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Letter to the Editor

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

Kumar et al.[1] recently published a meta-analysis concluding that fluoride exposure relevant to community water fluoridation is not associated with lower IQ in children. Although addressing an important public health concern, the publication lacks essential methodological details to allow others to reproduce the reported findings.[2]

Kumar et al.[1] did not reference or register a protocol that defined methods a priori. A predefined protocol is important for preventing confirmation bias (e.g., deciding which studies to include or exclude based on whether results were expected or desired by the researcher). Knowledge of the evidence can influence the defined research question, choice of study eligibility criteria, and selection of outcomes analyzed, all of which may bias results.[2]

The study selection process in Kumar et al.[1] is not transparently reported. The authors state reliance on a literature search from the Draft 2020 NTP Monograph,[3] that "identified 46 studies for SMD [standardized mean difference] meta-analysis". However, Kumar et al.[1] only identifies 28 studies, and does not cite or fully explain why the other 18 studies were excluded. For example, four studies were excluded because of "unusual low IQ scores"; however, no definition of "unusual low IQ" was provided, and there is no explanation of how this issue was considered for individual studies.

The authors also inconsistently apply their inclusion and exclusion criteria. For example, the exclusion criteria specify studies "where the higher exposure was greater than 1.5 mg/L"; however, 20 studies used in the random effects meta-analysis have fluoride exposure groups >1.5 mg/L. There are also up to seven studies,[1] that had a higher fluoride exposure group <1.5 mg/L yet were not included in the meta-analysis. One of these studies[4] is inaccurately described as having a population that overlaps with another study. Given that these additional studies and their extracted data are available and downloadable from the Draft 2020 NTP Monograph,[4] the inconsistency and lack of transparency in study selection suggests bias.

Best practices for risk-of-bias include pre-specified guidance and documentation that risk-of-bias criteria are applied consistently across studies. Kumar et al.[1] reported using an "adaptation" of the OHAT risk-of-bias tool but did not describe those adaptations and reports risk-of-bias ratings without any supporting documentation. Although not cited by the authors, their risk-of-bias assessments for eight studies are registered in the Health Assessment Workspace Collaborative (HAWC) (https://hawcproject.org/assessment/1238/). However, the rationales for these ratings are limited and inconsistently applied as illustrated for Bashash et al.,[5] which was conducted in an area where community fluoridation is accomplished by addition to salt. The authors rate the study "probably high" risk of bias for confounding because "*Salt fluoridation implies consumption of salt which may be indicative of poor-quality diet*"; however, the authors provide no evidence to support this assertion.

The authors are also less than forthcoming when describing their results. For example, they state that their "meta-analysis of non-linear regression with restricted cubic spline for SMD showed that population fluoride concentration exposure differential between recommended F levels and lower areas was not associated with SMD (Supplementary Fig B)".[1] By demonstrating that smaller contrasts in fluoride exposure are not associated with SMDs (which can also be true at higher exposure levels), the figure simply confirms the inherent difficulty in observing an adverse effect at lower exposure levels. There are also concerns with the statement "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). "[1] This analysis is not described in the methods, so it is not clear how IQ scores were standardized, and authors do not account for intra-study correlation for eight studies that contribute more than one data point to the regression analysis. In addition, the authors inappropriately include IQ scores and corresponding water or urinary fluoride levels from only the reference/lower fluoride group of 20 studies, identified previously by authors as meeting exclusion criteria for being conducted in "endemic" regions, biasing associations towards the null. Finally, the results of this analysis are only described as a "model Likelihood-ratio test: *P*-value = 0.34" with no explanation of what the p-value indicates, leaving the authors' conclusion that this analysis "did not show a relationship between F concentration and IQ scores"

[1] Additional five studies cited belowBai A, Li Y, Fan Z, Li X, Li P. [Intelligence and growth development of children in coal-burning-borne arsenism and fluorosis areas: An investigation study]. *Chin J Endemiol.* 2014; 33(2):160–163.Ding Y, Sun H, Han H et al. The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China. *J Hazard Mater.* 2011; 186:1942–1946.Li F, Chen X, Huang R, Xie Y. The impact of endemic fluorosis caused by the burning of coal on the development of intelligence in children. *J Environ Health.* 2009; 26(4):838–840.Yao Y. Comparable analysis on the physical and mental development of children in endemic fluorosis area with water improvement and without water improvement. *Lit* Inf *Prev Med.* 1997; 3(1):42–43.Yu X, Chen J, Li Y et al. Threshold effects of moderately excessive fluoride exposure on children's health: A potential association between dental fluorosis and loss of excellent intelligence. *Environ Int.* 2018; 118:116–124. doi:https://doi.org/10.1016/j.envint.2018.05.042Guo B, Yu J, Cui Y et al. DBH gene polymorphism, iodine and fluoride and their interactions and their interaction with children's intelligence. *J Environ Hygiene.* 2021; 11(02):134–140.Zhang S, Zhang X, Liu H et al. Modifying effect of COMT gene polymorphism and a predictive role for proteomics analysis in children's intelligence in endemic fluorosis area in Tianjin, China. *Toxicol Sci.* 2015; 144:238–245.

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unsupported.

Considering the serious limitations in both methodology and transparency that preclude reproducing their findings, extreme caution should be exercised in considering conclusions regarding the association between fluoride exposure and IQ in children as presented in Kumar et al.[1]

Author statements

Ethical approval

Nothing to declare.

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Competing interests

Nothing to declare.

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Kyla W. Taylor[a,*], John R. Bucher[a], Sorina E. Eftim[b], Robyn B. Blain[b], Andrew A. Rooney[a]

[a] *Division of Translational Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA*

[b] *ICF, Reston, VA, USA*

[*] Corresponding author. P.O. Box 12233, Mail Drop K2-04 RTP, NC, 27709, USA.
E-mail address: kyla.taylor@nih.gov (K.W. Taylor).