Prenatal exposure to fluoride in public water and child cognition in the US ECHO Cohort, 2006-2019

Katrina R. Simon, PhD[1]; Tessa Bloomquist, MS[1]; Tushara Rajeev, MSPH[1]; Alexis Hernandez, MS[2]; Sharon Kulali, BS[1]; Mohamad Burjak, MS[3]; Amii M. Kress, PhD[3]; Meredith Palmore, MHS[3]; Anahid Akbaryan, BS[4]; Tiffany R. Sanchez, PhD[5]; Yoshira Ornelas Van Horne, PhD[6]; Hyeong-Moo Shin, PhD[7]; Dana E. Goin, PhD[8]; Marcella Tamayo-Ortiz, ScD[1]; Gaurav Patel, MD, PhD[9]; Lauren C. Shuffrey, PhD[4]; Akhgar Ghassabian, MD, PhD[10]; Margaret R. Karagas, PhD[11]; Bennett Leventhal, MD[12]; Rebecca C. Fry, PhD[13]; Rachel Miller, MD[14]; Julie Herbstman, PhD[1]; Santiago Morales, PhD[2]; Amy E. Margolis, PhD[15,16*]; Anne E. Nigra, ScM, PhD[1*] for the ECHO Cohort Consortium

1 Department of Environmental Health Sciences, Columbia University Mailman School of Public Health
2 Department of Psychology, University of Southern California
3 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
4 Department of Child and Adolescent Psychiatry, NYU Langone Medical Center
5 Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus
6 Department of Environmental Health Sciences, University of California Los Angeles
7 Department of Environmental Science, Baylor University
8 Department of Epidemiology, Columbia University Mailman School of Public Health, New York, New York
9 Department of Psychiatry, Columbia University Irving Medical Center/New York State Psychiatric Institute
10 Department of Pediatrics, NYU Grossman School of Medicine
11 Geisel School of Medicine at Dartmouth
12 Department of Psychiatry and Behavioral Neuroscience, The University of Chicago
13 Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, UNC Chapel Hill
14 Icahn School of Medicine at Mount Sinai
15 Department of Psychiatry and Behavioral Health, The Ohio State University Wexner College of Medicine
16 The Child Mind Institute, New York, NY

*Amy E. Margolis and Anne E. Nigra are co-senior authors
**See Supplemental Materials for full list of collaborators

Corresponding author:
Anne E. Nigra, ScM, PhD
Aen2136@cumc.columbia.edu
722 W 168th St,
11th Floor Rm 1107A
New York, NY 10032

Funding: Katrina Simon and Meredith Palmore had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This study was supported by the National Institutes of Health (NIH) Office of the Director and NIDCR grant DP5OD031849, NICHD grant P2CHD058486, and NIEHS grants P30ES009089 and T32ES007322. Research reported in this publication was supported by the Environmental influences on Child Health Outcomes (ECHO) Program, Office of the Director, National Institutes of Health, under Award Numbers U2COD023375 (Coordinating Center), U24OD023382 (Data Analysis Center), U24OD023319 with co-funding from the Office of Behavioral and Social Science Research (Measurement Core), U24OD035523 (Lab Core), ES0266542 (HHEAR), U24ES026539 (HHEAR Barbara O'Brien), U2CES026533 (HHEAR Lisa Peterson), U2CES026542 (HHEAR Patrick Parsons, Kannan Kurunthacalam), U2CES030859 (HHEAR Manish Arora), U2CES030857 (HHEAR Timothy R. Fennell, Susan J. Sumner, Xiuxia Du), U2CES026555 (HHEAR Susan L. Teitelbaum), U2CES026561 (HHEAR Robert O. Wright), U2CES030851 (HHEAR Heather M. Stapleton, P. Lee Ferguson) UG3/UH3OD023251 (Akram Alshawabkeh), UH3OD023320 and UG3OD035546 (Judy Aschner), UH3OD023332 (Clancy Blair, Leonardo Trasande), UG3/UH3OD023253 (Carlos Camargo), UG3/UH3OD023248 and UG3OD035526 (Dana Dabelea), UG3/UH3OD023313 (Joseph M. Braun, Daphne Koinis Mitchell), UH3OD023328 (Cristiane Duarte), UH3OD023318 (Anne Dunlop), UG3/UH3OD023279 (Amy Elliott), UG3/UH3OD023289 (Assiamira Ferrara), UG3/UH3OD023282 (James Gern), UH3OD023287 (Carrie Breton), UG3/UH3OD023365 (Irva Hertz-Picciotto), UG3/UH3OD023244 (Alison E Hipwell and Kate Keenan), UG3/UH3OD023275 (Margaret Karagas), UH3OD023271 and UG3OD035528 (Catherine Karr), UH3OD023347 (Barry Lester), UG3/UH3OD023389 (Leslie Leve), UG3/UH3OD023344 (Debra MacKenzie), UH3OD023268 (Scott Weiss), UG3/UH3OD023288 (Cynthia McEvoy), UG3/UH3OD023342 (Kristen Lyall), UG3/UH3OD023349 (Thomas O'Connor), UH3OD023286 and UG3OD035533 (Emily Oken), UG3/UH3OD023348 (Mike O'Shea, Rebecca Fry), UG3/UH3OD023285 (Jean Kerver), UG3/UH3OD023290 (Julie Herbstman), UG3/UH3OD023272 (Susan Schantz), UG3/UH3OD023249 (Joseph Stanford), UG3/UH3OD023305 (Leonardo Trasande), UG3/UH3OD023337 (Rosalind Wright), UG3OD035508 (Sheela Sathyanarayana), UG3OD035509 (Anne Marie Singh), UG3OD035513 and UG3OD035532 (Annemarie Stroustrup), UG3OD035516 and UG3OD035517 (Tina Hartert), UG3OD035518 (Jennifer Straughen), UG3OD035519 (Qi Zhao), UG3OD035521 (Katherine Rivera-Spoljaric), UG3OD035527 (Emily S Barrett), UG3OD035540 (Monique Marie Hedderson), UG3OD035543 (Kelly J Hunt), UG3OD035537 (Sunni L Mumford), UG3OD035529 (Hong-Ngoc Nguyen), UG3OD035542 (Hudson Santos), UG3OD035550 (Rebecca Schmidt), UG3OD035536 (Jonathan Slaughter), UG3OD035544 (Kristina Whitworth).

Role of Funder:
The sponsor, NIH, participated in the overall design and implementation of the ECHO Program, which was funded as a cooperative agreement between NIH and grant awardees. The sponsor approved the Steering Committee-developed ECHO protocol and its amendments including COVID-19 measures. The sponsor had no access to the central database, which was housed at the ECHO Data Analysis Center. Data management and site monitoring were performed by the ECHO Data Analysis Center and Coordinating Center. All analyses for scientific publication were performed by the study first author, independently of the sponsor. The lead author wrote all drafts of the manuscript and made revisions based on co-authors and the ECHO Publication Committee (a subcommittee of the ECHO Operations Committee) feedback without input from the sponsor. The study sponsor did not review or approve the manuscript for submission to the journal.

NIH Disclaimer:
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Keywords:
fluoride; drinking water; cognition; child psychology

ECHO Acknowledgments: The authors wish to thank our ECHO Colleagues; the medical, nursing, and program staff; and the children and families participating in the ECHO cohort. We also wish to thank Cara Wychgram for developing the map.

ABSTRACT

Prior studies suggest fluoride exposure in drinking water above 1,500 μg/L is associated with lower child cognition, but evidence is limited at lower exposure levels and in U.S. populations. We evaluated whether prenatal exposure to fluoride in regulated public drinking water was associated with cognition in a pooled U.S. cohort. We analyzed observational data from the Environmental influences on Child Health Outcomes (ECHO) Cohort, including 2,514 children born 2006–2019 across 17 sites in 23 states. Individual prenatal time-weighted average public water fluoride concentrations were estimated by linking census tract-level concentrations to residential addresses across pregnancy. Fluid and crystallized cognition were assessed using NIH Toolbox scores. Generalized estimating equation models estimated adjusted mean differences using restricted cubic spline and linear change-point models. Individual prenatal time-weighted average water fluoride concentrations ranged from <1.0–1,940.0 μg/L (mean=396.9 μg/L). Cubic spline models showed significant inverse associations for fluid cognition above 1,107.0 μg/L. Linear change-point models identified 675 μg/L as the best-fitting change-point for fluid cognition; above this value, fluid scores were 0.67 points lower (95% CI: -0.92, -0.42) per 100 μg/L higher fluoride. These findings indicate that prenatal fluoride exposure in regulated public water is nonlinearly associated with lower fluid cognition scores in U.S. children at concentrations below current WHO and U.S. EPA thresholds.

INTRODUCTION

Fluoride is a naturally occurring element, and fluoride compounds are commonly added to public drinking water in the United States (U.S.) and other countries for the prevention of dental caries. The U.S. Environmental Protection Agency (USEPA) sets the maximum contaminant level (MCL) for fluoride in public water systems (4.0 mg/L or 4,000 µg/L) based on cost, feasibility, and public health considerations.[1] The USEPA MCL for fluoride is higher than the World Health Organization (WHO) guidance limit (1,500 µg/L) and the U.S. Public Health Service's (USPHS) optimal concentration (700 µg/L). The USPHS optimal fluoride concentration is set to maximize dental benefits while minimizing skeletal/enamel fluorosis risk, but does not consider potential adverse effects on cognition.[2,3] Recent estimates suggest that over 2.9 million (~0.8% of population) and 20.5 million (~6% of population) U.S. residents are served by public systems with fluoride exceeding 1,500 µg/L and 700 µg/L, respectively.[4]

In a recent review, the National Toxicology Program (NTP) found, with "moderate confidence," that fluoride exposures >1,500 µg/L are associated with lower child IQ.[5] The report notes that assessments evaluating fluoride in drinking water <1,500 µg/L were limited, with few studies on U.S. populations.[5,6] To our knowledge, no studies have specifically evaluated prenatal fluoride in U.S. public water systems as measured via routine compliance monitoring, which directly reflects the regulatory environment.[5] Moreover, maternal urinary fluoride has been associated with lower child Performance Intelligence Quotient (IQ) scores (reflecting nonverbal reasoning, spatial processing, and visual-motor skills), but not Verbal IQ scores (reflecting verbal reasoning and reading comprehension).[7,8,9] Conceptually, these domains correspond to fluid and crystallized cognition, respectively, as measured on the NIH Toolbox Cognition Battery (NIHTB-CB). Fluid abilities are thought to more closely reflect underlying

neurobiology, whereas crystallized abilities are more reflective of accumulated learning experiences such as schooling.[10,11] Full-Scale IQ, reflecting global intellectual functioning that collapses across IQ domains, corresponds conceptually with NIHTB-CB total cognition, which similarly aggregates across fluid and crystallized performance.[11] NIHTB-CB composites demonstrate convergent validity with established measures of intellectual and general cognitive ability in validation studies.[11]

We evaluated associations between prenatal public drinking water fluoride and child cognition in the Environmental influences on Child Health Outcomes (ECHO) Cohort.[12] We estimated prenatal public water fluoride concentrations using measurements in public water systems reported for regulatory compliance, reflecting federal drinking water regulatory requirements. Child cognition was assessed using domain-specific fluid and crystallized cognition scores derived from NIHTB subtests. For completeness, total cognition was calculated by averaging scores across subtests, but was not a primary outcome given that it aggregates conceptually distinct domains. Consistent with prior findings,[5] we hypothesized that higher prenatal water fluoride would be inversely associated with fluid cognition scores, even at concentrations below 1,500 µg/L.

METHODS

Study population: Environmental influences on Child Health Outcomes (ECHO) Cohort

The ECHO Cohort (cycle 1) comprises 69 ongoing pregnancy and pediatric cohort sites across the U.S. and Puerto Rico.[12] Possible participants were children whose birth parents were recruited to a general population cohort site, reported residential address history covering at least 80% of pregnancy, consented to sharing residential address, and completed an NIHTB

assessment. Children were further excluded if they were from a multiple gestation pregnancy, enrolled in an outcome-enriched or randomized control trial-based cohort, born outside of 2006-2019 (to align with exposure data), or if public water fluoride data was not available for reported residence. We further excluded one cohort reliant almost exclusively on private wells, for a final sample of 2,514 children across n=17 cohort sites (Figure S1, **Supplement**).

Exposure assessment: Prenatal public water fluoride

We leveraged previously developed census tract-level estimates of average, population-weighted public water fluoride concentrations from 2006-2019.[13] Tract-level estimates were developed from >690,000 routine compliance monitoring records collected by public water systems to evaluate compliance with the MCL and reported to USEPA.[14] This exposure assessment approach was previously validated for arsenic and uranium in two multi-site cohorts with biomarker data.[13,15] To reduce differential missingness and bias,[16] tract-level estimates were aggregated to three-year periods corresponding to the USEPA Standardized Monitoring Framework from 2006 through 2019 (e.g., 2017-2019).[13,17] Fluoride concentrations were reported in both mg/L and µg/L (1,000.0 µg/L = 1.0 mg/L). We report concentrations in µg/L to preserve precision across the exposure range, facilitate comparison with other contaminants, and improve communication, consistent with updated reporting conventions for other low-level exposures including lead.[18] Tract-level fluoride concentrations less than or equal to 1.4 µg/L reflect either (a) fluoride concentrations measured below the limit of detection, which were imputed with the limit of detection divided by the square root of two, or (b) very low fluoride concentrations measured at laboratories with unusually high precision and low detection limits. We assigned tract-level water fluoride concentrations to each month of pregnancy using birthing

parent residential address. Time-weighted average public water fluoride estimates during pregnancy were calculated from monthly estimates. This approach accounted for residential moves across tracts and time-varying exposures for pregnancies spanning multiple exposure periods. Detailed exposure assignment information was previously published[13] and is summarized in Appendix S1, **Supplement.**

Child cognition: the NIH Toolbox Cognition Battery (NIHTB-CB)

Child cognition was assessed using subtests from the NIH Toolbox Cognition Battery (NIHTB-CB).[19] Because sites differed in age at administration and subtests assessed,[12] we constructed harmonized measures across the sample by averaging age-corrected standardized scores (normative mean = 100; SD = 15) from subtests completed by the majority of participants. Fluid cognition was calculated as the average of Dimensional Change Card Sort, Flanker Inhibitory Control and Attention, and Picture Sequence Memory age standardized scores; crystallized cognition was assessed using Picture Vocabulary age standardized scores. Total cognition reflects the average of the four subtests. Additional details are provided in Appendix S1, **Supplement**.

Covariates

Individual-level covariates included conception season, child sex at birth, birthing parent education, birthing parent age at delivery, prenatal tobacco use, and parity. Area-level covariates included tract-level population density, and social vulnerability index (SVI) scores.[20] Additional details are provided in Appendix S1, **Supplement**.

Statistical analysis

Statistical analyses were performed in R version 4.5.0.[21] We evaluated adjusted mean differences in cognition scores per higher prenatal public water fluoride exposure for all children

and stratified by age (<7 years old, ≥7 years old). Primary outcomes were fluid and crystallized cognition. Total cognition was evaluated in follow-up analyses. Associations were evaluated with generalized estimating equation (GEE) models with exchangeable correlation structure to account for clustering of children by cohort site. Primary models examined prenatal public water fluoride continuously using restricted cubic splines to allow for a non-linear exposure-response. Knots were placed at the 50th (347.8 µg/L) and 75th (681.2 µg/L) percentile of the analytic sample fluoride distribution (two equally spaced knots between the reference and maximum). To improve interpretability, we centered predicted values at the 25th percentile (55.2 µg/L) when plotting results. We further evaluated mean differences in cognition using linear change-point models.[22] Optimal slope-change values were identified for each outcome by assessing model fit at incremental water fluoride concentrations of 25 µg/L (Appendix S1, **Supplement**). Mean differences in performance per 100 µg/L higher fluoride before and after the optimally chosen slope change value were evaluated. We ran two models per analytic approach: Model 1 adjusted for child sex and birthing parent age and education. Model 2 further adjusted for parity, prenatal tobacco use, season of conception, tract-level population density, and SVI. Consistent with guidance in the field of social epidemiology, we did not adjust for race or ethnicity because racism is a structural determinant of health, and we assessed potential differential effects by race/ethnicity (effect measure modifier) (Appendix S1, **Supplement).**[23] A directed acyclic graph (DAG) is available in Figure S2, **Supplement**. We did not control for child age at outcome ascertainment in primary analyses, as subtest scores were age-adjusted prior to harmonization. For all models, we used multiple imputation by chained equations (MICE, n=5 iterations and 10 imputed datasets)[24] to impute missing covariates (Appendix S1, **Supplement**). In interpreting effect estimates, following best current practices, we evaluated the direction, magnitude,

consistency, and precision of effect estimates rather than relying solely on dichotomous significance testing.[25]

Exploratory subgroup analyses

We explored potential differential associations (effect measure modification) between prenatal public water fluoride concentrations and cognition across subgroups in stratified analyses. Models were stratified by child race, ethnicity, sex, and age at outcome ascertainment; by birthing parent education; and by area-level SVI. Differential associations by race, ethnicity, education, and SVI could be related to other social and environmental exposures inequitably distributed across subgroups, or differential measurement error of the outcome. Differential associations by age at outcome ascertainment could reflect postnatal water fluoride exposure or other postnatal experiences associated with changes in cognition (e.g., schooling). For each outcome, we used the optimally selected change-point from primary change-point models on the full sample and included interaction terms between the change-point fluoride term and subgroup indicators. Statistical interaction was assessed using *p*-values from Wald tests for the change-point fluoride × subgroup interaction terms. To aid interpretation, we evaluated stratified linear change-point models in subgroups and report mean differences in cognition per 100 µg/L higher prenatal fluoride concentration for the slope above the selected change-point, holding the change-point consistent across each outcome. We did not report effect estimates for stratified subgroups with fewer than 50 participants, as models were less likely to converge or produce stable estimates.

Sensitivity analyses

To evaluate if knot placement influenced the shape and point of departure from the null in spline models, we evaluated alternative placements for the second knot (60th, 70th, 80th and 90th percentile). To assess the impact of measurement error of the exposure, we restricted analyses to participants (a) residing in states that publish high-quality shapefiles of public water system distribution boundaries, where measurement error of the exposure is smaller[13] (Figure S4, **Supplement)**; (b) who did not move during pregnancy and (c) who reported public water consumption (Appendix S1, Table S1, **Supplement**).

We repeated linear change-point models after excluding participants with a recorded developmental diagnosis, after removing each cohort site (leave-one-out analysis) to identify potentially influential cohorts, and after further adjustment for child age at assessment, prenatal public water arsenic (potential confounder), and gestational age at birth and birthweight-for-gestational age z-score (potential mediators). We also used inverse probability weighting to evaluate potential selection bias, weighting our analytic sample to reflect participant characteristics before exclusion for missing exposure or outcome data (Appendix S1, **Supplement**). In all sensitivity analyses, we used optimal change-points from main models and evaluated mean differences in cognition above the change-point per 100 μg/L higher water fluoride.

RESULTS

At birth, children resided in 1,347 tracts within 106 counties and 23 U.S. states (**Figure 1**). Prenatal water fluoride concentrations ranged from <1.0–1,940.0 μg/L (mean: 396.9 μg/L, **Table 1**). A total of n=411 participants (16.3%) had prenatal water fluoride ≤1.4 μg/L, and n=431 (17.1%) had fluoride ≥700 μg/L. See Table 1 for additional descriptive statistics.

In fully adjusted restricted cubic spline models, higher prenatal water fluoride was non-linearly associated with lower fluid cognition scores (**Figure 2**). In the full sample, associations were inverse and statistically significant beyond 1,107.0 µg/L for fluid cognition. Associations were not statistically significant in restricted cubic spline models for crystallized cognition. The shape of the exposure-response and the point of departure from the null were consistent at alternative knot locations (Figure S3, **Supplement**), and the shape of the exposure-response was consistent when restricting to participants with the highest quality exposure assessment (n=1,114, Figure S4, **Supplement)**. Linear change-point models identified the optimal slope-change value as 675 µg/L for fluid cognition and 275 µg/L for crystallized cognition (Table 2; Figure S5, **Supplement**). Beyond optimal slope-change values, the mean difference in performance per 100 µg/L higher fluoride was significant -0.67 (95% CI: -0.92, -0.42) for fluid cognition, but not for crystallized cognition, -0.21 (95% CI: -0.59, 0.16; Table 2). For total cognition, in restricted cubic spline models, higher water fluoride was non-linearly and inversely associated with total cognition beyond 1,134.7 µg/L (Figure 2). Linear change-point models identified an optimal slope-change value of 250 µg/L, with a significant mean difference of -0.22 (95% CI: -0.38, -0.06) per 100 µg/L higher fluoride beyond 250 µg/L (Table 2).

Results were consistent when considering alternative model adjustments and in leave-one-out analyses. In linear change-point analyses incorporating inverse probability weighting, post-change-point effect estimates were attenuated toward the null for fluid and total cognition. Associations for crystallized cognition remained null across sensitivity analyses (Table S1, Figure S6, **Supplement**).

In stratified analyses, we observed heterogeneity in post-change-point effect estimates for fluid cognition by age at assessment (*p*-interaction<0.01; Figure S7, **Supplement**). We observed

larger mean differences per 100 µg/L higher prenatal water fluoride for children <7 years old (-2.70; 95% CI: [-4.24, -1.16]) compared to children ≥7 years old (-0.45; 95% CI: [-0.76, -0.14]). Associations for crystallized cognition differed by child ethnicity (*p*-interaction=0.03; Figure S7, **Supplement**), with stratified analyses indicating larger and more negative mean differences per 100 µg/L higher prenatal water fluoride for non-Hispanic children (-0.33; [95% CI: -0.69, 0.03]) compared to Hispanic children (0.21; [95% CI: -0.70, 1.12]). We also observed differences by sex at birth for total cognition (*p*-interaction=0.02; Figure S7, **Supplement**), with stratified models indicating larger mean differences per 100 µg/L higher prenatal water fluoride for males (-0.25; 95% CI: [-0.42, -0.09]) compared to females (-0.23; 95% CI: [-0.45, -0.01]).

DISCUSSION

In this pooled study of 17 cohort sites across the U.S., prenatal public water fluoride concentrations were nonlinearly associated with child fluid cognition at levels below the current WHO guideline (1,500 µg/L) and at concentrations near the current USPHS optimal concentration (700 µg/L). At levels beyond 675 µg/L, the change-point selected based on best model fit, exposure was associated with a possible decline of up to 3.36 points (approximately 22.4% of a standard deviation) in fluid cognition per 500 µg/L higher water fluoride.[19] Associations with fluid cognition were largest when assessed before age 7, with results suggesting possible declines of up to 13.5 points (90% of a standard deviation) per 500 µg/L higher water fluoride beyond 675 µg/L. These findings suggest that at concentrations below both the current WHO guideline (1,500 µg/L) and the current USEPA MCL (4,000 µg/L), prenatal public water fluoride exposure is inversely associated with child fluid cognition in the US. Taken together with conclusions from the NTP report, our findings suggest that downward revision of the USEPA MCL may be warranted. Although most public water systems that fluoridate water

report fluoride levels near the USPHS optimal concentration of 700 µg/L and the mean water fluoride level in our sample was 396.9 µg/L, over 2.9 million U.S. residents receive public water with fluoride concentrations exceeding 1,500 µg/L.[4] Higher fluoride levels typically result from geogenic fluoride in source water, with or without additional fluoridation. These findings suggest that additional efforts to remediate higher levels of water fluoride may be warranted.

Consistent with our findings, prior studies of prenatal fluoride measured via maternal urine have reported associations with cognition that are primarily driven by performance IQ,[8] which closely corresponds to fluid cognition.[19] Fluid cognition reflects the capacity for new learning and information processing and is more influenced by neurobiological processes than by learning experiences.[10, 11] In contrast, crystallized cognition reflects learned knowledge and skills (such as vocabulary) and is more influenced by accumulated learning experiences, which are often predicted by socioeconomic status and education, versus neurobiology.[10, 11] The observed pattern of differential associations with fluid versus crystallized cognition could reflect potential influences of fluoride on the development of the prefrontal cortex, which supports key indices of fluid cognition including working memory, cognitive flexibility, and problem-solving.[26,27] Critically, fluoride crosses the placenta and blood-brain barrier, and in animal models prenatal fluoride exposure alters neural development and synaptic integrity in brain regions supporting cognition such as the PFC.[5,28,29] Together, these findings suggest a potential mechanism through which prenatal fluoride exposure might affect fluid cognition in humans, though future studies are needed to test potential pathways more directly.

In linear change-point analyses, we observed larger magnitude inverse associations at exposure levels above the optimally selected change-point of 675 µg/L with fluid cognition among children under 7. In age-stratified analyses, where subgroup-specific optimal change-

points were estimated, the optimal change-point for fluid cognition was higher for older (850 µg/L) compared to younger children (675 µg/L; the same optimal change-point identified from the full sample). The effects of prenatal fluoride on cognition may appear larger in magnitude when ascertained in younger children because early childhood is a period of rapid neurodevelopment, during which the downstream effects of prenatal exposure may be more readily detectable. When the outcome is ascertained in older children, however, cumulative postnatal experiences (e.g., schooling and other educational experiences) may partially buffer earlier effects, resulting in smaller but still detectable associations. One study examining prenatal maternal urinary fluoride observed smaller negative effects in performance IQ (analogous to fluid cognition) at ages 6-12 compared to ages 4-5 in age-stratified analyses, though formal age interactions were not reported.[8] Together, these findings suggest that the effects of prenatal fluoride on cognition may be larger when the outcome is ascertained at a younger age. However, further research is needed to characterize developmental patterns more clearly.

While not a primary outcome, we observed inverse associations between prenatal water fluoride concentrations and total cognition in full and age-stratified models. However, our harmonized measure of total cognition was primarily composed of fluid reasoning tests (three fluid and one crystallized subtest). As such, associations likely reflect the observed associations with fluid cognition rather than generalized effects across cognitive domains (consistent with prior findings suggesting domain-specific associations of fluoride exposure with fluid, but not crystallized, cognition).

Contrary to our hypotheses, we observed positive associations between prenatal water fluoride and crystallized and total cognition at fluoride levels below 275 µg/L. However, the interpretability of this association at the lowest ends of the exposure distribution is limited by

low analytic precision and low variability in water fluoride measurements at this range. Among those with prenatal water fluoride concentrations below 275 µg/L (n=1,153), 36% (n=411) had assigned water fluoride concentrations ≤1.4 µg/L, reflecting undetectable water fluoride measurements. Observed positive associations with crystallized and total cognition at this range are likely driven by measurement error and should be interpreted with caution.

This study fills an important gap identified by the NTP in the growing body of literature evaluating fluoride exposure and child cognition at water fluoride levels below 1,500 µg/L.[5,6] Prior studies of child outcomes from the U.S. and countries with comparable water fluoride levels (i.e., Canada and Mexico) have relied on maternal urinary fluoride, an individual measure that integrates all exposure sources[7–9,30]. However, urine fluoride is not regulated and can be challenging to interpret because fluoride exposure may influence renal function and thus fluoride excretion and measurement in urine.[7–9,31] We instead evaluated public water fluoride concentrations using compliance monitoring, making our findings translatable to water policy. The consistency of findings across these complementary exposure metrics strengthens confidence in our findings.

Our exposure-response analysis has direct implications for future risk assessment efforts. Our findings suggest that prenatal public water fluoride concentrations above 675 µg/L are inversely associated with fluid cognition in ECHO. Consistent with USEPA risk assessment guidance to derive an oral reference dose,[32] applying uncertainty factors to this point of departure would result in a reference value below the level at which we observed an adverse effect. Policymakers assessing risk-benefit tradeoffs should weigh potential neurodevelopmental risks against the potential benefits of water fluoridation on dental health, which itself has been associated with measures of school performance and child well-being.[33,34] A recent Cochrane

review suggests that the dental health benefits of adding fluoride to drinking water may be smaller now than before fluoride toothpaste was widely available.[35,36] Future research should integrate both outcome domains for a more comprehensive assessment and to better inform public health decision-making.

Our study has several limitations, including measurement error of the exposure. Our exposure of interest was fluoride measured in public drinking water systems (directly reflecting federal regulatory requirements). We did not aim to evaluate total fluoride exposure or total drinking water fluoride exposure, and our analysis was not designed to do so. Nevertheless, we lacked sufficient data on individual tap water sources, bottled water/filtration use, or variation in water intake across our sample. We could not account for postnatal exposure or other sources of fluoride exposure. Assigning tract-level fluoride likely produced Berkson measurement error which would bias results towards the null.[37] Measurement error was also likely differential by cohort site, as some states poorly model water system distribution boundaries. Further research is needed to robustly characterize geospatially assigned public water exposure measurement error in large studies. Inverse probability weighted models suggested potential for selection bias, as associations were attenuated toward the null for fluid and total cognition, though point estimates remained negative. We also observed differences by child ethnicity for crystallized cognition, which could reflect differential environmental/social exposures across groups that influence the association (i.e., structural inequities), residual confounding, differential measurement error of the exposure, selection bias within ECHO and differential missingness by race/ethnicity, or insufficient sampling of participants from some racial/ethnic groups. Lastly, our sample, although large, was predominantly White, non-Hispanic, and college-educated, representing only 41% of ECHO participants with cognition outcomes. Among excluded participants, 20.4%

lacked sufficient water fluoride data across gestation or residential history, and 28.9% came from an outcome-enriched/RCT-based site. Overall, these findings warrant replication in samples that are more representative of the US population, include more highly exposed groups, and assess postnatal water fluoride levels as a potential modifier.

CONCLUSIONS

In this pooled cohort study of children across the U.S., we observed nonlinear, inverse associations between prenatal public water fluoride and child fluid cognition at concentrations below the current WHO guideline (1,500 µg/L) and near the current USPHS optimal fluoridation guideline (700 µg/L). Noting study limitations, additional research is needed to identify susceptible windows of exposure across the prenatal, postnatal, and early childhood periods and elucidate potential neural pathways that mediate associations. These results highlight the need to re-evaluate the current USEPA MCL for fluoride in public water systems (4,000 µg/L), which may not adequately protect neurodevelopment.

Data Availability:
Select de-identified data from the ECHO Program are available through NICHD's Data and Specimen Hub (DASH). Information on study data not available on DASH, such as some Indigenous datasets, can be found on the ECHO study DASH webpage.

REFERENCES

1. *Safe Drinking Water Act (Title XIV of Public Health Service Act).* 1974:682. Accessed May 1, 2025. https://www.govinfo.gov/content/pkg/COMPS-892/pdf/COMPS-892.pdf

2. World Health Organization. *Guidelines for Drinking-Water Quality*. 2017.

3. U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation. U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries. *Public Health Reports®*. 2015;130(4):318-331. doi:10.1177/003335491513000408

4. Hefferon R, Goin DE, Sarnat JA, Nigra AE. Regional and racial/ethnic inequalities in public drinking water fluoride concentrations across the US. *J Expo Sci Environ Epidemiol*. 2024;34(1):68-76. doi:10.1038/s41370-023-00570-w

5. National Toxicology Program (NTP). *NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition: A Systematic Review*. National Institute of Environmental Health Science; 2024. doi:10.22427/NTP-MGRAPH-8

6. Taylor KW, Eftim SE, Sibrizzi CA, et al. Fluoride Exposure and Children's IQ Scores: A Systematic Review and Meta-Analysis. *JAMA Pediatr*. 2025;179(3):282. doi:10.1001/jamapediatrics.2024.5542

7. Green R, Lanphear B, Hornung R, et al. Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada. *JAMA Pediatr*. 2019;173(10):940. doi:10.1001/jamapediatrics.2019.1729

8. Goodman CV, Bashash M, Green R, et al. Domain-specific effects of prenatal fluoride exposure on child IQ at 4, 5, and 6–12 years in the ELEMENT cohort. *Environ Res*. 2022;211:112993. doi:10.1016/j.envres.2022.112993

9. Farmus L, Till C, Green R, et al. Critical windows of fluoride neurotoxicity in Canadian children. *Environ Res*. 2021;200:111315. doi:10.1016/j.envres.2021.111315

10. Morales S, Bowers ME, Shuffrey L, et al. Maternal education prospectively predicts child neurocognitive function: An environmental influences on child health outcomes study. *Dev Psychol*. 2024;60(6):1028-1040. doi:10.1037/dev0001642

11. Akshoomoff N, Beaumont JL, Bauer PJ, et al. VIII. NIH TOOLBOX COGNITION BATTERY (CB): COMPOSITE SCORES OF CRYSTALLIZED, FLUID, AND OVERALL COGNITION. *Monogr Soc Res Child Dev*. 2013;78(4):119-132. doi:10.1111/mono.12038

12. Knapp EA, Kress AM, Parker CB, et al. The Environmental Influences on Child Health Outcomes (ECHO)-Wide Cohort. *Am J Epidemiol*. 2023;192(8):1249-1263. doi:10.1093/aje/kwad071

13. Bloomquist TR, Spaur M, Cerna-Turoff I, et al. Public drinking water contaminant estimates for birth cohorts in the Environmental Influences on Child Health Outcomes (ECHO) Cohort. *J Expo Sci Environ Epidemiol*. Published online August 4, 2024. doi:10.1038/s41370-024-00699-2

14. U.S. Environmental Protection Agency. *Six-Year Review 3 Compliance Monitoring Data (2006-2011)*. Accessed May 15, 2025. https://www.epa.gov/dwsixyearreview/six-year-review-3-compliance-monitoring-data-2006-2011

15. Spaur M, Glabonjat RA, Schilling K, et al. Contribution of arsenic and uranium in private wells and community water systems to urinary biomarkers in US adults: The Strong Heart Study and the Multi-Ethnic Study of Atherosclerosis. *J Expo Sci Environ Epidemiol*. 2024;34(1):77-89. doi:10.1038/s41370-023-00586-2

16. Nigra AE, Chen Q, Chillrud SN, et al. Inequalities in Public Water Arsenic Concentrations in Counties and Community Water Systems across the United States, 2006–2011. *Environ Health Perspect*. 2020;128(12):127001. doi:10.1289/EHP7313

17. *U.S. Environmental Protection Agency. The Standardized Monitoring Framework: A Quick Reference Guide.* https://nepis.epa.gov/Exe/ZyPDF.cgi/3000667K.PDF?Dockey=3000667K.PDF

18. Caravanos J, Nassif J, Lanphear B, Landrigan PJ, Hu H, Fuller R. Invited Perspective: An Argument for Changing the Reporting Units for Lead in Blood. *Environ Health Perspect*. 2023;131(9):091303. doi:10.1289/EHP12382

19. Weintraub S, Dikmen SS, Heaton RK, et al. Cognition assessment using the NIH Toolbox. *Neurology*. 2013;80(11_supplement_3). doi:10.1212/WNL.0b013e3182872ded

20. CDC/ATSDR Social Vulnerability Index 2018 Database US. *Centers for Disease Control and Prevention/ Agency for Toxic Substances and Disease Registry/ Geospatial Research Analysis and Services Program.*

21. R Core Team. R: A Language and Environment for Statistical Computing. https://www.R-project.org/

22. Muller HG. Change-Points in Nonparametric Regression Analysis. *Ann Stat*. 1992;20(2). doi:10.1214/aos/1176348654

23. Swilley-Martinez ME, Coles SA, Miller VE, et al. "We adjusted for race": now what? A systematic review of utilization and reporting of race in *American Journal of Epidemiology* and *Epidemiology* , 2020–2021. *Epidemiol Rev*. 2023;45(1):15-31. doi:10.1093/epirev/mxad010

24. Buuren SV, Groothuis-Oudshoorn K. **mice** : Multivariate Imputation by Chained Equations in *R*. *J Stat Softw*. 2011;45(3). doi:10.18637/jss.v045.i03

25. Savitz DA, Wise LA, Bond JC, et al. Responding to Reviewers and Editors About Statistical Significance Testing. *Ann Intern Med*. 2024;177(3):385-386. doi:10.7326/M23-2430

26. Ferrer E. Fluid reasoning and the developing brain. *Front Neurosci*. 2009;3(1). doi:10.3389/neuro.01.003.2009

27. Friedman NP, Robbins TW. The role of prefrontal cortex in cognitive control and executive function. *Neuropsychopharmacology*. 2022;47(1):72-89. doi:10.1038/s41386-021-01132-0

28. Veneri F, Vinceti M, Generali L, et al. Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis. *Environ Res*. 2023;221:115239. doi:10.1016/j.envres.2023.115239

29. Bartos M, Gumilar F, Baier CJ, et al. Rat developmental fluoride exposure affects retention memory, leads to a depressive-like behavior, and induces biochemical changes in offspring rat brains. *NeuroToxicology*. 2022;93:222-232. doi:10.1016/j.neuro.2022.10.006

30. Malin AJ, Eckel SP, Hu H, et al. Maternal Urinary Fluoride and Child Neurobehavior at Age 36 Months. *JAMA Netw Open*. 2024;7(5):e2411987. doi:10.1001/jamanetworkopen.2024.11987

31. Bashash M, Thomas D, Hu H, 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. doi:10.1289/EHP655

32. U.S. Environmental Protection Agency. *A REVIEW OF THE REFERENCE DOSE AND REFERENCE CONCENTRATION PROCESSES*. Risk Assessment Forum, U.S. Environmental Protection Agency; 2002. https://archive.epa.gov/raf/web/pdf/rfd-final.pdf

33. Guarnizo-Herreño CC, Wehby GL. Children's Dental Health, School Performance, and Psychosocial Well-Being. *J Pediatr*. 2012;161(6):1153-1159.e2. doi:10.1016/j.jpeds.2012.05.025

34. Ruff RR, Senthi S, Susser SR, Tsutsui A. Oral health, academic performance, and school absenteeism in children and adolescents. *J Am Dent Assoc*. 2019;150(2):111-121.e4. doi:10.1016/j.adaj.2018.09.023

35. Iheozor-Ejiofor Z, Walsh T, Lewis SR, et al. Water fluoridation for the prevention of dental caries. Cochrane Oral Health Group, ed. *Cochrane Database Syst Rev*. 2024;2024(11). doi:10.1002/14651858.CD010856.pub3

36. Water fluoridation less effective now than in past. *Cochrane*. https://www.cochrane.org/about-us/news/water-fluoridation-less-effective-now-past

37. Edwards JK, Keil AP. Measurement Error and Environmental Epidemiology: a Policy Perspective. *Curr Environ Health Rep*. 2017;4(1):79-88. doi:10.1007/s40572-017-0125-4

TABLES AND FIGURE LEGENDS

Figure 1 Census tract-level, population-weighted, average public drinking water fluoride concentrations (2017-2019) across the US overlaid with the number of participants from each state (n=2,514 participants).

Table 1 Participant characteristics overall and stratified by prenatal public drinking water fluoride quartiles (n= 2,514)

Figure 2 Restricted cubic spline models of the association between prenatal public drinking water fluoride exposure and NIH Toolbox Cognition Battery composite scores in the ECHO Cohort (n= 2,514).

Table 2 Adjusted mean difference (95% CIs) in NIH Toolbox Cognition Battery composite scores per higher prenatal public water fluoride exposure in the ECHO Cohort in linear change-point models (n=2,514).

Figure 1. Census tract-level, population-weighted, average public drinking water fluoride concentrations (2017-2019) across the US overlaid with the number of participants from each state (n=2,514 participants). Due to the national scale of the map, smaller census tracts may not be visible. Individual-level, time-weighted prenatal exposure estimates were derived using birthing parent residential address, gestational timing, and tract-level fluoride concentrations averaged across the three-year time periods (available from 2006-2019). Concentration categories correspond to quartiles within our analytic sample. The US Environmental Protection Agency's maximum contaminant level is 4,000 µg/L, the World Health Organization Guidance Limit is 1,500 µg/L, and the United States Public Health Service's (USPHS) optimal concentration for fluoridated water is 700 µg/L.

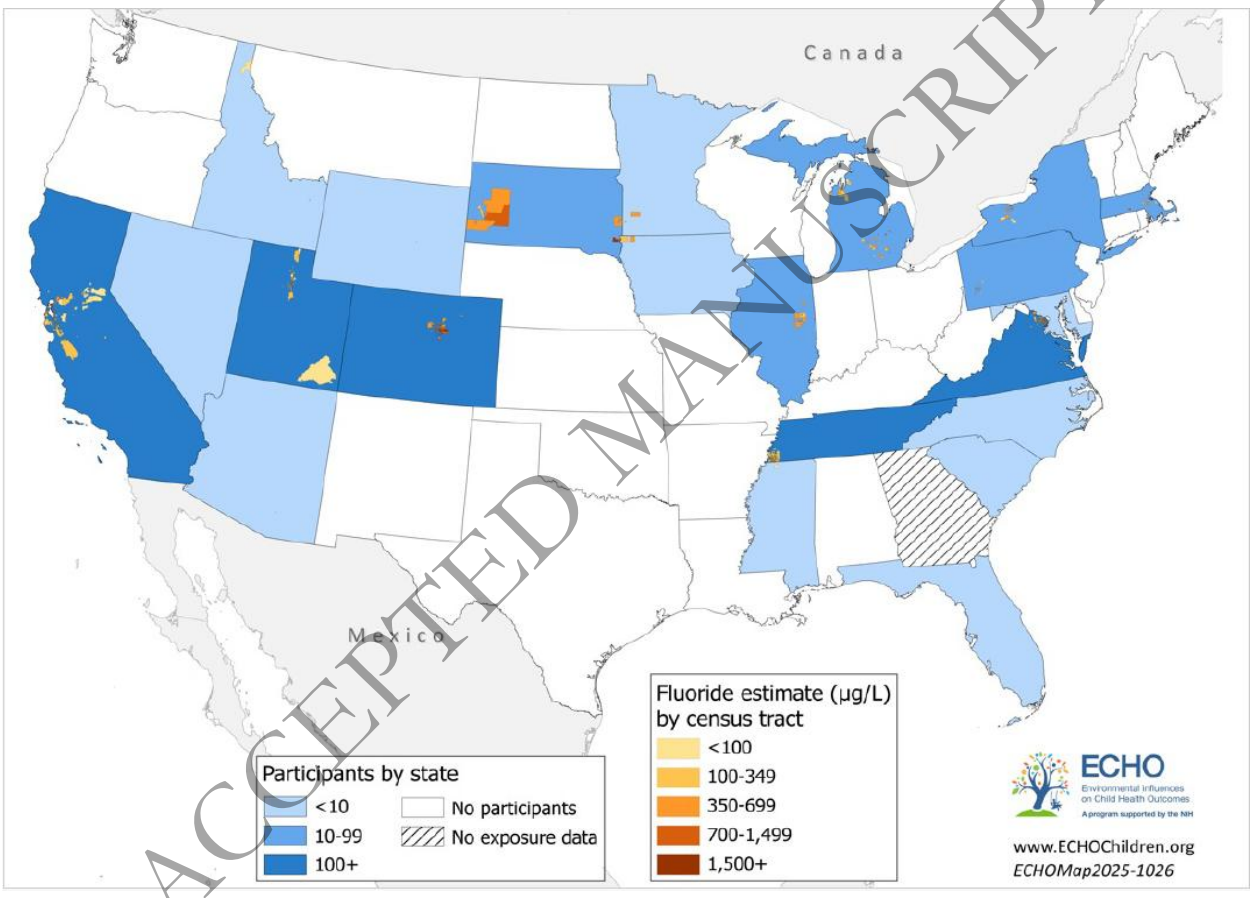

Table 1. Participant characteristics overall and stratified by prenatal public drinking water fluoride quartiles (n= 2,514). Prenatal public drinking water fluoride concentrations were assigned via birthing-parent reported residential address histories during pregnancy. Exposure estimates are individual, time-weighted, prenatal averages derived using birthing parent residential address histories and tract-level average community water system fluoride concentrations.

		Prenatal time-weighted average public water fluoride			
	Overall	**≤55.2 µg/L**	**>55.2 – 347.8 µg/L**	**>347.8 – 681.2 µg/L**	**>681.2 µg/L**
	(N=2,514) No. (%)	(N=628, 24.9%) No. (%)	(N=629, 25%) No. (%)	(N=648, 25.8 %) No. (%)	(N=609, 24.2%) No. (%)
Birthing parent characteristics					
Age at birth (mean, SD)	30.4 (5.5)	29.0 (5.7)	30.2 (5.0)	32.0 (5.0)	30.4 (5.7)
Missing (n, %)	2 (0.1%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0%)
Education (n, %)					
≤High school deg. or equivalent	249 (9.9%)	78 (12.4%)	34 (5.4%)	54 (8.3%)	83 (13.6%)
Some college or Associate's deg.	602 (23.9%)	197 (31.4%)	147 (23.4%)	105 (16.2%)	153 (25.1%)
≥Bachelor's deg.	1643 (65.4%)	353 (56.2%)	448 (71.2%)	472 (72.8%)	370 (60.8%)
Missing (n, %)	20 (0.8%)	0 (0%)	0 (0%)	17 (2.6%)	3 (0.5%)
Prenatal tobacco use (n, %)					
No	2268 (90.2%)	596 (94.9%)	588 (93.5%)	524 (80.9%)	560 (92.0%)
Yes	89 (3.5%)	28 (4.5%)	19 (3.0%)	18 (2.8%)	24 (3.9%)
Missing (n, %)	157 (6.2%)	4 (0.6%)	22 (3.5%)	106 (16.4%)	25 (4.1%)
Parity (n, %)					
Multiparous	1466 (58.3%)	381 (60.7%)	395 (62.8%)	379 (58.5%)	311 (51.1%)
Nulliparous	948 (37.7%)	239 (38.1%)	219 (34.8%)	228 (35.2%)	262 (43.0%)
Missing (n, %)	100 (4.0%)	8 (1.3%)	15 (2.4%)	41 (6.3%)	36 (5.9%)
Child characteristics					
Race (n, %)					
AI/AN/NH/PI [a]	25 (1.0%)	<10	<10	<10	<10
Other Race	66 (2.6%)	<10	<25	<25	<25
Asian	173 (6.9%)	43 (6.8%)	38 (6.0%)	54 (8.3%)	38 (6.2%)
Black	422 (16.8%)	250 (39.8%)	70 (11.1%)	39 (6.0%)	63 (10.3%)
Multiple Races	284 (11.3%)	47 (7.5%)	84 (13.4%)	72 (11.1%)	81 (13.3%)
White	1466 (58.3%)	265 (42.2%)	397 (63.1%)	434 (67.0%)	370 (60.8%)
Missing (n, %)	78 (3.1%)	14 (2.2%)	17 (2.7%)	21 (3.2%)	26 (4.3%)
Ethnicity (n, %)					
Hispanic	544 (21.6%)	96 (15.3%)	118 (18.8%)	132 (20.4%)	198 (32.5%)
non-Hispanic	1956 (77.8%)	530 (84.4%)	510 (81.1%)	506 (78.1%)	410 (67.3%)
Missing (n, %)	14 (0.6%)	2 (0.3%)	1 (0.2%)	10 (1.5%)	1 (0.2%)
Sex (n, %)					
Female	1263 (50.2%)	317 (50.5%)	303 (48.2%)	333 (51.4%)	310 (50.9%)
Male	1251 (49.8%)	311 (49.5%)	326 (51.8%)	315 (48.6%)	299 (49.1%)
Social vulnerability index score [b] (mean, SD)	0.45 (0.29)	0.54 (0.30)	0.42 (0.27)	0.38 (0.26)	0.46 (0.30)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Child age at testing (mean, SD)	7.37 (2.82)	8.90 (3.25)	7.66 (2.94)	6.22 (2.32)	6.75(1.76)
Child cognition scores [c]					
Fluid cognition (mean, SD)	101 (11.5)	97.6 (12.2)	101 (11.1)	103 (11.4)	101 (10.5)
Crystallized cognition (mean, SD)	103 (15.9)	98.8 (15.8)	105 (15.7)	104 (15.4)	104 (15.9)
Total cognition (mean, SD)	101 (10.6)	97.9 (11.3)	102 (10.0)	103 (10.6)	102 (9.6)

[a] American Indian/Alaska Native/ Native Hawaiian or Pacific Islander
[b] Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry's social vulnerability index (range 0-1; 1=most vulnerable). Assigned at the census tract level via birthing parent prenatal residential address.
[c] Total cognition scores represent the averages of four tests from the NIH Toolbox Cognition Battery: Dimensional Change Card Sort (DCCS), Picture Vocabulary, Flanker, and Picture Sequence Memory. Fluid cognition scores represent the average of subtests assessing fluid reasoning (DCCS, Flanker, and Picture Sequence Memory). Crystallized cognition scores correspond to the Picture Vocabulary Test subtest scores. All subtest scores were age-corrected and standardized (normative mean = 100, SD = 15) prior to averaging.

Figure 2. Restricted cubic spline models of the association between prenatal public drinking water fluoride concentration and cognition scores in the ECHO Cohort (n= 2,514). Models are generalized estimating equations (GEE) with participants clustered within cohorts (n=17) using an exchangeable correlation structure. Model 1 (purple, solid line) is adjusted for child sex at birth and birthing parent age (categorical) and education (categorical). Model 2 (red, dashed line) is further adjusted for parity (dichotomous), prenatal tobacco use (dichotomous), season of conception, tract-level population density, and social vulnerability index score. Missingness for all covariates was imputed via multiple imputation with chained equations (via the *mice* package in R;[24] n= 5 iterations and 10 imputed datasets). The reference is set to 55.2 μg/L (corresponding to the 25th percentile) with equally spaced knots at the 50th (347.8 μg/L) and 75th (681.2 μg/L) percentiles of the distribution. Dotted vertical line represents the U.S. Public Health Service's recommended optimal fluoridation guideline of 700 μg/L. The x-axis is shown on a $\log_2$ scale. Total cognition scores represent the averages of four NIH Toolbox cognition subtests: Dimensional Change Card Sort (DCCS), Picture Vocabulary, Flanker, and Picture Sequence Memory. Fluid cognition scores represent the average of subtests assessing fluid reasoning (DCCS, Flanker, and Picture Sequence Memory). Crystallized cognition scores correspond to Picture Vocabulary subtest scores. All subtest scores were age-corrected and standardized (normative mean = 100, SD = 15) prior to averaging. The second and third column represent spline models stratified by age group (<7 years old; ≥7 years old) for derived cognition scores.

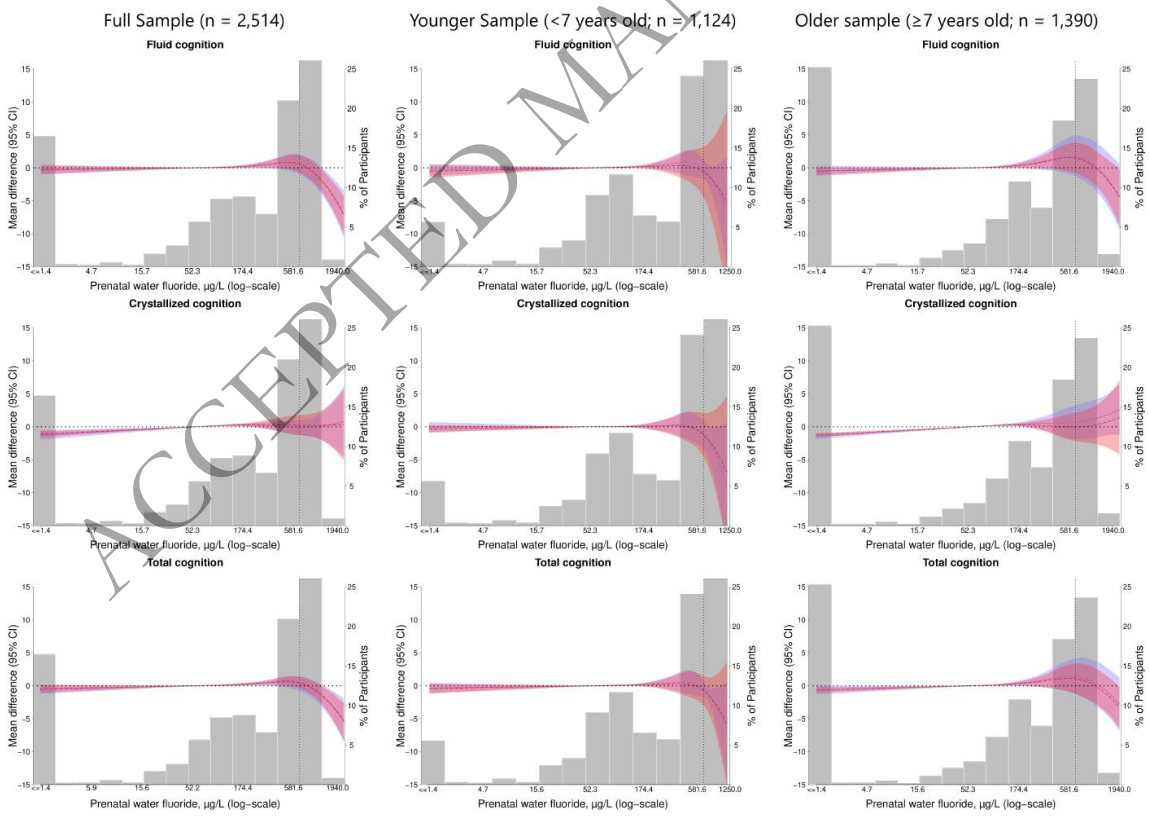

Table 2. **Adjusted mean difference (95% CIs) in cognition scores per higher prenatal public water fluoride exposure in the ECHO Cohort in linear change-point models across the full sample and stratified across age group.** Optimal change-point values were determined by the exposure value at which the RSS was smallest and contained at least 200 observations on either side of the exposure value: (See Appendix S1 for additional details). All scores are age-corrected and standardized (normative mean = 100, standard deviation = 15). Models are generalized estimating equations (GEE) with participants clustered within cohort sites (n=17) using an exchangeable correlation structure. Missingness for all covariates was imputed via multiple imputation with chained equations (via the *mice* package in R;[24] n= 5 iterations and 10 imputed datasets). Models were adjusted for birthing parent education (≤ high school degree or equivalent [reference] / some college or Associate's degree / Bachelor's degree or higher) and age (<25 [reference] / 25-29 / 30-34 / and ≥35), child sex at birth, parity (dichotomous), prenatal tobacco use (dichotomous), tract-level population density (centered), season of conception, and social vulnerability index (continuous). Mean differences and 95% confidence intervals that are statistically significant are shown in bold.

					Adjusted mean difference in scores (95% CI) per 100 µg/L higher water fluoride		**Adjusted mean difference in scores (95% CI) per 500 µg/L higher water fluoride**
	Optimal change-point (CP) value (µg/L)	**Total n**	**n < CP**	**n ≥ CP**	**Before change-point value**	**After change-point value**	**After change-point value**
All children							
Fluid cognition[1]	675	2514	1831	683	0.16 (-0.10, 0.42)	**-0.67 (-0.92, -0.42)**	**-3.36 (-4.61, -2.10)**
Crystallized cognition[2]	275	2514	1153	1361	**0.98 (0.41, 1.55)**	-0.21 (-0.59, 0.16)	-1.08 (-2.97, 0.80)
Total cognition[3]	250	2514	1139	1375	**0.66 (0.32, 0.99)**	**-0.22 (-0.38, -0.06)**	**-1.09 (-1.88, -0.30)**
Younger Children (Ages <7)							
Fluid cognition	675	1124	788	336	0.06 (-0.16, 0.27)	**-2.70 (-4.24, -1.16)**	**-13.50 (-21.18, -5.83)**
Crystallized cognition	300	1124	475	649	**0.95 (0.23, 1.66)**	**-0.91 (-1.67, -0.16)**	**-4.58 (-8.36, -0.81)**
Total cognition	675	1124	788	336	-0.00 (-0.20, 0.20)	**-2.13 (-3.73, -0.53)**	**-10.66 (-18.66, -2.67)**
Older Children (Ages ≥ 7)							
Fluid cognition	850	1390	1176	214	0.26 (-0.14, 0.66)	**-0.85 (-1.33, -0.37)**	**-4.27 (-6.66, -1.89)**
Crystallized cognition	300	1390	719	671	**0.95 (0.30, 1.59)**	-0.07 (-0.49, 0.34)	-0.37 (-2.48, 1.73)
Total cognition	500	1390	828	562	0.40 (-0.10, 0.90)	**-0.25 (-0.43, -0.05)**	**-1.24 (-2.18, -0.28)**

[1] Fluid cognition scores represent the average of age-corrected, standardized scores on subtests assessing fluid reasoning (Dimensional Change Card Sort Test [DCCS], Flanker Inhibitory Control and Attention Test [Flanker], and Picture Sequence Memory Test).
[2] Crystallized cognition scores correspond to age-corrected standardized scores on the Picture Vocabulary Test.
[3] Total cognition scores represent the average of the four test scores used to derive fluid and crystallized cognition. All test scores were age-corrected and standardized to a normative mean of 100 (SD = 15).