

"Fluoride benefits and risks: Lessons from 70 years of water fluoridation in Singapore": Correspondence

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Dear Editor,

Recently Yee et al. published a commentary in the *Annals*,¹ focusing on a meta-analysis of 74 human observational studies by Taylor et al. published in *JAMA Pediatrics*,² which found an inverse association between fluoride exposure and children's intelligence quotient (IQ). Although many of the authors' critiques are directly addressed in Taylor et al. and in their previous commentary,³ the group would like to take this opportunity to respond.

As reported in Taylor et al.² the meta-analysis was performed to the highest standards of transparency and objectivity, following a pre-established, peer-reviewed protocol that outlined all aspects of the analyses including the inclusion and exclusion criteria for study selection to avoid bias.⁴ The comprehensive literature search captured all relevant literature across 8 international databases without language restriction. Two reviewers extracted data and performed risk-of-bias (study quality) evaluations independently, for each relevant study. Data are publicly available and downloadable for anyone to repeat or extend this work (<https://hawcproject.org/assessment/405/>).

Yee et al. are correct that most studies were conducted in countries where fluoride levels in water are above 1.5 mg fluoride/L, and that Taylor et al. included studies with both higher and lower risk of bias. However, they do not also note that the inclusion of all studies, regardless of quality or level of exposure, is consistent with best practices for meta-analyses in environmental epidemiology. The findings by Taylor et al. are not based solely on a single combined set of studies; the study also includes numerous subgroup analyses restricted to studies with exposures below the US Environmental Protection Agency's (EPA's) or the World Health Organization's upper exposure guidelines of 4 mg/L, 2 mg/L and 1.5 mg/L of fluoride in drinking water. Importantly, analyses restricted to the high-quality studies—which represent the strongest and most reliable evidence—consistently supported

the inverse association between fluoride exposure and children's IQ.

Yee et al. noted that there was "evidence of substantial heterogeneity," but did not acknowledge that this is expected for observational studies with a variety of study locations, populations and exposure metrics. In contrast to meta-analyses of randomised controlled trials, where heterogeneity in results can reduce confidence in the findings, heterogeneity in methods across observational studies that provide consistent evidence of an association can strengthen confidence in the findings.³

Yee et al. also claimed that Taylor et al. did not provide justification for the exclusion of studies or explain the "calculated individual effect sizes" for the main analysis. In fact, reasons for exclusion of each study are provided in the Interactive Reference Flow Diagram (eFigure 1b) in the study selection section of the main paper, and are listed for individual studies in eTable 2 of the supplemental materials in Taylor et al.² Additionally, the study selection section of the supplemental material states: "Studies that did not report quantitative effect estimates (mean outcome measures or regression coefficients), measures of variability (95% CIs, SEs, or standard deviations [SDs]), or numbers of participants were excluded. Studies with missing measures of variability but with reported p-values were included, and SDs were calculated following the approach in the Cochrane Handbook for Systematic Reviews."⁵

As explained in the main text and supplemental material for the mean effects meta-analysis, effect estimates were the standardised mean differences (SMDs) for heteroscedastic population variances. SMDs were calculated from the difference in mean IQ scores between an exposed and reference group.²

Yee et al. critiqued Taylor et al.'s reliance on studies reporting spot urinary fluoride values as estimates of total exposure to fluoride. They claim, without supporting evidence or citation, that spot urine

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samples are not "a reliably valid measure of long-term fluoride exposure in individuals." First, it is important to recognise that urinary fluoride data was only one of the measures considered; the inverse associations between fluoride exposure and children's IQ were consistently observed across multiple exposure metrics including fluoride levels in drinking water and estimated fluoride intake. Second, while Taylor et al. acknowledge there are limitations in using spot urinary data, when corrected for dilution, they have been shown to be moderately correlated across individual pregnant women sampled in each trimester of gestation. Spot urinary data have also successfully distinguished between populations consuming fluoridated versus non-fluoridated drinking water;⁶ correction for dilution was an element of the exposure risk-of-bias assessment in Taylor et al. Additionally, regulatory agencies like the US EPA, routinely rely on urinary exposure estimates for risk assessment purposes.

Yee et al. suggest that confounding factors were not "well controlled", to which Taylor et al. disagree. Although confounding factors or covariates were not uniformly accounted for across all studies, the potential for confounding was a critical element of the risk-of-bias evaluation. Studies were only rated as having low risk of bias for confounding if they adequately accounted for key covariates including age, sex, socioeconomic status and co-exposure to other neurotoxicants. Consideration of clustering by city was also included in the risk-of-bias assessment if relevant to the study. A subset of the literature collected through October 2023 was specifically examined for evidence of a pattern of confounding bias that could explain the consistent inverse association between higher exposure to fluoride and lower IQ in children. No such pattern could be discerned, indicating that confounding cannot account for the direction of association.⁷

Finally, regarding the validity of IQ tests, Taylor et al. note that regulatory agencies have relied on IQ tests to evaluate neurotoxicity of substances, such as lead and mercury. The risk-of-bias assessment by Taylor et al. had also considered whether IQ tests were culturally appropriate, blinded to exposure and normed against country-specific populations. The authors appreciate the opportunity to respond and provide these clarifications.

Ethics statement

Not applicable as no study participants were recruited for this Letter to the Editor.

Declaration

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