EDITORIAL

Caution Needed in Interpreting the Evidence Base on Fluoride and IQ

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The article by Taylor et al [1] summarizes the results of the systematic review and meta-analysis that investigated the associations between fluoride exposure and children's IQ scores in epidemiological studies for the US National Toxicology Program's (NTP's) "NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition: A Systematic Review."[2] Among 74 studies, 64 were cross-sectional studies and 10 were prospective cohort studies; they rated 52 as having high risk of bias and 22 as having low risk of bias. For meta-analyses, 59 had group-level measures of fluoride exposure and 13 had individual-level measures of it. Analyses were conducted both with all studies regardless of risk of bias and limited to studies with lower risk of bias. Taylor and colleagues reported "inverse associations and a dose-response association between fluoride measurements in urine and drinking water and children's IQ"[1] and "limited data and uncertainty in the dose-response association between fluoride exposure and children's IQ when fluoride exposure was estimated by drinking water alone at concentrations less than 1.5 mg/L."[1]

Related article

This Editorial provides an alternative perspective about the findings by Taylor et al.[1] Due to the limitations of available data and authors' choices about study inclusion and exclusion criteria, analysis, and interpretation, their results and conclusions do not properly present our current knowledge about possible associations of fluoride with neurodevelopment and cognition, especially related to community water fluoridation (CWF). Specifically, several considerations raise substantial concerns about the validity and usefulness of the article, so readers should be cautious in using it for hazard determination. This caution is extremely important since fluoride in many forms is foundational for dental caries prevention at both the community and individual levels. Moreover, the NTP[2] removed the "presumed neurodevelopmental hazard determination" from earlier drafts of their report that were closely linked to this article. This change was based on 2 rounds of review by an independent National Academies of Science, Engineering, and Medicine (NASEM) committee that found many deficiencies in this meta-analysis that could make the findings invalid.[3,4] Also, a federal district court judge, based largely on the NTP report,[2] recently ruled that fluoride from CWF could pose an unreasonable risk and that the US Environmental Protection Agency (EPA) "is thus obliged to take regulatory action in response."[5] Thus, as EPA proceeds with an appeal of the ruling or to implement the court-ordered regulatory action, better understanding of the limitations of the article's data, analyses, and interpretation are extremely important.

Herein, I summarize major areas of concern.

Lack of Transparency

The first major consideration is the authors not meeting their stated purpose to "increase transparency."[1] They have not provided important background and context about these analyses' origins (in the main article or supplemental materials). Readers are not informed that there was a multiyear effort by staff at NTP, begun in 2015, that culminated in publication of the "NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition: A Systematic Review."[2] Taylor et al mention it once that this is "part of a larger systematic review."[1] NTP submitted their draft of the monograph in 2019 for NASEM expert panel review,[3] with the revised document submitted to NASEM in 2020 for review,[4] and do not discuss the lack of support for neurodevelopmental hazard determination.

Also, readers are not told that NASEM's independent reviews expressed concerns and recommended reconsideration of many important scientific aspects, including inconsistent application of risk-of-bias criteria, lack of data transparency, and inadequate attention to statistical rigor.[3,4] The committee found that these weaknesses decreased the systematic review process' reproducibility and transparency and were deficiencies to be addressed.[4] The NTP responses provided on their website[6,7] were only targeted responses and apparently did not attempt to systematically address all the important points NASEM reviewers raised, so many concerns remain.

In addition, readers are not informed of NTP's systematic review of animal studies of fluoride[8] or of their experimental study "designed to address issues identified in the NTP systematic review[8] of determining low to moderate levels of evidence for effects of F− [fluoride] exposure on learning and memory and to address the paucity of quality studies conducted at exposure levels near the recommended level for community water fluoridation in the USA."[9] They found that, at appropriate fluoride levels, there were "…no exposure-related differences in motor, sensory, or learning and memory performance on running wheel, open-field activity, light/dark place preference, elevated plus maze, pre-pulse startle inhibition, passive avoidance, hot-plate latency, Morris water maze acquisition, probe test, reversal learning, and Y-maze."[9]

Most Publications Are at High Risk of Bias

Specifically, the main meta-analysis focused mostly on all publications combined (n = 59), with most at higher risk of bias (n = 47), rather than on publications with lower risk of bias (n = 12). The studies with lower risk of bias showed a negligible effect (standardized mean difference [SMD], −0.19; 95% CI, −0.35 to −0.04) with very high heterogeneity (I^2 = 87%), and a majority of publications (8 of 12) did not show a negative association between fluoride and childhood IQ (eFigure 7 in Supplement 1 in the article by Taylor et al[1]). In fact, 3 of 4 maternal urinary fluoride–IQ cohort studies also showed no association (eFigure 27 in Supplement 1 in the article by Taylor et al[1] and the study by Ibarluzea et al[10]). Two cohort studies[11,12] with water fluoride as the group-level exposure also did not show negative associations. In addition, it is important to note that the terms *higher* and *lower* should be used instead of *high* and *low* for risk of bias and quality since many of the studies described as low risk of bias are only low compared with other, more flawed studies and not in an absolute sense.

Inadequate Justification of Studies and Lack of Clarity About Effect Sizes

Taylor et al[1] do not adequately justify selection or omission of studies or explain or justify the calculated individual effect sizes presented in the main analysis. Also, readers are not told which are the studies with lower risk of bias included in the subanalyses for water fluoride levels less than 1.5 mg/L, less than 2.0 mg/L, and less than 4.0 mg/L; therefore, readers cannot independently consider important differences across these studies.

This is further compounded by inclusion of multiple publications from a study in Tianjan City, China, even though they said they included only 1 publication per study.[13-21] Also, the urinary fluoride regression coefficients presented by Yu et al,[15] Feng et al,[19] and Xia et al[21] showed positive coefficients below 1.6 mg/L urinary fluoride. However, the meta-analysis by Taylor et al[1] uses a negative coefficient averaged inappropriately from a nonlinear association.

Lack of Substantive Discussion of Important Recent Publications

The study by Taylor et al[1] lacks substantive discussion of important recent publications. These include important individual studies from nonendemic fluorosis areas[10,22-25] and 2 recent major meta-analyses.[26,27] There is also lack of consideration of important methodological concerns about the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) study.[28] It is surprising that Taylor et al[1] did not use the more comprehensive analysis by Farmus et al[22] of the MIREC data that included postnatal exposure, instead of the article by Green et al.[29] Farmus et al[22] did not find associations between fluoride exposure during pregnancy, infancy, or childhood and full-scale IQ.

In their introduction, Taylor and colleagues stated that "Since the most recent meta-analysis, 4 new studies on exposure to fluoride and children's IQ have been published, including 3 studies that measured individual-level maternal and children's urinary fluoride concentration"[1] and "To incorporate newer evidence..., we conducted..." the study.[1] However, there are major gaps in their discussion of the newer-evidence studies, such as those by Ibarluzea et al,[10] Farmus et al,[22] Aggeborn and Öhman,[23] Do et al,[24] and Grandjean et al,[25] all showing no association.

In the Discussion,[1] text concerning previous meta-analyses is confusing and misleading, saying "results of the mean-effects meta-analysis were consistent with 6 previous meta-analyses," including that by Kumar et al.[26] However, the main reason Kumar et al[26] conducted their study was to assess associations of fluoride intake with IQ separately for lower (<1.5 mg/L) vs higher (≥1.5mg/L) levels of fluoride, with results reported separately. Thus, results do not agree with those found by Kumar et al,[26] and it is not appropriate to include only the single, combined result (across fluoride levels) from the study by Kumar et al[26] in eTable 6 in Supplement 1 under "other meta-analyses." It is very important to focus separately on lower and higher categories of fluoride to be consistent with Kumar et al,[26] since their test for subgroup differences (χ^2 = 48.23; P < .001; I^2, 97.9%) very strongly shows they should not be combined.[26]

Concerns With Validity Deriving Point Estimates With High Data Heterogeneity

Imrey[30] cautions us about use of single point estimates derived from meta-analyses with substantial heterogeneity and that use of random-effects modeling averages "provides only very modest guidance on what to expect for any given situation because the studies are so heterogeneous."[30] Also, NTP guidance for evidence-based systematic reviews and evidence integration[31] states that high heterogeneity means that confidence in the results needs to be reduced. However, throughout their article, Taylor et al[1] relied on synthesized effect estimates based on random-effects models to convey best estimates of fluoride's common effect on IQ. With high unexplained heterogeneity and both positive and negative effects in individual studies, pooled effects should not be generalized to any given population.[30]

As an example of heterogeneity from studies conducted in the same location, several articles report on results from Tianjin City, China, with different sample sizes and results (smaller samples for Zhang et al,[13] Cui et al,[14] and Zhao et al[20] and larger ones for Cui et al[16] and Yu et al[15]). Specifically, a large study[15] (24 villages, N = 2886) compared children with 2.0 mg/L water fluoride vs 0.5 mg/L fluoride (mean fluoride concentrations), finding a modest IQ point difference of 1 point, with no significant changes in IQ below 3.4 mg/L water fluoride or 1.6 mg/L urinary fluoride; Zhang et al[13] compared children (2 schools, N = 180) with mean water fluoride concentrations of 1.4 mg/L vs 0.63 mg/L and reported a 7-point IQ difference. The regression coefficients shown in Figure 2 of the meta-analysis by Taylor et al[1] also show substantial differences. Furthermore, recent studies from China show inconsistent findings. Feng et al[19] reported a mean IQ 1 point higher with higher fluoride exposure (creatinine-adjusted urinary fluoride mean [SD] concentration of 2.15 [0.91] mg/L vs 0.83 [0.30] mg/L), with all 683 children having normal or higher intelligence (IQ >120). This type of heterogeneous outcome cannot be attributed to fluoride. This issue is further compounded by the lack of adjustment for the cluster sample design effects, which results in a confidence interval narrower than it should be, artificially low P values, and inappropriate statistically significant findings.

Questionable Validity of the Studies Using Urinary Fluoride Measures of Fluoride Exposure

The statement by Taylor and colleagues that "Unlike drinking water levels, individual-level urinary fluoride concentrations include all ingested fluoride and are considered a valid estimate of total fluoride exposure"[1] is not correct. There is scientific consensus that the urinary sample collection approaches used in almost all included studies (ie, spot urinary fluoride or a few 24-hour samples, many not adjusted for dilution) are not valid measures of individuals' long-term fluoride exposure, since fluoride has a short half-life and there is substantial variation within days and from day to day.[32-34] Thomas et al[35] found no association between spot urinary fluoride and plasma fluoride in the Early Life Exposures in Mexico to Environmental Toxicants study. Unfortunately, the acceptance by Taylor and colleagues of spot urinary fluoride as a valid measure will only lead to more low-quality studies.

Lack of Context for Fluoride Exposures

Another major concern relates to the article's almost complete lack of context for fluoride exposures. There is no mention of clinically relevant fluoride exposure ranges and no meaningful discussion of the lack of relevance of most of the article's findings to public health or to lay individuals' dental self-care practices using fluoride. Thus, the article probably will unnecessarily scare many people about their routine use of dental products and CWF. Kumar et al stated clearly that their "meta-analyses show that fluoride exposure at the concentration used in CWF is not associated with lower IQ scores"[26] but that "the reported association at higher fluoride levels in endemic areas requires further investigation."[26] This perspective about public health importance is completely lacking here.

Several Other Important Concerns and Limitations to Consider

As presented, the magnitudes of all possible IQ differences are inflated substantially. For the US and most of the world, the recommended CWF fluoride level is 0.7 mg/L, so the difference between a community with low fluoride (eg, approximately 0.2 mg/L) and an optimally fluoridated community would be approximately 0.5 mg/L. However, Taylor and colleagues use a difference of 1.0 mg/L in their calculations, artificially doubling the estimated impact on IQ.

There is no acknowledgment that the more recent studies, both those included in the meta-analysis tables and figures and those not included, are generally of somewhat higher quality and generally show weaker or no associations of fluoride with IQ.

Also, there appears to be a factual error in the abstract where it states there is the same pattern of negative associations with fluoride in the studies with lower risk of bias limited to a fluoride concentration less than 1.5 mg/L, but this is not correct (see Table 2 in the article by Taylor et al[1]). In fact, there are very small, not statistically significant associations across studies in areas with water fluoride levels less than 1.5 mg/L, whether considering all studies or just those at lower risk of bias.

Taking these many important concerns together, readers are advised to be very cautious in drawing conclusions about possible associations of fluoride exposures with lower IQ. This is especially true for lower water fluoride levels.

Public Health Aspects

As a public health dentist, I am most interested in the relevance of the study findings to public health policy related to use of fluoride at the levels of individuals' self-care, dental and medical practitioners' professional use of fluoride, and use of fluoride through CWF. Thus, it is critical that we focus on the results from studies looking at lower water fluoride levels comparable to those used in CWF, which is recommended at 0.7 mg/L throughout the US. Considering these data and other studies that have investigated the data relevant to lower water fluoride levels, it is important to emphasize that there is no evidence of association of IQ with water fluoride levels below 1.5 mg/L. Kumar et al[26] conducted extensive meta-analyses of studies' results from nonendemic areas (<1.5 mg/L fluoride), including SMD, regression coefficients, SMD metaregression, and cubic spline regression of 31 data points. They found that fluoride exposure in this range relevant to CWF was not associated with lower IQ or cognition scores. There is nothing in the NTP meta-analysis, when properly interpreted, that contradicts the results found by Kumar et al.[26] This conclusion of a lack of association is bolstered further by more recent individual studies[23,24] that were not included in the meta-analysis by Taylor et al.[1]

Thus, despite the presentation of some evidence of a possible association between IQ and high fluoride levels in water, there is no evidence of an adverse effect at the lower water fluoride levels commonly used in CWF systems. Therefore, public policy concerning the addition of fluoride to community water systems and recommendations concerning the use of topical fluoride in its many forms should not be affected by the study findings, and the widespread use of fluoride for caries prevention should continue.

ARTICLE INFORMATION

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Published Online: January 6, 2025. doi:10.1001/jamapediatrics.2024.5539

Conflict of Interest Disclosures: Dr Levy reported receiving grants in the past from the National Institute of Dental and Craniofacial Research related to fluoride, dental caries, dental fluorosis, and bone development, receiving small grant funding from the Centers for Disease Control and Prevention related to fluoride, dental caries, and fluorosis, serving as consultant to the Centers for Disease Control and Prevention and the National Institute of Dental and Craniofacial Research, and serving on the National Fluoride Advisory Committee for the American Dental Association. No other disclosures were reported.

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