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Ecological Fluoride and Neurodevelopment Studies—An Important Starting Point

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Over the past decade, there has been growing interest in whether chronic low-level fluoride exposure may impact neurodevelopment. Recently, several US-based ecological studies have examined that question.[1-3] Hernandez et al[4] is the latest comparable study. It examined prenatal water fluoride exposure and behavioral problems in approximately 5500 children across the US from the Environmental Influences on Child Health Outcomes (ECHO) cohort (2005-2019) and estimated area-level, time-weighted, average fluoride concentrations in public water based on residential addresses during pregnancy. The study assessed internalizing and externalizing behaviors among children aged 1.5 to 17 years using caregiver reports on the Child Behavior Checklist. Water fluoride concentrations were low on average, and the authors generally did not observe associations between prenatal water fluoride exposure and child internalizing or externalizing problems. However, they observed positive associations with externalizing problems among children older than 6 years and for water fluoride levels greater than 625 µg/L.[4]

Findings from prior US ecological fluoride and neurodevelopment studies have generally been mixed. The first of these, published in 2015, found that higher prevalence of community water fluoridation per state was associated with higher attention-deficit/hyperactivity disorder prevalence among children aged 4 to 17 years.[5] Although the subgroup findings of Hernandez et al[4] are consistent with the 2015 findings, their general null findings were not. However, like the current study, a recent ecological study by Warren et al[2] also observed null associations between community water fluoridation and a different neurodevelopmental outcome—adolescent IQ. That study was larger and included more than 10 000 individuals from a Wisconsin high school graduating class of 1957; however, community water fluoridation had not yet begun during the participants' prenatal development. Interestingly, an earlier study by Warren et al[1] that included approximately 58 000 US high school students in 1980 even observed a beneficial association between childhood water fluoride exposure and adolescent cognition. However, a recent study of more than 70 000 children enrolled in Florida Medicaid between 1990 and 2012 had divergent findings.[3] It found that fluoridated water exposure over the first 10 years of life was associated with increased risk of intellectual disability and autism spectrum disorder. Furthermore, a study just published by authors for the ECHO Cohort Consortium[6] found that prenatal public water fluoride exposure near the current US-recommended level (700 µg/L) was inversely associated with fluid cognition scores among 2514 children born between 2006 and 2019 in the US. The different findings among these studies underscore the need for rigorous prospective research, especially considering the limitations with correctly classifying exposure in an ecological design.

Hernandez et al[4] builds on prior ecological designs by providing a fine-grained modeling approach for ecological water fluoride exposure assessment. The study used geocoded maternal residential address histories to apply census tract–level water fluoride estimates to each month of pregnancy. Furthermore, it accounted for residential moves.[4] However, despite this more comprehensive approach, the design was still subject to the same fundamental limitation that all ecological fluoride studies are: It does not allow for measurement of how much fluoride each participant is consuming. The authors appropriately acknowledge this limitation. Measurement of fluoride consumption is important because some people who live in a fluoridated community may filter their tap water such that it removes most of the fluoride. Conversely, those living in unfluoridated regions may regularly consume black tea or other foods and beverages containing fluoride, resulting in exposure levels that exceed those of people in fluoridated communities. As

such, an ecological or area-level design increases the likelihood of exposure misclassification and corresponding bias toward the null. Detection of true associations between prenatal fluoride exposure and child neurobehavioral outcomes may thus be limited. Furthermore, uncertainty is introduced regarding the implications of study findings.

While drinking water fluoride measures can be informative, they might best be measured at the individual level. The National Health and Nutrition Examination Survey does this by measuring fluoride in household tap water samples and providing a questionnaire about drinking water and tea consumption habits. Biomarkers in general better approximate how much fluoride from all sources an individual is exposed to at a given time. Moreover, as the Hernandez et al[4] study notes, fluoride in urine (a widely used biomarker for fluoride exposure assessment) has been shown to strongly correlate with drinking water fluoride levels in several studies. It would be interesting to see a follow-up to Hernandez et al[4] that uses the ECHO cohort's rich biorepository to measure fluoride concentrations in biospecimens. Researchers could then determine whether water fluoride concentrations ascertained via this novel area-level approach are associated with more well-established fluoride exposure biomarkers. Such a determination would not only help assess the validity of the census tract–level water fluoride measure but also enable individual-level examination of fluoride exposure and its association with neurodevelopment across the nation.

Interestingly, the rigorous prospective studies on prenatal fluoride exposure and neurodevelopment in North America that included individual measures of fluoride exposure assessment yielded consistent findings. However, there have been some inconsistencies in the international literature.[7] In North America, regardless of whether the study assessed prenatal fluoride exposure via maternal urine alone,[8] food and beverage intake,[9] or maternal urine and daily water or beverage consumption,[10] higher prenatal fluoride exposure has been consistently associated with worse child neurodevelopmental outcomes. These outcomes include more attention-deficit/hyperactivity disorder symptoms, worse cognitive development, and lower IQ.[7,9] Furthermore, findings from the first US-based prospective cohort study on prenatal fluoride exposure and child neurobehavior also converged.[8] Contrary to Hernandez et al,[4] the study found that women in Los Angeles, California, with higher urinary fluoride levels during pregnancy tended to rate their children higher on overall neurobehavioral problems and internalizing behaviors.[8] However, the study included predominately Hispanic women with low income, while Hernandez et al[4] included mostly White women with average socioeconomic hardship. These discrepancies highlight the importance of considering whether sociodemographic differences are associated with potential neurodevelopmental risks from fluoride exposure.

In conclusion, Hernandez et al[4] provide an innovative and more precise approach to ecological water fluoride assessment than prior studies; however, this is a challenging area to study, and conclusions cannot be drawn from ecological or area-level research alone. In general, there is still so much to learn about how fluoride exposure in the US may or may not be affecting our brains. Indeed, research on this topic has only been conducted starting in the past 10 years or so, 70 years after fluoride was first added to community drinking water. Perhaps the most accurate conclusion to reach at present is that we still do not know for sure whether chronic low-level fluoride exposure is damaging the developing brains of children in the US—it may or may not be.

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