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Developmental Fluoride Neurotoxicity: Clinical Importance versus Statistical Significance

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We were interested to read the article by Choi et al. (2012), who investigated the effects of increased fluoride exposure and delayed neurobehavioral development by reviewing published studies and performing a meta-analysis. Of the 39 studies identified, the authors considered 27 to be eligible. Choi et al. reported a mean difference in IQ (intelligence quotient) score between exposed and reference populations of -0.4 (95% confidence interval: $-0.5, -0.3$) using a random-effects model. Thus, children in high-fluoride areas had significantly lower IQ scores than those who lived in low-fluoride areas.

Even if we ignore the weaknesses of the study (Choi et al. 2012), including a lack of individual-level information and the high probability of confounding because the authors did not adjust for covariates, a difference of 0.4 in mean IQ is clinically negligible (Jeckel et al. 2007; Rothman et al. 2008; Szklo and Nieto 2007) even though it was statistically significant. In general, clinical importance takes priority over statistical significance. The *p*-value can easily change from significant to nonsignificant because of sample size or the mean difference and standard deviation of the variable in the study population (Jeckel et al. 2007; Rothman et al. 2008; Szklo and Nieto 2007). As Choi et al. (2012) pointed out in their conclusion, there is a “possibility of an adverse effect of high fluoride exposure on children’s neurodevelopment.” Such a conclusion can be considered an ecological fallacy, which can easily lead to misinterpretation of the results. It is important to know that statistics cannot provide a simple substitute for clinical judgment (Jeckel et al. 2007; Rothman et al. 2008; Szklo and Nieto 2007).

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Developmental Fluoride Neurotoxicity: Choi et al. Respond

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Sabour and Ghorbani’s comments about the reported mean difference in IQ (intelligence quotient) scores reported in our article (Choi et al. 2012) suggest a misunderstanding of the scale unit we used and the public health significance of even a small decrease in the average IQ associated with exposure. We appreciate this opportunity to clarify the factual information about the reported IQ measure.

The standardized weighted mean difference (SMD) in IQ score between exposed and reference populations was -0.45 (95% confidence interval: $-0.56, -0.35$) using a random-effects model (Choi et al. 2012). We used the SMD because the studies we included used different scales to measure the general intelligence. The SMD is a weighted mean difference standardized across studies, giving the average difference in standard deviations for the measure of that outcome. For commonly used IQ scores with a mean of 100 and an SD of 15, 0.45 SDs is equivalent to 6.75 points (rounded to 7 points). As research on other neurotoxicants has shown, a shift to the left of IQ distributions in a population will have substantial impacts, especially among those in the high and low ranges of the IQ distribution (Bellinger 2007).

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Arsenic and Diabetes

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Maull et al. (2012) reviewed evidence linking arsenic with diabetes in an evaluation that I believe could divert research resources from where they should properly be allocated. I wish to make two points:

- The review gives credibility to flawed studies that conclude that the prevalence of diabetes is increased in people having urine arsenic concentrations in the upper 20% of the general U.S. population.
- The authors implied that we need studies assessing arsenic concentrations $< 150 \mu\text{g/L}$ in drinking water, whereas research should actually focus on $150\text{--}500 \mu\text{g/L}$.

Regarding the first point, Table 2 of the review by Maull et al. (2012) reported an adjusted odds ratio (OR) of 3.58 for diabetes in the upper quintile of U.S. urinary arsenic concentrations (Navas-Acien et al. 2008). When adjusted for sex, age, race, and creatinine (Navas-Acien et al. 2008), the OR was 0.82, and adjustment for four more factors resulted in an OR of 1.05. Navas-Acien et al. inserted two more variables into the regression model, including arsenobetaine (a nontoxic form of arsenic originating from fish), and the OR jumped up to 3.58. Never in the history of epidemiology have valid findings emerged from results like these. For > 20 years, arsenic researchers have been subtracting arsenobetaine from total arsenic in urine when assessing exposure to inorganic arsenic. When this is done, the OR estimate is 1.15 (Steinmaus et al. 2009a).

If the OR of 3.58 were valid, then very low concentrations of arsenic in water would be a major risk factor for diabetes. Among the 40 million or so adults within the highest quintile of urinary arsenic concentrations in the United States, > 4 million would become diabetic, attributable to low arsenic exposure. However, the OR estimate lacks scientific plausibility, with urine arsenic concentrations in the United States about 10 times lower than those related to diabetes in Taiwan, Bangladesh, and elsewhere, and with U.S. water arsenic concentrations about 50 times lower.

In their Table 2, Maull et al. (2012) also cited another paper by the same authors that claims there are increased risks of diabetes related to arsenic in the United States (Navas-Acien et al. 2009). Again, the OR suddenly jumped up after inappropriately adding variables into the multivariate analysis (Steinmaus et al. 2009b). Yet this review from Maull et al. (2012) presented Navas-Acien et al.’s results as if they were from valid methods of analyzing the data. These analyses should not have been cited or their mistakes should have been acknowledged.