could have a great impact on the direction of bias due to measurement of outcomes.

The outcome, exposure and covariate data were not available for all, or nearly all, participants. Over one third of initial sample were excluded due to missing data of MUF, water fluoride, and covariates. Of the 601 mother-child pairs, 369 pairs were used for urine fluoride association analysis and 400 pairs for fluoride intake association analysis. There was no information regarding the proportion of participants and reasons for missing data between exposure to higher fluoride level and lower fluoride level. There is a potential risk of bias due to missing data.

The study did not report R-squared values for the regression lines, and *P* values were reported instead, which are known to be misleading.[22] In the first analysis with MUF_{SG}, the *P* value for interaction in boys was 0.02, and the second analysis with daily fluoride intake, the *P* value was 0.04. No sample size calculation was performed. Thus, it is unclear if the study was sufficiently powered to detect a meaningful effect, and whether or not there was a strong association between maternal fluoride exposure and children's IQ.

In summary, multiple methodological weaknesses that potentially affect the internal validity of the study results limit the generalizability of the findings to all pregnant persons in Canada.

Summary of Findings

The main findings and conclusion of the identified study[13] are presented in Table 4 of Appendix 4.

What are the neurological or cognitive effects of community water fluoridation, compared with non-fluoridated or different fluoride levels in drinking water, in individuals less than 18 years of age?

Children's FSIQ

The mean FSIQ score of the total children sample was 107.16 ± 13.26. The mean FSIQ scores of non-fluoridated and fluoridated groups were 108.07 ± 13.31 and 108.21 ± 13.72, respectively.

Boys had mean FSIQ scores of 104.61 ± 14.09 in the total sample, 106.31 ± 13.60 in non-fluoridated group, and 104.78 ± 14.71 in fluoridated group.

Girls had FSIQ scores of 109.56 ± 11.96 in the total sample, 109.86 ± 12.83 in non-fluoridated group, and 111.47 ± 11.89 in fluoridated group.

Associations between MUF_{SG} and FSIQ in children

Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L MUF_{SG} and FSIQ in the total sample of boys and girls, or in girls. In boys, an increase of 1 mg/L MUF_{SG} was associated with a significant reduction of 4.49 FSIQ score (95% confidence interval [CI] -8.38 to -0.60) after adjusting for covariates (city, Home Observation for Measurement of the Environment [HOME] score, maternal education, race/ethnicity, and child sex interaction). Likewise, an increase of 0.33 mg/L MUF_{SG} (a value spanning the interquartile range between 25th to 75th percentiles) or an increase of 0.70 mg/L MUF_{SG} (a value spanning the 80th central range between 10th to 90th percentiles) was associated with a significant reduction of 1.48 (95% CI -2.76 to -0.19) or 3.14 (95% CI -5.86 to -0.42) FSIQ score in boys, respectively.

Sensitivity analyses

Adjusting for maternal blood concentrations of lead, mercury, perfluorooctanoic acid, arsenic, manganese, or maternal secondhand smoke exposure alone did not change the overall estimate for the association between MUF_{SG} and FSIQ in boys or girls. Excluding data from two boys with FSIQ lower than 60 or use of the adjusted MUF for creatinine in the models did not markedly change the regression coefficient in boys.

Associations between maternal daily fluoride intake and FSIQ in children

Both unadjusted and adjusted estimates showed a significant association between daily fluoride intake and FSIQ in the total sample of boys and girls. An increase of 1 mg fluoride intake was associated with a significant reduction of 3.66 FSIQ score (95% CI -7.16 to -0.15) after adjusting for covariates (city, HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). Likewise, an increase of 0.62 mg fluoride intake (a value spanning the interquartile range between 25th to 75th percentiles) or an increase of 1.04 mg fluoride intake (a value spanning the 80th central range between 10th to 90th percentiles) was associated with a significant reduction of 2.26 (95% CI -4.45 to -0.09) or 3.80 (95% CI -7.46 to -0.16) FSIQ score, respectively. A subgroup analysis was not performed here, as the authors stated that the interaction between child sex and maternal fluoride intake was not statistically significant.

Associations between community water fluoride concentration and FSIQ in children

A 1-ppm (or 1-mg/L) increase in fluoride concentration in the community water was associated with a significant reduction of 5.29 FSIQ score in the total sample after adjusting for covariates (city, HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). No subgroup analysis was conducted, or reported, by sex.

Associations between MUF_{SG} and PIQ in children

Adjusted estimates showed no significant association between an increase of 1 mg/L MUF_{SG} and PIQ in total sample of boys and girls, or in girls. In boys, an increase of 1 mg/L MUF_{SG} was associated with a significant reduction of 4.63 PIQ score.

Associations between maternal daily fluoride intake and PIQ in children

Adjusted estimates showed no significant association between an increase of 1 mg daily fluoride intake and PIQ in total sample of boys and girls. Subgroups analyses based on child sex was either not performed or reported.

Associations between community water fluoride concentration and PIQ in children

A 1-ppm (or 1-mg/L) increase in fluoride concentration in the community water was associated with a significant reduction of 13.79 PIQ score (95% CI -18.82 to -7.28) in total sample after adjusting for covariates (HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). The city covariate was excluded from the model because it was strongly multi-collinear with water fluoride concentration. No subgroup analysis was conducted, or reported, by sex.

Associations between MUF_{SG} and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 mg/L MUF_{SG} and VIQ in the total sample, in boys, or in girls.

Associations between maternal daily fluoride intake and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 mg daily fluoride intake and VIQ in the total sample. A subgroup analysis based on child sex was not performed or reported.

Associations between community water fluoride concentration and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 ppm fluoride concentration in the community water and VIQ in the total sample. A subgroup analysis based on child sex was not performed or reported.

Limitations

The study by Green et al., 2019[13] concluded that "*maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years.*" (p. E1) This conclusion was not supported by the data. Between nonfluoridated and fluoridated maternal exposure (assessed by MUF_{SG} or daily fluoride intake), the difference in mean FSIQ in total children (108.07 ± 13.31 versus 108.21 ± 13.72) was minimal. The average FSIQ in boys in the non-fluoridated and fluoridated groups were 106.31 ± 13.60 and 104.78 ± 14.71, respectively, and in girls were 109.86 ± 12.83 and 111.47 ± 11.89, respectively. According to the WPPSI test scoring,[17] these numbers were considered as normal, as a score of 90 to 109 represents average intelligence. Given that these values were available during data collection period, it was unclear about the authors' rationale to further explore the associations between maternal fluoride exposure and children's IQ. Indeed, adjusted estimates with a limited set of covariates showed no statistically significant association between an increase of 1 mg/L in MUF_{SG} and FSIQ, PIQ or VIQ in all children. These were not discussed or considered when formulating the conclusion. The authors performed subgroups analysis based on child sex and found that an increase of 1 mg/L MUF_{SG} was significantly associated with a 4.49 point lower (95% CI -8.38 to -0.60) in FSIQ only in boys. In contrast, there was a non-significant increase in IQ scores in girls associated with increase maternal fluoride exposure. No pre-registered protocol was reported as available, and it is possible that the decision to conduct a subgroup analysis based on sex was made post hoc. As indicated by the authors, further investigation is needed examining differences in boys versus girls regarding their vulnerability to neurocognitive effects associated with fluoride exposure. Further, no rationale is provided to suggest why an increase in daily fluoride intake was significantly associated with lower FSIQ in total children, while no association was seen with MUF_{SG}. For the interaction with child sex, the effect on fluoride exposure was seen in analysis with MUF_{SG} but not in analysis with fluoride intake. These results were inconsistent.

The 1-mg/L increase in MUF_{SG} that was used to examine the association between fluoride exposure and childrens' IQ was far larger than the MUF_{SG} difference between fluoridated and nonfluoridated exposure in reality, which was 0.29 mg/L (difference between 0.69 mg/L and 0.40 mg/L), corresponding with a deficit of 1.53 points in FSIQ in boys (difference between 104.78 and 106.31). This was corroborated with the 1.48 point deficit in FSIQ in boys, corresponding to a MUF_{SG} difference spanning the 25th to 75th percentile range, which was 0.33 mg/L. Given that the reliability coefficients of WPPSI test range from 0.89 to 0.95,[17] the 1.5 points or even 4.5 points deficit is within the range of error (i.e., 5% to 11%).

The estimated level of IQ deficit in boys is likely to be reflected by non-homogeneous distribution of data as relative to fluoride intake, or biases due to uncontrolled confounders. Most of the FSIQ data were concentrated in the lower end of the MUF_{SG} concentrations, with few observations at the extreme level; therefore, an assumption for a linear correlation may not be appropriate. It appears that the effect was not observed at low MUF_{SG} concentrations, and the overall association may be driven by some outliers and few points at the extreme MUF_{SG} concentrations. There were some boys in the sample with extremely low IQ with at least two with FSIQ scores in the 50s and five with FSIQ scores below 75, while all the girls' data points were above 80, as shown in Figure 3 of the study report.[13] Although the authors stated that a sensitivity analysis removing two boys with FSIQ scores in the 50s did not substantially change the overall estimate, data of boys below 75 were not taken into consideration in the sensitivity analysis. No attempt was made to control for potential important confounding factors including parental IQ, father's education, socioeconomic status, duration of breast feeding, postnatal exposure to fluoride, postnatal diet and nutrition, child's health status, and other confounders between birth and the children's age of 3 or 4 when IQ was measured.[18,19] Although the authors controlled for and performed sensitivity analysis to test the robustness of association estimates for a number of substances (including lead, mercury, arsenic) in the mothers' blood samples, they did not consider postnatal exposure of children to these substances. Lead, in particular has been found to have a high association with IQ in children.[23] With incomplete control for potential confounders, it remains uncertain to know if the effect is true, and if it is due to prenatal exposure or postnatal exposure.

Conclusions and Implications for Decision or Policy Making

This review identified one prospective birth cohort study[13] examining the association between fluoride exposure of mothers during pregnancy and subsequent children's IQ scores at age 3 to 4 years. Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L in MUF_{SG} and FSIQ in the total sample of boys and girls, or in girls. Adjusted estimates also showed no statistically significant association between an increase of 1 mg/L in MUF_{SG} and PIQ or VIQ in all children. In boys, every 1 mg/L increased in mothers' urine fluoride levels was associated with 4.49 points lower in FSIQ score. Every 1 mg increase in daily fluoride intake of mothers corresponded with 3.66 points lower in total children's FSIQ score. The interaction between child sex and maternal fluoride intake was not statistically significant. Given multiple aforementioned limitations (e.g., non-homogeneous distribution of data, potential errors and biases in the estimation of maternal fluoride exposure and in IQ measurement, uncontrolled potential important confounding factors), the findings of this study should be interpreted carefully.

A recent CADTH Review of Dental Caries and Other Health Outcomes report on CWF[12] found that water fluoridation levels relevant to the Canadian context is associated with reducing dental caries in children and adults, and there was no evidence that water fluoridation is associated with adverse effects on human health outcomes including cancer, hip fracture, Down syndrome, and IQ and cognitive function. For the IQ and cognitive function, the HTA report[12] identified three studies that were relevant to the Canadian context (a prospective cohort study in New Zealand,[24] an ecological study in Sweden,[25] and a cross-sectional study in Canada).[26] The New Zealand study[24] assessed IQ among participants at age 7 to 13 years, and subsequently at age 38 years, who were residents in areas with CWF (0.7 ppm to 1.0 ppm) and areas without CWF (≤ 0.3 ppm). The study found no clear differences in IQ between fluoridated and non-fluoridated groups and concluded that CWF programs at 0.7 ppm to 1.0 ppm is not neurotoxic. The Swedish study[25] investigated the effect of fluoride exposure through the drinking water throughout life on cognitive and non-cognitive ability, as well as math test scores in participants up to age 18 years. Fluoride in the community water supply in Sweden is naturally occurring and its level is kept at or below 1.5 ppm. The study found that water fluoride levels in Swedish drinking water had no effects on cognitive ability, non-cognitive ability, and math test scores. The Canadian study[26] examined the relationship between fluoride exposure (estimated from urine fluoride levels and tap water samples) and reported diagnosis of learning disability among children aged 3 to 12 years. The study found no association between fluoride exposure and reported learning disability (i.e., attention deficit disorder and attention deficit hyperactivity disorder) diagnosis among Canadian children.

The findings reported by the identified study[13] in this review provided weak evidence and should be interpreted carefully, given the multiple aforementioned limitations. This, along with other evidence described in the CADTH Review of Dental Caries and Other Health Outcomes on CWF[12] which demonstrated no association with IQ and cognitive function should be considered. The identified study should be viewed as part of the research effort to investigate possible associations between fluoride exposure and neurological development in children. Together with a larger body of evidence on this topic, further well conducted research is needed to reduce uncertainty.

CADTH

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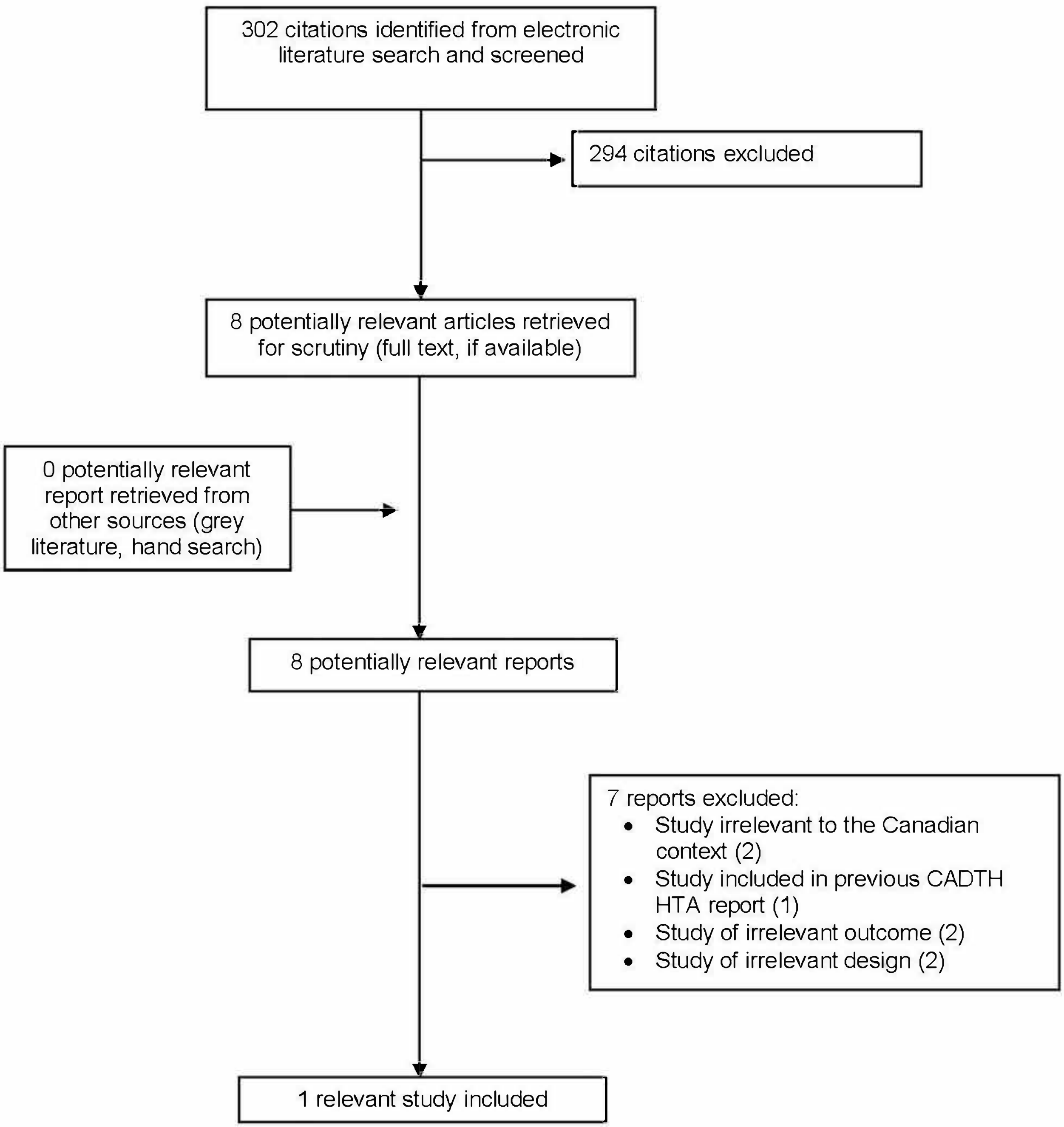
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Primary Study

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Green et al., 2019[13] Canada Funding: Public	Prospective birth cohort study Multicentre Sample size calculation: No Cohort was from the MIREC program that recruited 2,001 pregnant women from 10 cities across Canada A subset of 610 mother-child pairs from 6 out of 10 cities of the MIREC study was selected for neurodevelopment testing of children at ages 3 to 4 years	Mothers: Pregnant women within the first 14 weeks of pregnancy Mean age (SD): 32.33 (5.07) years White: 90 % Married or common law: 97% Bachelor's degree or higher: 68% Employed at time of pregnancy: 88% Net income household > $70,000 CAD: 71%	Exposure to higher levels of fluoride determined by MUF or fluoride intake, and correlated with living area having CWF	Exposure to lower levels of fluoride determined by MUF or fluoride intake, and correlated with living areas having non-CWF	Primary outcome: – FSIQ (measuring global intellectual functioning) Other outcomes: – VIQ (measuring verbal reasoning and comprehension) – PIQ (measuring nonverbal reasoning, spatial processing, and visual-motor skills)

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
	Up to 241 mother-child pairs were excluded due to various reasons, leaving 369 mother-child with MUF, IQ, complete covariates and water fluoride data, and 400 mother-child pairs with fluoride intake, IQ, complete covariates and water fluoride data Two sets of measurements: By MUF By fluoride intake Statistical analysis: Multiple linear regression analyses	Smoked in trimester 1: 2% Secondhand smoke at home: 4% Alcohol consumption (drink/month): None: 83% < 1: 8% ≥ 1: 9 Parity (first birth): 46% Children: Female: 52% Mean age (SD) at testing: 3.42 (0.32) years Mean gestation (SD): 39.12 (1.57) weeks Mean birth weight (SD): 3.47 (0.49) kg	Maternal fluoride exposure[a] measurements: Mean MUF_{SG} (SD) – Total sample: 0.51 (0.36) mg/L – Non-fluoridated areas: 0.40 (0.27) mg/L – Fluoridated areas: 0.69 (0.42) mg/L Mean daily fluoride intake (SD) – Total sample: 0.54 (0.44) mg – Non-fluoridated areas: 0.30 (0.26) mg – Fluoridated areas: 0.93 (0.43) mg Mean water fluoride level (SD) – Total sample: 0.31 (0.23) ppm – Non-fluoridated areas: 0.13 (0.06) ppm – Fluoridated areas: 0.59 (0.08) ppm		

CWF = community water fluoridation; FSIQ = Full Scale IQ; IQ = intelligence quotient; MIREC = Maternal-Infant Research on Environment Chemicals; MUF = maternal urine fluoride; PIQ = performance IQ; VIQ = verbal IQ

[a] Fluoride came from any source, not specifically from CWF

Appendix 3: Quality Assessment of Included Study

Table 3: Quality Assessment of Included Prospective Cohort Study

NICE Checklist[14]	Green et al., 2019[13]	
Question	**Answer**	**Comment**
SECTION 1: POPULATION		
1.1 Is the source population or source area well described?	Yes	The Maternal-Infant Research on Environment Chemicals (MIREC) recruited pregnant persons within the first 14 weeks of pregnancy from 10 cities in Canada. A subset of 610 mother-child pairs in the MIREC study were recruited from 6 of 10 cities: Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax. Children aged 3 to 4 years.
1.2 Is the eligible population or area representative of the source population or area?	Probably no	The recruitment of individuals, clusters or areas was not defined. It was unclear how 6 of 10 cities were chosen.
1.3 Do the selected participants or areas represent the eligible population or area?	Probably no	The method of selection of participants from the eligible population was not described. There was no report on the percentage of selected individuals or clusters who agreed to participate. Risk of selection bias.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)		
2.1 Selection of exposure (and comparison) group. How was selection bias minimized?	Acceptable	Fluoride exposure assessed by areas of fluoridation or non-fluoridation, and by mother urine fluoride and daily fluoride intake. There was no clear pre-defined level of fluoride exposure that was considered as low or high at start of the study. Mother-child pairs were sorted out based on maternal urine fluoride and fluoride intake after mother had been exposed to fluoride, and the knowledge of children's IQ might have affected the classification of exposure status of the mothers.
2.2 Was the selection of explanatory variables based on sound theoretical basis	Probably no	Evidence for the hypothesis that maternal fluoride exposure was associated with lower IQ in children was drawn from studies conducted in countries not applicable to the Canadian context (e.g., use of fluoridated salts, or water fluoride levels many folds higher

NICE Checklist[14]	Green et al., 2019[13]	
		than the current recommended level in Canada)
2.3 Was the contamination acceptable low?	No	Fluoride exposure did not specifically come from CWF; it could be from other sources such as foods or swallowing toothpaste after toothbrushing.
2.4 How well were likely confounding factors identified and controlled?	Partially	Some confounding factors such as city, HOME score, maternal education, race/ethnicity, child sex, and prenatal secondhand smoke exposure were adjusted in the regression analysis.
2.5 Is the setting applicable to the Canadian context?	Yes	The study was conducted in Canada
SECTION 3: OUTCOMES		
3.1 Were the outcome measures and procedures reliable?	Partially	Mother urine fluoride concentration was analyzed using biochemical method previously published. Childrens' IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence, third Edition. The questionnaire used to collect the information on consumption of tap water and other beverages (tea, coffee) and the methods to estimate and calculate fluoride intake were not validated. Self-reported of dietary intake tends to be an unreliable measure.
3.2 Were the outcome measurements complete?	No	Results form all recruited participants were not reported. Over one third were excluded due to missing data. Unclear if missing IQ data from excluded children could affect the findings.
3.3 Were all the important outcomes assessed?	Yes	Full Scale IQ, verbal IQ and performance IQ were measured.
3.4 Was there a similar follow-up time in exposure and comparison groups?	Probably not	Unclear about the period of fluoride exposure of women. Some women might have a lifetime exposure, while others might just have exposure during pregnancy.
3.5 Was follow-up time meaningful?	Yes	All included children had lived in the areas since birth.
SECTION 4: ANALYSES		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?	Not reported	The study did not perform any sample calculation to obtain sufficient power to detect an intervention effect.
4.2 Were multiple explanatory variables considered in the analyses?	Yes	Two measures of fluoride exposure (maternal fluoride urine and fluoride intake) were used in the analyses for the association between fluoride exposure and children's IQ.

NICE Checklist[14]	Green et al., 2019[13]	
4.3 Were the analytical methods appropriate?	Probably Yes	Linear regression analyses were adjusted with some confounding factors. Multiple analyses of the intervention-outcome relationship (both unadjusted and adjusted data) were reported.
4.4 Was the precision of association given or calculable? Is association meaningful?	Probably yes	Test statistics and associated *P* values reported for all analyses. R-squared values for linear regression were not reported. Unclear if association was meaningful.
SECTION 5: SUMMARY		
5.1 Are the study results internally valid (i.e., unbiased)?	No	High risk of bias due to selection of participants, classification of intervention, confounding, missing data, and measurement of outcomes
5.2 Are the findings generalizable to the source population (i.e., externally valid)?	Probably not	Although the study was conducted in Canada, there was a risk of selection bias of the participants into the sample. The findings could not be generalizable to the entire Canadian population.

CWF = community water fluoridation; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Included Primary Study

Main Study Findings	Author's Conclusions
Green et al., 2019[13]	
Children's intellectual ability measurements[a] Mean FSIQ (SD) – Total sample: 107.16 (13.26) Boys: 104.61 (14.09) Girls: 109.56 (11.96) – Non-fluoridated areas: 108.07 (13.31) Boys: 106.31 (13.60) Girls: 109.86 (12.83) – Fluoridated areas: 108.21 (13.72) Boys: 104.78 (14.71) Girls: 111.47 (11.89) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and FSIQ** Measurements with MUF_{SG} Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -2.60 (-5.80 to 0.60) Boys: -5.01 (-9.06 to -0.97) Girls: 2.23 (-2.77 to 7.23) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.95 (-5.19 to 1.28) Boys: -4.49 (-8.38 to -0.60) Girls: 2.40 (-2.53 to 7.33) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.33 mg/L MUF_{SG} (a value spanning the interquartile range between 25th to 75th percentiles) – Total sample: -0.64 (-1.69 to 0.42) Boys: -1.48 (-2.76 to -0.19) Girls: 0.79 (-0.83 to 2.42) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.70 mg/L MUF_{SG} (a value spanning 80th central range between 10th to 90th percentiles) – Total sample: -1.36 (-3.58 to 0.90) Boys: -3.14 (-5.86 to -0.42) Girls: 1.68 (-1.77 to 5.13) *Measurements with daily Fluoride Intake* Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg of daily fluoride intake – Total sample: -3.19 (-5.94 to -0.44) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg of daily fluoride intake – Total sample: -3.66 (-7.16 to -0.15)	*"In this study, maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years. These findings indicate the possible need to reduce fluoride intake during pregnancy."*[13] p. E1

Main Study Findings	Author's Conclusions
Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.62 mg of daily fluoride intake (a value spanning the interquartile range between 25th to 75th percentiles) – Total sample: -2.26 (-4.45 to -0.09) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1.04 mg of daily fluoride intake (a value spanning 80th central range between 10th to 90th percentiles) – Total sample: -3.80 (-7.46 to -0.16) *Measurements with water fluoride concentration* Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: 3.49 (-9.04 to 2.06) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: -5.29 (-10.39 to -0.19) **Sensitivity analyses predicting the associations between an increased of 1 mg/L of MUF_{SG} and FSIQ in boys, regression coefficients *B* (95% CI)** – Model A[d]: -4.49 (-8. 8.38 to -0.60) – Model A adjusting for lead: -4.61 (-8.50 to -0.71) – Model A adjusting for mercury: -5.13 (-9.16 to -1.10) – Model A adjusting for perfluorooctanoic acid: -4.57 (-8.21 to -0.50) – Model A adjusting for arsenic: -4.44 (-8.35 to -0.54) – Model A adjusting for manganese: -4.55 (-8.42 to -0.69) – Model A adjusting for secondhand smoke exposure: -4.18 (-8.06 to -0.30) – Model A excluding two boys with FSIQ lower than 60: -4.11 (-7.89 to -0.33) – Model A adjusting for creatinine: -6.96 (-8.56 to -1.36) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and PIQ** *Measurements with MUF_{SG}* Unadjusted estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -5.81 (-9.31 to -2.30) Boys: -8.11 (-13.29 to -4.32) Girls: -0.56 (-6.09 to 4.97) Adjusted[b] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.24 (-4.88 to 2.40) Boys: -4.63 (-9.01 to -0.25) Girls: 4.50 (-1.02 to 10.05) *Measurements with daily Fluoride Intake* Unadjusted estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg daily fluoride intake – Total sample: -5.75 (-8.74 to -2.76) Adjusted[c] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg daily fluoride intake – Total sample: -2.74 (-6.82 to 1.34) *Measurements with water fluoride concentration*	

Main Study Findings	Author's Conclusions
Adjusted[c] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: -13.79 (-18.82 to -7.28) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and VIQ** *Measurements with MUF_{SG}* Unadjusted estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg/L MUF_{SG} – Total sample: 1.28 (-1.87 to 4.43) Boys: -0.21 (-4.19 to 3.77) Girls: 4.78 (-0.14 to 9.70) Adjusted[b] estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.60 (-4.74 to 1.55) Boys: -2.82 (-6.62 to 0.98) Girls: 0.50 (-4.32 to 5.33) *Measurements with daily Fluoride Intake* Unadjusted estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg daily fluoride intake – Total sample: -0.03 (-2.71 to 2.64) Adjusted[c] estimates, regression coefficient *B* (95% CI) of VIQ for an increased of 1 mg daily fluoride intake – Total sample: -3.08 (-6.40 to 0.25) *Measurements with water fluoride concentration* Adjusted[c] estimates, regression coefficient *B* (95% CI) of VIQ for an increased of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: 3.37 (-1.50 to 8.24)	

CWF = community water fluoridation; FSIQ = full Scale IQ; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient; MUF_{SG} = maternal urine fluoride concentration adjusted for specific gravity; ppm = part per million (or mg/L); PIQ = performance IQ; SD = standard deviation; VIQ = verbal IQ

[a] Children intellectual ability was assessed using the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III)[16] The WPPSI-III contains 14 subtests and two age ranges (from 2 years and 6 months to 3 years and 11 months, and from 4 years and 0 months to 7 years and 3 months). For children in the first age range, FSIQ, VIQ and PIQ scores are obtained from four core subtests. Seven core subtests are for children in the second age range.

[b] Adjusted for city, HOME score, maternal education, race/ethnicity, and child sex interaction.

[c] adjusted for city, HOME score, maternal education, race/ethnicity, child sex interaction, and prenatal secondhand smoke exposure.

ATTACHMENT E
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Review article

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

Federica Veneri [a,b], Marco Vinceti [c,d,*], Luigi Generali [a], Maria Edvige Giannone [c], Elena Mazzoleni [c], Linda S. Birnbaum [e], Ugo Consolo [a], Tommaso Filippini [c,f]

[a] *Department of Surgery, Medicine, Dentistry and Morphological Sciences with Transplant Surgery, Oncology and Regenerative Medicine Relevance (CHIMOMO), Unit of Dentistry & Oral-Maxillo-Facial Surgery - University of Modena and Reggio Emilia, Modena, Italy*
[b] *PhD Program in Clinical and Experimental Medicine, Department of Biomedical, Metabolic and Neural Sciences - University of Modena and Reggio Emilia, Modena, Italy*
[c] *Environmental, Genetic and Nutritional Epidemiology Research Center (CREAGEN), Department of Biomedical, Metabolic and Neural Sciences, Medical School - University of Modena and Reggio Emilia, Modena, Italy*
[d] *Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA*
[e] *Nicholas School of the Environment, Duke University, Durham, NC, USA*
[f] *School of Public Health, University of California Berkeley, Berkeley, CA, USA*

A R T I C L E I N F O

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A B S T R A C T

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

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

1. Introduction

The trace element fluoride (F) has been used since 1930 for the prevention and management of dental caries, which is considered a global health issue, especially in pediatric populations (ten Cate and Buzalaf, 2019; World Health Organisation, 2021). In nature, this mineral can be found in different amounts in water, plants, and food. Fluoride compounds are also used in aluminum, petroleum, chemical, and plastics industries, therefore workers in such industries may be exposed to higher levels of fluoride than the standard population (Choubisa and Choubisa, 2016). As a dental caries preventive approach, fluoride can be delivered through topical self- or professional applications (e.g. toothpastes, mouth rinses, gels, and varnishes), which are considered safe and cost-effective at the recommended amount, thus

* Corresponding author. Section of Public Health, Department of Biomedical, Metabolic and Neural Sciences, Medical School - University of Modena and Reggio Emilia, Modena, Italy.

E-mail address: marco.vinceti@unimore.it (M. Vinceti).

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

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

2. Methods

2.1. Protocol and registration

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

2.2. Search strategy and study selection

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

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

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

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

2.3. Data extraction

From each of the included studies, whenever available we extracted data regarding location and year, study design, total population, population age and sex, type and dose of exposure, assessment method of exposure, type of neurodevelopment assessment and assessment criteria, the methodology for quantification of the outcome and mean difference between each exposure category, along with its standard deviation (SD), standard error (SE), or 95% confidence interval (CI). We also extracted details regarding confounding factors or adjustments, when available.

2.4. Risk of bias assessment

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

2.5. Data analysis

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

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

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

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

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

3. Results

3.1. Study selection

The literature search retrieved 1996 potentially relevant records. After the removal of duplicate records (n = 162) and the screening of titles and abstracts of the remaining 1834 records, 1773 records were discarded. After a full text evaluation of the remaining 61 records, additional 32 records were excluded since 3 of them addressed a wrong outcome, 3 were not eligible as publication types, 2 did not have their full texts available, 8 addressed overlapping cohorts of subjects, 10 did not report a correlation between dose and IQ, 5 investigated the correlation between dental fluorosis and IQ, and one addressed only co-exposure to fluoride and arsenic. We eventually further excluded 3 studies that did not allow the analysis of the correlation between dose and IQ. Four papers were instead added to the database after having been retrieved though citation chasing, based on the reference lists of the included studies and the recent meta-analyses.

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

3.2. Study characteristics

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

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

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

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

3.3. Risk of bias analysis

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

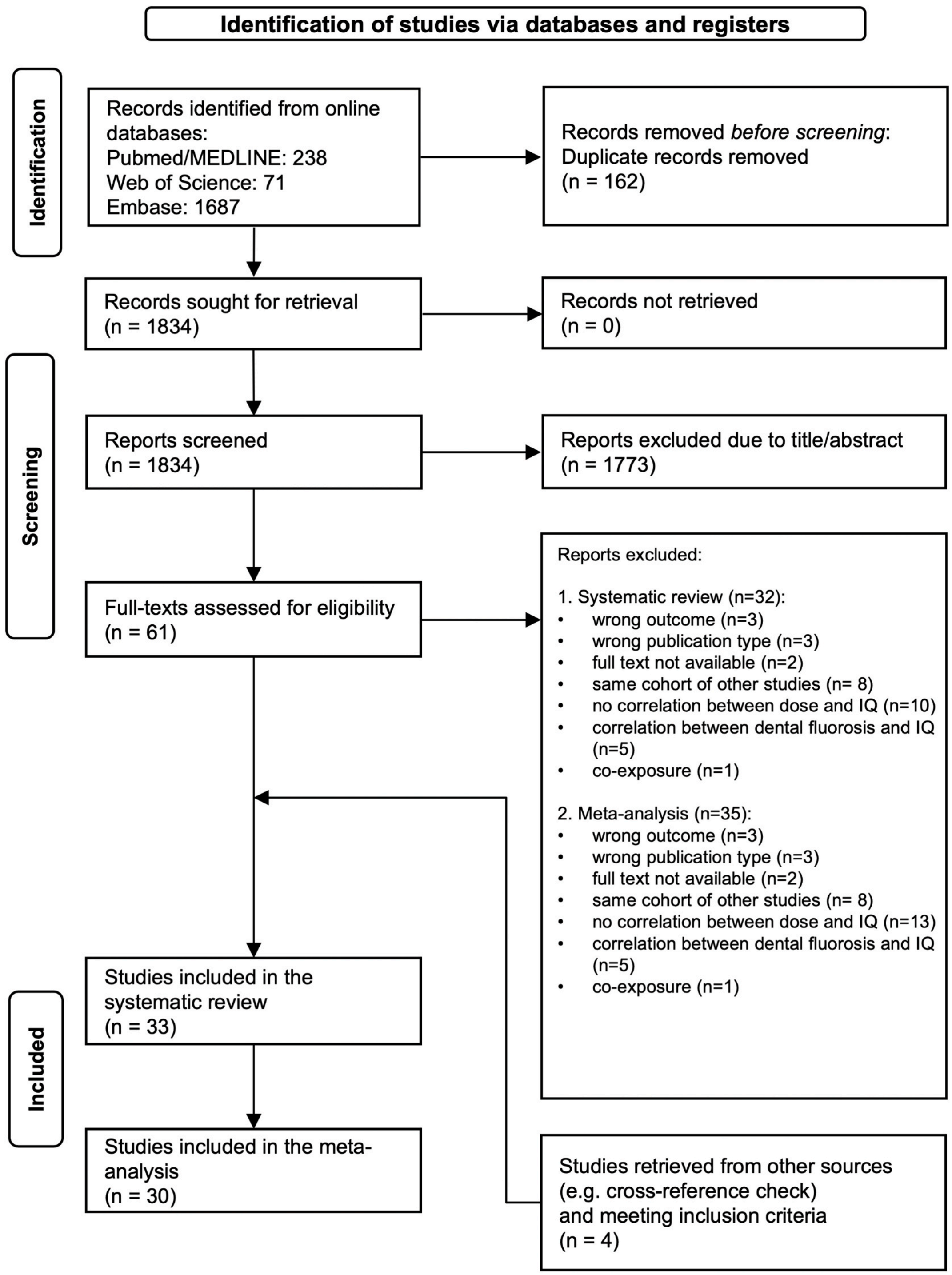

Fig. 1. PRISMA flow-chart of study selection process.

3.4. Quantitative analysis

The summary MD of IQ score, comparing the highest versus lowest fluoride categories considering all types of exposure was −4.68 (95% CI −6.45; −2.92). For less represented types of exposure, the summary IQ score MDs were −0.25 (95% CI −3.18; 2.68) for fluoride tablet supplementation (1 study), 1.92 (95% CI 1.56; 2.28) for hair fluoride (1 study), 0.61 (95% CI 0.30; 0.92) for nail fluoride (1 study), and −7.69 (95% CI −9.99; −5.38) for serum fluoride (2 studies). The individual and summary mean differences of IQ score, comparing the highest versus lowest fluoride categories considering all types of exposure are available in Supplementary Fig. S1.

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

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

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

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Table 1 (*continued*)

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

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Table 1 (*continued*)

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

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Table 1 (*continued*)

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

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Table 1 (*continued*)

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

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Table 1 (*continued*)

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

NR: not reported; CRT-RC: Combined Raven's Tests for Rural China; RCPM: Raven's Colored Progressive Matrices; RSPM: Raven's Standard Progressive Matrices; WISC-R: Wechsler Adult Intelligence Scale-Revised; WPPSI: Wechsler Preschool and Primary Scale of Intelligence.

Parentheses in the column "Management of confounders" indicate that such confounders have been considered, according to the plain text, but data are not shown.

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

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

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

4. Discussion

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

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

Table 2
Risk of bias assessment of included studies.

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

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

can vary along with different environmental and seasonal temperatures. Based on EFSA report, the European Commission for Health and Food Safety estimated a systemic fluoride intake from water and water-based beverages of approximately 0.4–0.5 mg/day for a water fluoride concentration of 0.8 mg/L and of 0.7–0.9 mg/day for a water fluoride concentration of 1.5 mg/L (European Commission, 2011). For instance in 5 years old child with 20 kg weight, the cumulative exposure, considering all additional sources, can easily be above the adequate daily intake (ADI) of 1 mg/day (i.e. 0.05 mg/kg, as established by EFSA for both adults and children) (EFSA - European Food Safety Authority, 2013). Although the ADI generally aims to provide a balanced effect in preventing dental caries without increasing the risk of dental fluorosis, the results of the present meta-analysis seem to indicate that such an ADI may not be deemed safe from a cognitive development perspective.

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

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

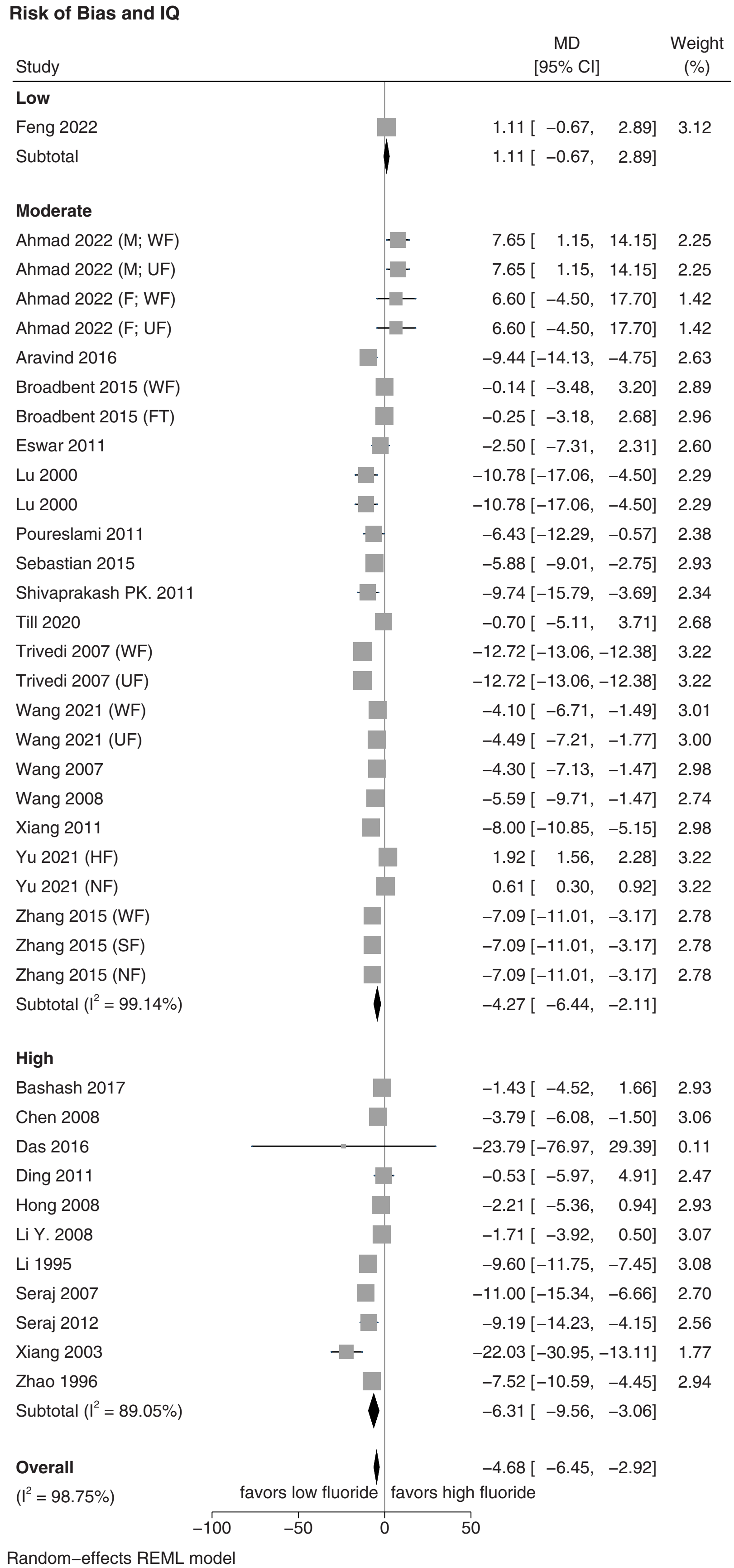

Fig. 2. Forest plot of the included studies stratified by Risk of Bias (RoB). Individual and summary mean differences (MD) of IQ for exposure to fluoride in relation to RoB levels. F: females; M: males; FT: fluoride tablets; HF: hair fluoride; NF: nail fluoride; SF: serum fluoride; UF: urinary fluoride;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

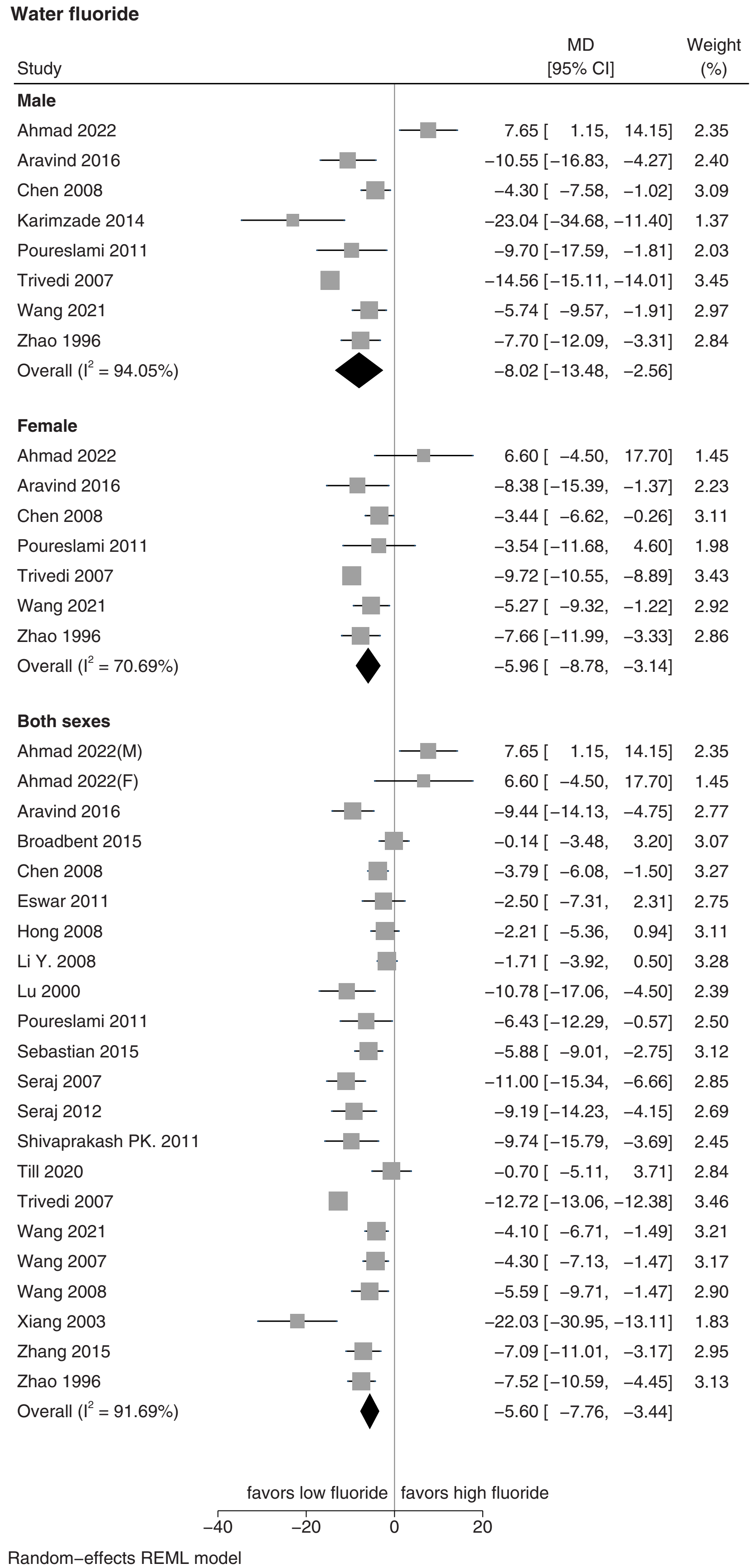

Fig. 3. Forest plot of the included drinking water studies. Mean difference (MD) in IQ with 95% confidence interval (CI) in relation to exposure to fluoride, stratified by sex. The squares represent risk estimate and horizontal lines represent their 95% CI. The area of each square is proportional to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

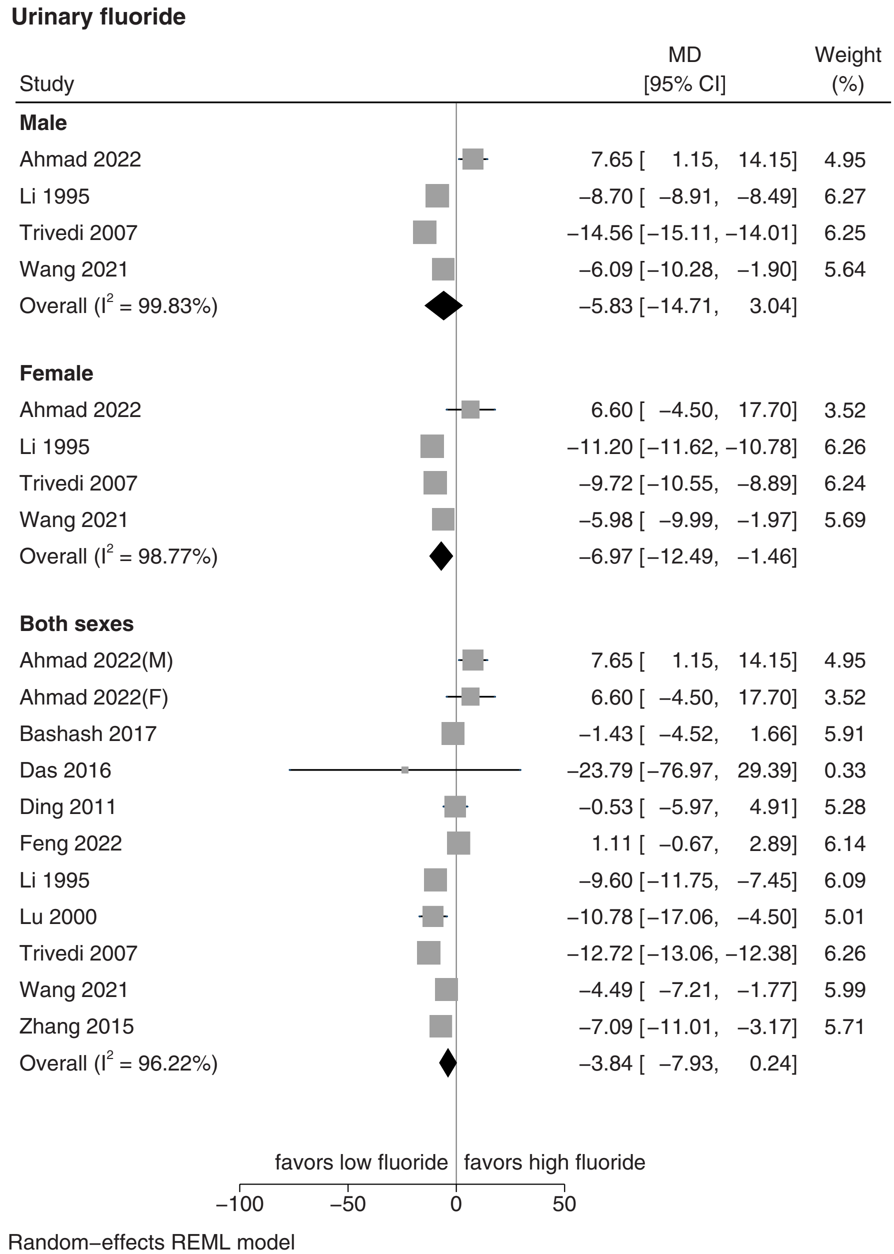

Fig. 4. Forest plots of the included urinary fluoride studies. Mean difference (MD) in IQ with 95% confidence interval (CI), stratified by sex. The squares represent risk estimate and horizontal lines represent their 95% CI. The area of each square is proportional to the weight of the study in the meta-analysis.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

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

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

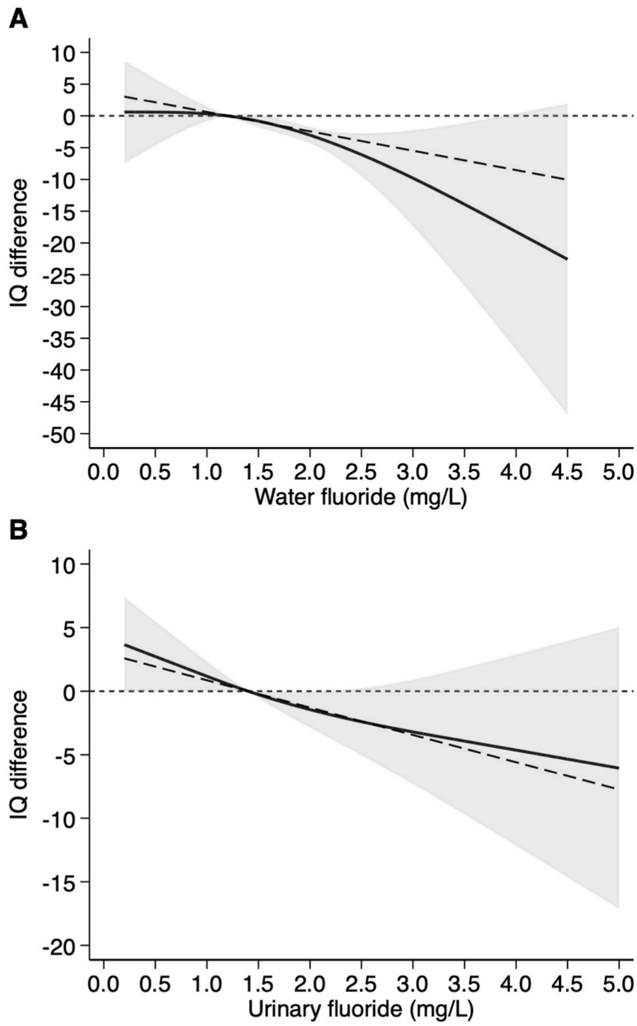

Fig. 5. Dose-response splines of intelligence (IQ score) and exposure to fluoride from drinking water (A) and urinary fluoride (B). Spline curve (black solid line) with 95% confidence limits (grey area), linear relation (black dotted line). Median values used as reference: 1.2 mg/L for drinking water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

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

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

Our results differ slightly from those of a recent meta-analysis, based on a linear meta-regression model, that indicated an early and linear decrease of IQ, with −2.94 IQ points per 1 mg/L fluoride increase (Neurath, 2020). However, among other possible common sources of heterogeneity, the fact that they considered water fluoride levels and urinary fluoride as equivalent for the purpose of pooled analyses, according to the National Toxicology Program guidance, may have affected their estimates, in addition to the choice of a linear regression model. Using instead a non-linear dose-response model, Duan et al. (2018) found an association between increasing water fluoride exposure and IQ decrease, also starting from concentrations as low as 1 mg/L, however they limited their analysis to fluoride exposure from drinking water. Despite the methodological differences and possible limitations, the effect direction resulting from these reviews, in line with our results, suggest a harmful effect from fluoride in drinking water within a concentration range previously considered as safe, such as 0.7–1.2 mg/L (CDC - Center for Disease Control and Prevention, 2021). In 2015, however, the safety threshold for community water fluoridation was set to 0.7 mg/L in the U.S. primarily to lower the risk of dental fluorosis (U. S. Department of Health and Human Services Federal Panel on Community Water Fluoridation, 2015).

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

Age at outcome evaluation, as a possible source of confounding, varied widely over the included studies, possibly affecting both the cumulative exposure and the adequacy of the intelligence tests that were administered, whose results cannot be easily compared, also explaining to some extent the heterogeneous results of the studies and of the subgroup analysis by age groups. We tried to overcome some of such limitations by performing a subgroup analysis stratified by age categories, and we found interestingly a slightly higher IQ loss in children over 6 years of age, compared to preschool children. This could be explained by a higher exposure to fluoride coming from an increased intake of water and water-based beverages of older children compared to younger ones, as supported by a recent report from the Food Safety Authority of Ireland (FSAI - Food Safety Authority of Ireland, 2018). However, current evidence from cohort studies seems to indicate that *in utero* exposure to fluoride has a stronger association to neurodevelopmental issues as compared to post-natal exposure (Bashash et al., 2017; Cantoral et al., 2021; Farmus et al., 2021; Goodman et al., 2022). Another possible limitation of the evidence generated by this review lies in the fact that many studies included in this review assessed water fluoride concentration and could not give a reliable insight on the total daily intake of fluoride. On the other hand, a considerable number of studies assessed urinary fluoride as the exposure marker, which reflects the cumulative exposure from all sources. Villa et al. (2010) estimated that in children 0–7 years old a daily fluoride intake of 0.07 mg leads to a neutral fluoride balance, being the fluoride retained equals zero. Differently, whatever the total daily fluoride intake might be and regardless of the sources, over approximately 0.5 mg/day a constant 55% of it will be retained, reaching teeth, bones, and brain regions, accounting for an increased 35% excretion through urine for each mg/day. Urinary fluoride excretion is therefore considered a valid biomarker of contemporary fluoride intake for population groups, although for individuals and different age groups it varies with renal function and acid-base balance (EFSA - European Food Safety Authority, 2013; Villa et al., 2010). In this regard, it should be noted that only a few studies reported the urinary fluoride adjusted for creatinine (Bashash et al., 2017; Feng et al., 2022; Wang et al., 2021). The differences, when reported, were however negligible, as renal function is generally efficient and comparable in the age groups considered by this review (Wang et al., 2018), thus only mildly affecting the estimates on the relation between intelligence and urinary fluoride.

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

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

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

Credit author statement

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

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Declaration of competing interest

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

Data availability

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

Appendix A. Supplementary data

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

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Original Research

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

Jayanth V. Kumar [a, *], Mark E. Moss [b], Honghu Liu [c], Susan Fisher-Owens [d]

[a] California Department of Public Health, MS 7208, 1616 Capitol Ave, Sacramento, CA 95814, USA
[b] ECU School of Dental Medicine, 1851 MacGregor Downs Road – MS 701, East Carolina University, Greenville, NC 27834-4354, USA
[c] Public and Population Health, School of Dentistry, Department of Medicine, University of California, Los Angeles (UCLA), CA 90095, USA
[d] School of Medicine and School of Dentistry, University of California, San Francisco, 1001 Potrero Ave, San Francisco, CA 94110, USA

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ABSTRACT

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

Introduction

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

* Corresponding author. Tel.: +1 916 440 7197.
E-mail address: jayanth.kumar@cdph.ca.gov (J.V. Kumar).

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

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

Methods

Search strategy

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

Study selection criteria

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

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

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

Data extraction

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

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

Data synthesis

SMD in IQ scores

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

Urinary fluoride and IQ

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

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

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

(*continued on next page*)

Table 1 (*continued*)

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

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

Risk of bias and quality assessment

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

Statistical analysis

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

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

Results

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

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

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

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

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

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

(*continued on next page*)

Table 2 (*continued*)

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

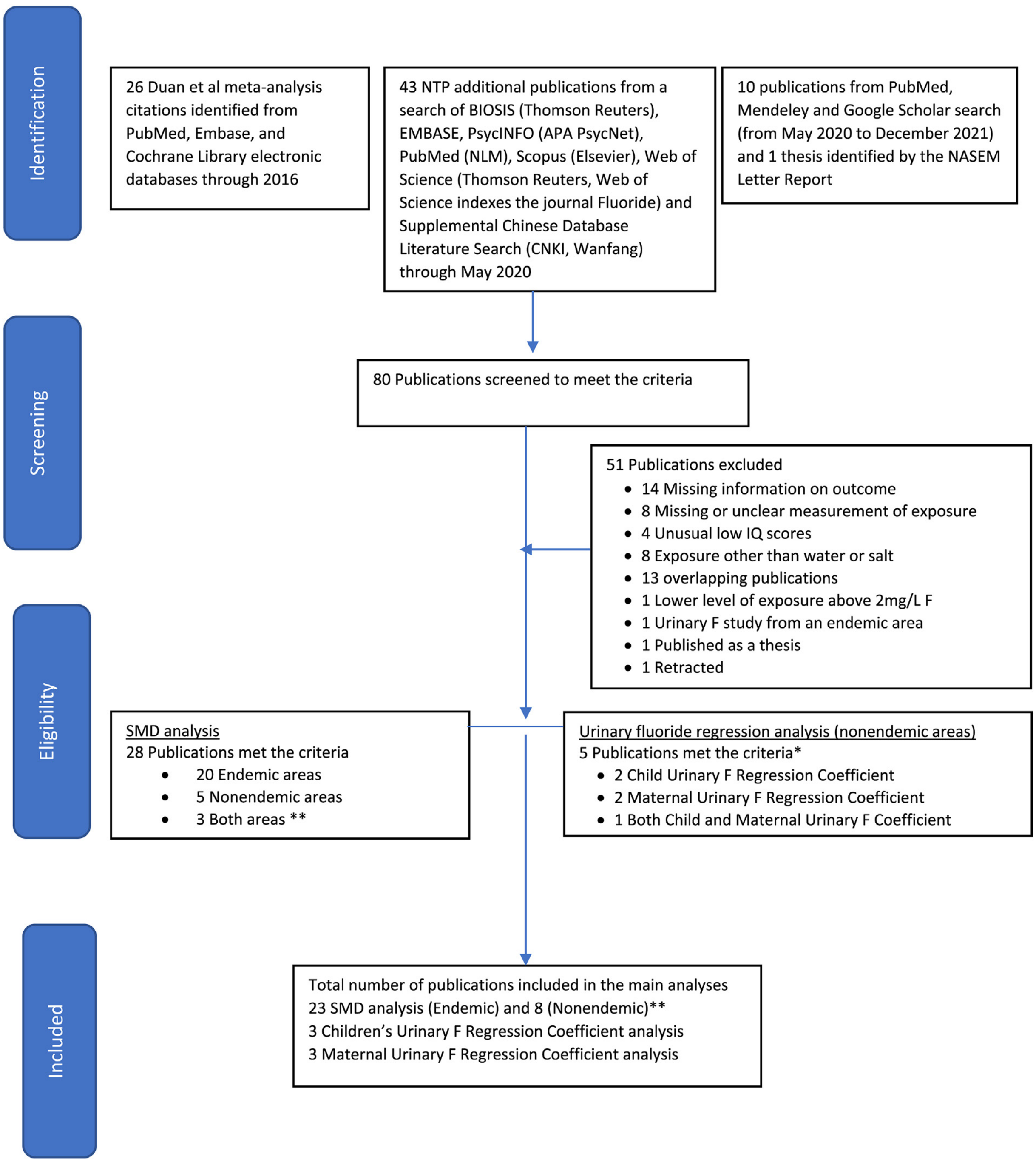
Note: Of 31 coefficients, five negative (two only in boys) and three positive (all in boys) statistically significant coefficients are shown in bold.
TSH, thyroid-stimulating hormone; WAIS, Wechsler Abbreviated Scale of Intelligence.

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

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

Discussion

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



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

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

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

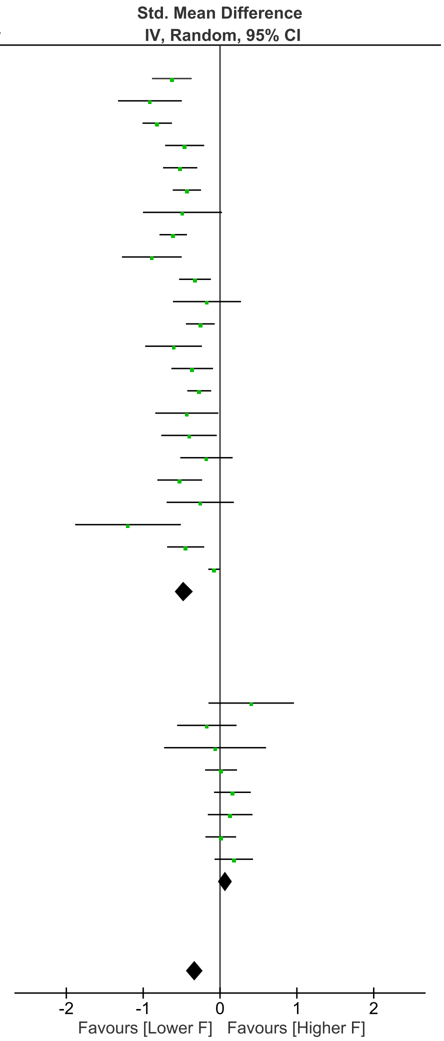


Fig. 2. Random effects analysis of standardized mean difference (SMD) and 95% CI of children's IQ score associated with exposure to higher fluoride. Forest plot of standardized mean difference (SMD) and 95% confidence interval of children's IQ scores according to endemic fluorosis and non-endemic fluorosis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

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

SMD analysis comparing higher and lower exposure groups

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

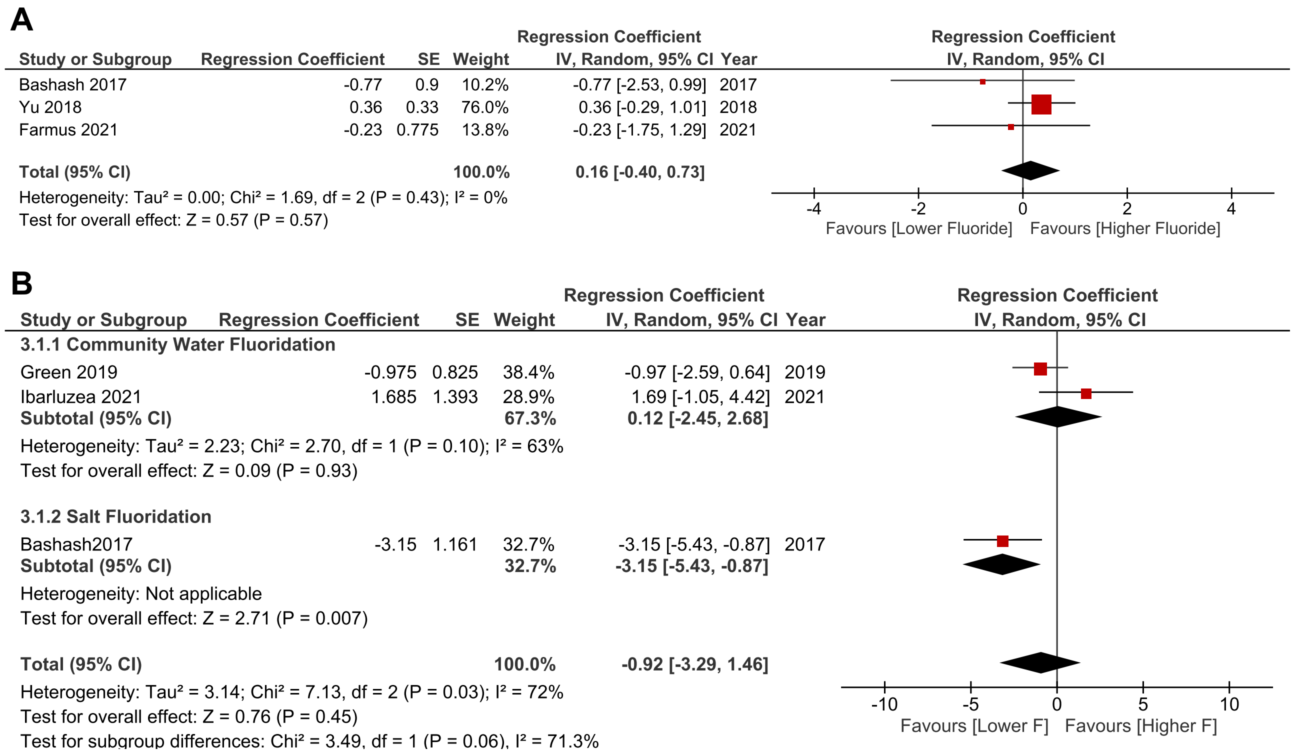


Fig. 3. (A) Random effects analysis of regression coefficients and 95% CI of children's IQ score associated with 0.5 mg/l increase in children's urinary fluoride in non-endemic areas. Forest plot of change in IQ score expressed as regression coefficient for every 0.5 mg/l increase in children's spot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

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

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

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

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

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

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

Strengths and limitations

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

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

Future direction for research

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

Conclusions

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

Author statements

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Ethical approval

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

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Competing interests

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

Appendix A. Supplementary data

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