

SYNOPSIS

Review of “Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6–12 years of age in Mexico City”

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Synopses are brief descriptions of original research articles and reviews such as those that appear in the evidence-based abstraction journals. Synopses may be evaluative, and are generally not written by the authors of the original work.

Key messages

- Research assessing adverse health effects of water fluoridation has gained attention given concern around the use of fluoride as a public health intervention to improve dental health. This article has assessed attention-deficit/hyperactivity disorder (ADHD) symptoms in 6–12 year olds as an outcome of prenatal fluoride exposure. It is the second study from the same cohort of pregnant women in Mexico, which earlier assessed the effect of prenatal fluoride exposure on cognitive outcomes in children at 4 and 6–12 years of age.¹
- Using creatinine adjusted maternal urinary fluoride (MUFcr; mean(SD) 0.85(0.33) mg/L) to assess prenatal fluoride exposure, and validated scales administered on mothers and children to assess ADHD in children, the study found that a 0.5 mg/L increase in MUFcr corresponded with increases of several measures of ADHD using the Conners' Rating Scales-Revised (CRS-R) (test based on mothers' reporting). Although statistically significant, these changes were within the normal range and would not be considered clinically significant. Authors found no significant associations between MUFcr and Conners' Continuous Performance Test (CPT-II) measurements (test administered on children to measure ADHD).
- Methodologically, the study is better than previous studies in the field and incorporates individual level, rather than ecological, exposure assessment. However, not all potential confounders were fully addressed and these remain possible explanations for the association found.
- The study population in Mexico City does not receive fluoridated drinking water although fluoride is added to salt in Mexico. As per the Canadian study, published on the same date

(October 10, 2017), MUF levels of pregnant women living in fluoridated regions of Canada (mean(SD) MUFcr 0.87(0.50) mg/L) are comparable to mean MUFcr levels of pregnant women in this study; therefore, findings may be relevant in the Ontario context.

Background

- Bashash et al.'s article, based on Early Life Exposures to Environmental Toxicants (ELEMENT) birth cohort data in Mexico, was published online on October 10th 2018; the same day that two other papers related to fluoride exposures were released. In 2017, the same authors published a study in Environmental Health Perspectives based on the same cohorts, where they assessed the relationship between prenatal and early life fluoride exposures and cognitive outcomes during childhood.¹ That study gained media attention and PHO prepared a review of that paper.² There were a number of media releases following the most recent publications. Community water fluoridation has been a source of controversy in some communities. Health units have requested that Public Health Ontario provide a review of the recently released studies to assist in addressing inquiries from the public, media and others.

Appraisal

Study Design

- This prospective cohort study used longitudinal birth cohort (Early Life Exposures to Environmental Toxicants (ELEMENT) data in Mexico, following children from the prenatal period through to school age. This study assessed the relationship between prenatal fluoride exposure and ADHD in 6-12 year olds. The MUFcr (the predictor) was collected by spot urine samples. To assess ADHD behaviours, the Conners' Rating Scales-Revised (CRS-R) was completed by mothers, and the Conners' Continuous Performance Test (CPT-II) was administered to their children aged 6-12.
- The environmental sources of fluoride for this population included fluoridated salt (250 ppm) and naturally-occurring fluoride in drinking water (estimated range: 0.15-1.38 mg/L). Mexico City does not fluoridate its drinking water. Mothers were recruited during the first trimester of pregnancy across two birth cohort studies during the periods 1997-1999 (cohort '2A') and 2001-2003 (cohort '3'). Cohort 2A was an observational birth cohort and cohort 3 was a randomized double-blind placebo-controlled trial in which subjects were either randomized to the calcium supplement (Cohort 3 – Ca +) or to placebo (Cohort 3 – placebo). There were differences in the distribution of covariates between the two study cohorts (described in the limitation section).

Main findings

- The mean(SD) of MUFcr of the study population was 0.85(0.33) mg/L. As per the analysis of 213 mother-children pairs, a 0.5 mg/L higher MUFcr corresponded with increases of several measures of ADHD as reported by mothers on the Conners' rating scale including: DSM-IV Inattention 2.84 points (95% CI: 0.84, 4.84); DSM-IV ADHD Total 2.38 points (95% CI: 0.42, 4.34); Cognitive Problems and Inattention 2.54 points (95% CI: 0.44, 4.63); and ADHD Index 2.47 points (95% CI: 0.43, 4.50).

- As per Table 1 of the article, the means and 95% CI values for the four CRS-R indices for study participants are as follows:
 - DSM-IV Inattention - 53.89 (52.48, 55.30)
 - DSM-IV ADHD Total - 55.61 (54.26, 56.97)
 - Cognitive Problems and Inattention - 54.62 (53.14, 56.10)
 - ADHD Index - 54.30 (52.88, 55.71)
- Overall, mean \pm SD scores across all of the CRS-R scales fell within the average range (i.e., mean $T=50 \pm 10$, which is 1 SD). The authors found that a 0.5 mg/L increase in MUFcr corresponded with approximately a 2.5 point increase across the four indices, which remains within normal boundaries. In other words, although the confidence intervals for each of the four outcomes above indicate the changes are statistically significant, the changes would not be clinically significant. That said, it is important to conduct more studies in the future, with robust methodologies, to further explore this association.
- Authors observed a possible ceiling effect of the exposure to CRS-R; this ceiling effect would essentially mean that after a particular threshold of exposure, no further increase in outcome can be observed. However, evidence for this effect is not consistent for all of the outcomes. Also, to the extent that non-linear effects are present, the coefficients given in Table 2 would not apply across the full range of MUFcr.
- Authors found no significant associations between maternal urinary fluoride and the performance of children on an objective test (the CPT-II) or on symptom scales assessing hyperactivity with MUF. The CPT-II measured errors of omission, commission, and reaction times. The mean scores of all three dimensions of the CPT-II were significantly different for children from cohort 2A versus those from cohort 3. Whether this is due to differences in the period of recruitment or other factors is not clear. It does raise questions about the merits of a combined analysis of the cohorts and the internal validity of findings.
- It is interesting that the authors choose to use gamma regression to model the data; the residual plot from the linear regression would be helpful in assessing the appropriateness of gamma regression. One would have greater confidence in the associations found if other methods of analysis had also been used and gave similar results. This is particularly true in light of the borderline statistical significance of some of the associations.
- Approximately 10% of the study participants fell in the clinically significant range (i.e. T-score ≥ 70 on the Index scores). The authors do not comment on whether their results are unusual or typical with respect to what has been found when using this screening questionnaire in other settings. The prevalence of ADHD in US children aged 8-15 is 8.7%, with a higher prevalence in those with lower socio-economic status, so these results may not be unusual.

Strengths

- This study was a longitudinal birth cohort with individual biomarkers of fluoride exposure obtained during pregnancy. Fluoride exposure was measured through a well-established method that has been used in several other research papers.

- Maternal urinary fluoride concentrations were adjusted for creatinine to account for variations in urine dilution.
- Attention outcomes were assessed using the Spanish version of the Conners' Rating Scales-Revised (CRS-R), a validated screening tool for ADHD. In addition, the Conners' Continuous Performance Test was administered on children to assess sustained attention and inhibitory control.
- The study adjusted for some covariates such as gestational age, birth weight, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. non-smoker), marital status (married vs. others), and education.

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*. It is not necessarily representative of the general population.
- The two cohorts were recruited at different time periods, under different study designs. There were differences in the distribution of covariates between the two study cohorts. For example, as per the authors’ previous study, participants in cohort 2A had higher mean bone lead levels (p -value 0.001) than participants in cohort 3. This study also shows differences between children’s ages between cohorts at outcome assessment ($p < 0.01$). Further, the CPT-II results for all three dimensions were significantly different between the two cohorts: omission errors ($p = 0.024$); commission errors ($p = 0.007$); and reaction time (0.016).
- This study did not assess source of fluoride exposure (e.g., consumption of foods high in fluoride or swallowing of toothpaste) contributing to total fluoride exposure. Therefore although the study showed an association with a biomarker of fluoride exposure it is not possible to attribute the fluoride exposure to any particular source.
- The authors used gamma regression for their analysis. While this choice is defensible, it would give greater confidence in the results if results for other regression models were used and gave similar results. This is particularly important given the marginal statistical significance of some of the associations found. A more detailed discussion of the analysis and the residuals would have been helpful.
- The curvilinear relationships found between fluoride and outcomes such as ‘cognitive problems and inattention’ are unusual. They depart from more common ‘dose-response’ relationships found in studies of environmental risk factors and are difficult to explain with respect to underlying mechanism. Although some adjustment for cohort was done during the analysis, the relationship reported in the study may reflect different relationships in the two cohorts.
- There was an attempt to adjust for maternal lead in this study, by measuring and adjusting for maternal bone lead levels of mothers where data were available. 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 umbilical cord blood lead or maternal blood lead during pregnancy 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 also lacks data on other environmental exposures that could potentially confound the association between fluoride and cognitive performance; for example, persistent organic pollutants, iodine and arsenic. The potential for confounding from other environmental exposures is a serious limitation with respect to interpreting the associations found with maternal urinary fluoride.

- Only 6.5% of women had urinary fluoride level data from each trimester of pregnancy. The majority, 57%, had only one urine sample. This has potential for exposure misclassification. The MUF levels vary over pregnancy, increasing from trimester 1 to trimester 3.³ Combining MUF values from different trimesters has a potential to affect the validity of the exposure variable. A study by Malin et al., published on the same date as this study (October 10, 2018) and conducted in Canada, used three urine samples, from each trimester, for all study participants, which is a better way of assessing the exposure.
- Spot samples may reflect acute, rather than ongoing fluoride exposure. It is not clear if any sample with severely high values (outliers) were excluded from analysis or not.
- There is no mention if assessors or participants in the study were blinded to the outcome. If not, then there is a potential for confirmation bias.⁴
- Covariates:
 - The study did not take into consideration any paternal covariates, such as father's mental health,⁵ education and smoking status.
 - Participants' marital status or mental health status was assessed only during the first trimester of pregnancy. This information was not updated at the time of ADHD testing, as it can change over time, and existing literature suggests that mothers with depression^{5,6} or single parent can report higher ADHD scores for their children.
 - The HOME score, an important predictor of home environment, was administered only to a subset of participants and therefore was not included in the adjusted model but was only a part of the sensitivity analyses.
 - Secular trends also need to be taken into consideration. In the last decade or so reporting and treatment of ADHD is on the rise.⁷

Reliability

- The authors are from established universities in Canada, the US, and Mexico.
- The 2016 impact factor for the journal *Environmental International* was 7.08.
- No declarations were made in regard to any conflicts of interest.
- This study was supported by U.S. NIH R01ES021446, NIH R01-ES007821, NIEHS/EPA P01ES022844, NIEHS P42-ES05947, NIEHS Center Grant P30ES017885 and the National Institute of Public Health/Ministry of Health of Mexico.
- Reporting issues:

- Not reported whether those administering the psychological tests were blinded for the outcome assessment.
- Authors present plots showing a curvilinear relationship while Table 2 implies linear relationship between MUFcr and outcomes. This is confusing and appears inconsistent with the authors' comments on a ceiling effect.
- Authors used gamma regression to address the skewness of the residuals; however, the residual plot from the linear regression is not reported.

Relevancy

- The effects found in this study were found at the population or group level; they would not be discernable in individuals, as such they do not appear to have clinical relevance.
- This study has limitations and by itself does not establish a link between fluoride intake during pregnancy and subsequent ADHD in children. However, it does add to a growing body of research studies suggesting possible associations between relatively low levels of fluoride exposure and neurocognitive outcomes. Careful monitoring of future studies in this area is warranted.
- As such, a number of studies in recent years have been conducted to assess the possible association between fluoridated water and adverse health effects. These have been reviewed in an evidence report.⁸

Ontario Applicability

- The practice of community water fluoridation is debated in many jurisdictions across North America, including Ontario. Mean urinary fluoride levels of pregnant women in this study are comparable to mean urinary fluoride levels of pregnant women living in fluoridated regions of Canada; therefore, findings may be relevant in the Ontario context, although the study cohort differed in numerous ways from the Ontario population. As such, it is essential to ensure the robustness of the study methodology and validity of results.

References

1. Bashash M, Thomas D, Hu H, Martinez-Mier EA, Sanchez BN, Basu N, et al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6–12 years of age in Mexico. *Environ Health Perspect.* 2017;125(9):097017. Available from: <https://ehp.niehs.nih.gov/doi/full/10.1289/EHP655>
2. Ontario Agency for Health Protection and Promotion (Public Health Ontario), MacIntyre E, Singhal S, Copes R. Article review on “Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6–12 years of age in Mexico” [Internet]. Toronto, ON: Queen’s Printer for Ontario; 2019 [cited 2019 Feb 8]. Available from : [www.publichealthontario.ca/en/eRepository/Fluoride IQ Mexico Article Review 2017.pdf](http://www.publichealthontario.ca/en/eRepository/Fluoride_IQ_Mexico_Article_Review_2017.pdf)
3. Till C, Green R, Grundy JG, Hornung R, Neufeld R, Martinez-Mier EA, et al. Community water fluoridation and urinary fluoride concentrations in a national sample of pregnant women in Canada. *Environ Health Perspect.* 2018;126(10):107001. Available from: <https://ehp.niehs.nih.gov/doi/full/10.1289/EHP3546>
4. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. *J Multidiscip Healthc.* 2016;9:211-7. Available from: www.dovepress.com/informatoin-bias-in-health-reserach-definition-pitfalls-and-adjustment-peer-reviewd-artcile-JMDH
5. Deault LC. A systematic review of parenting in relation to the development of comorbidities and functional impairments in children with attention-deficit/hyperactivity disorder (ADHD). *Child Psychiatry Hum Dev.* 2010;41(2):168-92.
6. Mahoney D. Maternal depression predicts ADHD in kids [Internet]. Parsippany, NJ: Frontline Medical Communications; 2007 [cited 2018 Oct 24]. Available from: www.mdedge.com/sites/default/files/issues/articles/70430_main_7.pdf
7. Davidovitch M, Koren G, Fund N, Shrem M, Porath A. Challenges in defining the rates of ADHD diagnosis and treatment: trends over the last decade. *BMC Pediatr.* 2017;17(1):218. Available from: www.bmcpediatr.biomedcentral.com/articles/10.1186/s12887-017-0971-0
8. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Evidence review for adverse health effects of drinking optimally fluoridated water: evidence since the 2010 Government of Canada Report. Toronto, ON: Queen’s Printer for Ontario; 2018. Available from: www.publichealthontario.ca/en/eRepository/evidence-review-effects-drinking-optimally-fluoridated-water.pdf

Appendix A

Quality assessment tool sourced from: NIH National Heart Lung and Blood Institute. Study quality assessment tools: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [Internet]. Bethesda, MD: National Heart Lung and Blood Institute; 2018 [cited 2018 Oct 18]. Available from: www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Bashash – Responses to criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	X		
2. Was the study population clearly specified and defined?	X		
3. Was the participation rate of eligible persons at least 50%?			X – could not determine
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?		X	
5. Was a sample size justification, power description, or variance and effect estimates provided?	X		
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	X		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	X		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	X		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		X	
10. Was the exposure(s) assessed more than once over time?		X	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	X		
12. Were the outcome assessors blinded to the exposure status of participants?	X		

Bashash – Responses to criteria	Yes	No	Other (CD, NR, NA)*
13. Was loss to follow-up after baseline 20% or less?		X	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		X	

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