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ARTICLE REVIEW

Article Review on "Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico"

Article Summary

The article by Bashash et al.,[1] published in *Environmental Health Perspectives* on September 19, 2017, describes a longitudinal birth cohort study that followed children from the prenatal period through to school age to assess the relationship between environmental fluoride exposures prenatally and in early life with cognitive outcomes during childhood. Fluoride exposure was assessed through urine taken from the mother during pregnancy (prenatal exposure) and from the child. Cognitive performance was assessed through standardized testing at preschool (4 years) and school age (6-12 years).

The study was conducted in Mexico City and used stored samples from cohorts set up as part of previous research studies. The environmental sources of fluoride for this population include fluoridated salt (250 ppm) and naturally occurring fluoride in drinking water (estimated range: 0.15-1.38 mg/L). Mexico City does not fluoridate their drinking water. Mothers were recruited during the first trimester of pregnancy across two birth cohort studies during the periods 1997-2001 (cohort '2A') and 2001-2006 (cohort '3'). Cohort 3 was a randomized double-blind placebo-controlled trial in which approximately half (334 out of 670 participants) of the study population received calcium supplements during pregnancy. Cohort 2A was an observational birth cohort designed to examine the influence of lead during pregnancy (327 participants).

Urine was collected from mothers up to three times during the study (once during each trimester of pregnancy) and from children at the time of their final cognitive performance assessment at 6-12 years. Many of the mothers did not provide a urinary fluoride for all trimesters. Creatinine-adjusted urinary fluoride concentrations and urinary fluoride values corrected for specific gravity were calculated for mothers and children, respectively. The authors found no correlation (p-value < 0.44) between maternal and childhood urinary fluoride concentrations. Creatinine-adjusted urinary fluoride concentrations were available for 512 mothers.

The authors measured cognitive performance at 4 years using the McCarthy Scales of Children's Abilities (measuring General Cognitive Index, GCI). Complete GCI and covariate data were available for 287 children. The authors measured cognitive performance at 6-12 years using the Wechsler Abbreviated Scale of Intelligence (measuring IQ). Complete IQ and covariate data were available for 211 children. The authors found a significant correlation (p-value < 0.01) between standardized testing scores at preschool and school age.

The authors used linear regression, adjusting for a number of potential confounders, to examine the relationship between fluoride exposure and cognitive performance. The authors found that a 0.5mg/L increase in maternal urinary fluoride was associated with a decrease in GCI of 3.15 points (95% CI: -5.42,-0.87), and a decrease in IQ of 2.50 points (95%CI: -4.12, -0.59). The association with GCI appeared linear across the complete range of maternal exposures while there was no clear association with IQ below maternal urinary fluoride concentrations of 0.8 mg/L. The authors found that a 0.5mg/L increase in child urinary fluoride was associated with a decrease in IQ of 0.77 (95%CI: -2.53, 0.99).

The authors conclude this study by stating:

"*Our findings must be confirmed in other study populations, and additional research is needed to determine how the urine fluoride concentrations measured in our study populations are related to fluoride exposures resulting from both intentional supplementation and environmental contamination.*"

Public Health Ontario Assessment

STRENGTHS

Previous research in the area of fluoride exposure and neurological outcomes during childhood has often been limited by small sample sizes and/or ecological study designs. The study by Bashash et al. is a considerable improvement over previous research given the large population size and the availability of individual level data to assess both exposure and outcome.

Another strength of the study design is that exposure was measured during what is perhaps the most vulnerable window of neurological development in children, the prenatal period.

This study measured fluoride exposure through a well established method that was first published in 2011.[2] The study also measured cognitive performance through well established methods.

LIMITATIONS

The study population was comprised of two cohorts (referred to as "Cohort 2A" and "Cohort 3") that were both recruited from hospitals in Mexico City that *serve low-to-moderate income populations*. This recruitment strategy has the potential to result in selection bias.

This study did not measure, or try to identify, environmental sources contributing to total fluoride exposure. There is no information on the contribution of drinking water and fluoridated salt to total fluoride intake, and there is also no information on other potential dietary sources of fluoride (e.g. consumption of foods high in fluoride or swallowing of toothpaste).

The study used two labs for urine analysis, and for one of these labs there was substantial data loss based on quality control criteria (305 out of 1,484 samples). This is unusually high but it is difficult to understand how this might have impacted the study results without additional details.

It is unclear why data outliers were excluded from the analysis. The authors also do not report the proportion of data that was excluded for this reason.

There was an attempt to adjust for maternal lead in this study, by measuring and adjusting for maternal bone lead levels. Bone lead is an excellent measure of long-term exposure to lead, but for a study such as this it would be preferable to have measured blood lead given that the interest is in circulating lead that would have the potential to cross the placenta and negatively affect neurological development in utero. Given the environmental levels of lead that would be present during the study period, and the well established link between lead and neurological outcomes in children, there is potential for unmeasured confounding. The study is also lacking data on other environmental exposures that could potentially confound the association between fluoride and cognitive performance, such as iodine and arsenic.

There were differences in the distribution of covariates between the two study cohorts, and the authors note that this might have resulted in potential biases. For example, participants in cohort 2A had higher mean bone lead levels (p-value 0.001) than participants in cohort 3. There were also differences between participants with and without missing data. For example, mean levels of maternal blood mercury for those included in the cognitive performance assessments were 28.5% (at age 4) and 24.9% (at age 6-12) higher compared with those who were excluded from cognitive assessments due to missing data.

Finally, the external validity (or generalizability) beyond the cohort to areas with markedly different socio-economic, cultural and environmental circumstances (e.g. Ontario) is limited.

Biological Plausibility

As an observational study, the article is not able to provide insight into possible mechanisms behind the association observed. There is good evidence that low doses of non-essential elements may have adverse effects on health. A large body of evidence links relatively low level exposure to lead and methyl mercury to neurotoxicity and adverse effects on neurocognitive development at the population level. A similar body of evidence does not exist for fluoride.

The US National Academy of Sciences (NAS), in a 2006 review on fluoride in drinking water, made reference to Chinese studies reporting IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water and concluded they lacked sufficient detail to assess their quality and relevance to the US population.[3] Reference was also made to animal studies reporting behavioural changes after administration of fluoride, although the changes were not large in magnitude. The NAS found studies on molecular, cellular and anatomical changes in the nervous system after fluoride exposure more compelling. The NAS review called for more research on the effects of fluoride on intelligence, brain chemistry and function. The current article can viewed as a part of the research effort recommended by the NAS.

Key Messages from the Article

- This is an important area for research given the level of public concern around the use of fluoride as a public health intervention to improve dental health. This article adds to our growing knowledge in this area.
- The study is methodologically better than many others in the literature and incorporates individual level, rather than ecological, exposure assessment. However, not all potential confounders were fully addressed and this remains a possible explanation for the association found.
- The study population in Mexico City does not receive fluoridated drinking water although fluoride is added to salt in Mexico. Although we do not have urinary fluoride levels specifically for pregnant women in Canada, the urinary fluoride levels found in the study are within the range that may be found in some individuals in Canadian communities with fluoridated water supplies (or in some individuals without fluoridated water but with other sources of fluoride exposure).

- The study did not find any clear relationship between IQ and urinary fluoride levels less than 0.8 mg/L. Whether or not this reflects a threshold for effect is unclear.
- Given the socio-economic, cultural and environmental differences between the study population in Mexico City and residents of Ontario communities, caution should be exercised in generalizing the results beyond cohort studied.
- This study should be viewed in the context of a growing body of literature which investigates possible relationships between low dose fluoride exposure and possible effects on neurocognitive development. While many published studies have reported an association, considered individually, there are at present, no methodologically strong studies of direct relevance to Ontario.

References

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