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COMMENTARY

Flawed MIREC fluoride and intelligence quotient publications: A failed attempt to undermine community water fluoridation

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Abstract

Objective: To assess the evidence presented in a set of articles that use the Canadian Maternal–Infant Research on Environmental Chemicals (MIREC) study database to claim that community water fluoridation (CWF) is associated with harm to foetal and infant cognitive development.

Methods: Critical appraisal of measurements and processes in the MIREC database, and articles derived therefrom. MIREC's cohort is approximately 2000 pregnant women recruited in 10 centres across Canada, 2008–2011, leading to measuring 512 children aged 3–6 years in six cities. Fluoride exposure was measured by city fluoridation status, self-reports and maternal spot urine samples. Intelligence Quotient (IQ) was measured using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) by different assessors in each city.

Results: MIREC's fluoride and IQ measurements are invalid and therefore cannot support the claim that CWF is associated with IQ decline in children.

Conclusions: The MIREC fluoride-IQ articles' results should be considered unacceptable for legal and policy purposes; other water fluoridation studies and systematic reviews show no effect of fluoridation on cognition.

KEYWORDS
community water fluoridation, fluoride exposure, IQ

1 | INTRODUCTION

Community water fluoridation (CWF) is a public health success in reducing dental decay safely, economically and equitably.[1] Yet, CWF has continually faced opposition, mostly based on emotion, and using tenuous links to evidence to attempt to justify such opposition.[2] Each alleged scientific reason for opposition has been refuted, but another allegation often arises, like a zombie from the grave.

A current false claim holds that even the recommended low level of fluoride in water can affect the brains of a foetus and child. That claim is made by fluoride opponents to cease CWF, and was accepted by decision-makers who ceased CWF in 2022 in State College, Pennsylvania.[3] The 'harm to babies' brain' claim is the basis for litigation to end water fluoridation, potentially for the entire United States, in litigation underway (as of this writing) in the United States Federal District Court.[4] Therefore, it is essential to appraise the quality of the evidence currently being used to oppose this valuable public health measure.

The claim that levels of fluoride associated with CWF are associated with harm to cognition was made most prominently in 2019 in *JAMA Pediatrics* by Green et al.[5] The Green et al. article, which

has been previously criticized for failure to provide robust evidence on exposure to fluoride and impaired intelligence,[6] is one of a series of six articles,[5,7-11] reporting similar analyses conducted by overlapping groups of researchers, using the Canadian Maternal–Infant Research on Environmental Chemicals (MIREC) Study[12] (Table 1). The articles seek to determine whether foetal exposure to fluoride in utero, and through early feeding and infancy, are causally linked to intellectual impairment in childhood. To make such a determination, the MIREC fluoride-IQ authors must measure foetal fluoride exposure and childhood Intelligence Quotient (IQ) accurately, perform appropriate statistical analyses and interpret their results appropriately. These authors have not done so. Therefore, the articles are of no utility. To demonstrate this fact, we first describe the MIREC database and its methods, and then these authors' use of measurements and their statistical analyses. We offer our analysis to show the fatal flaws in these measurements that the authors have not addressed.

2 | THE MIREC STUDY

The MIREC study aimed to create a research database to study the effects of environmental chemicals on pregnant women and their children.[12] Funded by Health Canada, the Ontario Ministry of the Environment and a grant from the Canadian Institutes of Health Research,[12] the study focused on the effects of prenatal exposure to 'priority environmental chemicals'. The chemicals of specific interest[13] included heavy metals, phthalates, brominated flame retardants and bisphenol A (BPA), but not fluoride. Consequently, measurements of fluoride were not included in the original data set. The MIREC database has since been used in secondary analyses by the MIREC fluoride-IQ authors to study the effects of maternal and infant exposure to fluoride on the IQ of the resulting child.

The MIREC participants were women recruited from prenatal clinics in cities across Canada. The recruitment sites, response rates and participant characteristics differed between centres,[12] consequently comparisons among them must be corrected for a variety of social factors, such as parental education and social status.

3 | MEASUREMENT QUALITY

3.1 | Measurement of exposure: fluoride

For a foetus to be exposed to fluoride, fluoride must reach the foetus via the bloodstream. Because foetal blood samples are not available, measuring fluoride exposure of the foetus is necessarily indirect. The researchers presumed that maternal intakes and blood levels of fluoride correspondingly affected the foetus. The MIREC database used three methods to attempt to determine fluoride exposure of the pregnant woman as a proxy measure of foetal exposure: (1) Maternal exposure through community water fluoridation; (2) Analysis of self-reports by the pregnant woman of what the woman drank; and (3) Measurement of fluoride in three untimed spot urine samples from the pregnant woman.

The first measure is uncontroversial; community water fluoridation was a practice in three of the six cities that were studied—Hamilton, Toronto and Halifax, and not in Vancouver, Kingston and Montreal. The concentrations of fluoride in the water are publicly available information. This is a measure of fluoride exposure experienced by the whole community. But these authors wished to undertake individual intake analyses to provide greater precision in determining effects, so they analysed two other exposure measures.

The second exposure measure—self-reports of intake—is weak. The self-reports provide estimates of how many 'cups' of tap water and water-based beverages were usually consumed daily, during the pregnancy at trimesters one and three. Yet, neither the MIREC beverage questionnaire nor the estimates of fluoride intake from those data has been validated, as stated by some of these authors themselves.[5] Such estimates are subject to recall error. Self-reports of usual energy intake by dietary questionnaire are unreliable.[14] Reports of fluid intake based on people's estimates of what they usually drink are similarly uncertain.

The third fluoride measurement—measuring fluoride in maternal urine—is an attempted proxy measure of maternal blood levels. The MIREC database contains only spot urine samples from the pregnant women collected in each trimester of the pregnancy, at delivery and in the early postnatal period (up to 10 weeks). (These 'spot' samples had no limits or requirements on time of day, or recent intake of fluoride.) The researchers detail how the fluoride levels in the urine samples were chemically assayed, with checks for validity. However, there are at least two problems with this third measure of chronic (i.e. duration of pregnancy) fluoride exposure to the foetus.

First, spot urine tests are inadequate to measure chronic (i.e. duration of pregnancy) fluoride exposure accurately in an individual, let alone in the foetus of a pregnant woman, because they measure fluoride concentration in urine at only one point in the day. Fluoride levels vary throughout the day with a short half-life, depending upon whether a person has been recently exposed to fluoride; these levels also vary from day to day. For example, if the individual had just brushed her teeth with fluoridated toothpaste or had just drunk black tea (which has high fluoride levels), then the spot urine test would misrepresent her average fluoride exposure in a day; current or concurrent exposure measurements are not useful because they are so variable. Indeed, some of the MIREC fluoride-IQ authors, who assert that maternal fluoride exposure is associated with decreased IQ, have conceded that spot urine tests are not useful in estimating the duration and persistence of fluoride exposure, such as here:[15]

> [U]se of one spot urine sample may have introduced error given the short half-life of fluoride and the impact of consuming tea or inadvertent ingestion of fluoridated dental products prior to urine sampling. [...]
>
> Taken together, urinary fluoride level varies substantially depending on participant behaviour prior to

TABLE 1 Published studies arising from MIREC database, testing for intelligence quotient effects of fluoride exposure during foetal development.

Publication	Authors	Exposure	Outcome	Reported main results
Association between Maternal Fluoride Exposure during Pregnancy and IQ Scores in Offspring in Canada. JAMA Pediatrics 2019, 173(10), pp. 940–948	Green, R., Lanphear, B., Hornung, R., Flora D., Martinez-Mier, E.A., Neufeld, R., Muckle, G., Till, C.	Fluoride: water fluoridation by city, individual levels by maternal intake questionnaire, maternal spot urine levels.	Intelligence Quotient (IQ) measured by Wechsler Preschool and Primary Scale of Intelligence-III Outcome Full-scale IQ at 3–4 years, by IQ tests with no validation.	No differences in IQ between children in fluoridated and non-fluoridated cities. No main effect of maternal urinary fluoride on full-scale IQ was observed in a regression analysis. Subgroup analysis: A 1 mg/L increase in specific gravity adjusted maternal urinary fluoride was associated with a 4.49-point lower IQ score (95% CI: −8.38 to −0.60) in boys. In contrast, there was a 2.4-point increase in FSIQ in girls, but it was not statistically significant.
Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. Environment International 2020, 134, 105315	Till, C., Green, R., Flora, D., Hornung, R., Martinez-Mier, E. A., Blazer, M, Farmus, L., Ayotte, P., Muckle, G., Lanphear, B.	Estimation of fluoride exposure from formula: not validated. Maternal spot urine tests.	IQ measured by Wechsler Preschool and Primary Scale of Intelligence-III.	Breast-fed children had better Performance IQ scores than formula-fed children in fluoridated areas. Fluoride from tap water elevated the estimate of fluoride exposure arising from infant formula. Adjustment for foetal fluoride exposure did not explain the observed association. Likely confounded by higher maternal education and income levels among breastfeeding women.
Critical windows of fluoride neurotoxicity in Canadian children. Environmental Research 2021, 200, 111315	Farmus, L., Till, C., Green, R., Hornung, R., Martinez-Mier, E. A., Ayotte, P., Muckle, G., Lanphear, B.P., Flora, D.B.	Three exposure 'windows' to fluoride examined: prenatal; infancy; and childhood, using, *inter alia*, maternal spot urine levels.	IQ measured by Wechsler Preschool and Primary Scale of Intelligence-III.	Many models were investigated and covariates were not selected in a systematic manner. Performance IQ was most strongly linked to fluoride exposure during the prenatal period. Fluoride exposure was not associated with Verbal IQ across any exposure window. However, fluoride exposures during pregnancy, infancy and childhood were not associated with Performance IQ once the city-level effect was controlled and adjustments were made for multiple testing.

(Continues)

TABLE 1 (Continued)

Publication	Authors	Exposure	Outcome	Reported main results
Iodine Status Modifies the Association between Fluoride Exposure in Pregnancy and Preschool Boys' Intelligence. Nutrients 2022, 14(14), 2920	Goodman, C., Hall, M., Green, R., Hornung, R., Martinez-Mier, E. A., Lanphear, B., Till, C.	Fluoride: Maternal spot urine levels. Iodine: Spot urine levels.	IQ measured by Wechsler Preschool and Primary Scale of Intelligence-III.	A three-way interaction term examined maternal spot urinary fluoride and maternal spot urinary iodine on child IQ by child sex. Low iodine status was associated with a stronger fluoride effect in boys but not in girls. Among girls, IQ increased with increasing levels of fluoride in low and adequate iodine status groups but was not statistically significant.
Fluoride exposure and hypothyroidism in a Canadian pregnancy cohort. Science of the Total Environment 2023, 869, 161149	Hall, M., Lanphear, B., Chevrier, J., Hornung, R., Green, R., Goodman, C., Ayotte, P., Martinez-Mier, E. A., Zoeller, R. T., Till, C.	Fluoride: Water fluoride concentration, maternal spot urinary fluoride and maternal fluoride intake.	IQ measured by Wechsler Preschool and Primary Scale of Intelligence-III.	Water fluoride concentration and fluoride intake were associated with primary hypothyroidism but maternal urinary fluoride was not.
Dose dependence of prenatal fluoride exposure associations with cognitive performance at school age in three prospective studies. European Journal of Public Health 2024, 34(1), 143–149	Grandjean, P., Meddis, A., Nielsen, F., Beck, I. H., Bilenberg, N., Goodman, C. V., Hu, H., Till, C., Budtz-Jørgensen, E.	Fluoride: Maternal spot urinary fluoride.	IQ measured by Wechsler Preschool and Primary Scale of Intelligence-III.	Maternal urinary fluoride was not associated with full-scale IQ for the MIREC cohort or in the Odense Child Cohort. However, the authors combined these non-comparable cohorts with the ELEMENT cohort to generate a bench mark concentration analysis that purports to show a relationship of fluoride exposure to IQ.

> sampling and may not be representative of long-term fluoride exposure.

Elsewhere, some of the MIREC fluoride-IQ authors also have conceded that spot urine tests are not a valid method to determine chronic exposure:[16]

> […] overnight fasting or 24-h urine samples are considered to be the optimal dosimeter for measuring chronic fluoride exposure (WHO 2014). In contrast, the present study measured the concentration of fluoride in a spot urine sample that did not control for recent fluoride ingestion.

But later, some of these authors have confusingly argued that spot urine samples *are* reliable to assess chronic fluoride exposure in individuals. They write[17]

> Urinary fluoride is not a perfect measure of **fluoride intake**, but it is reliable, and it is the optimal biomarker of concurrent fluoride exposure (Rugg-Gunn et al., 2011)[18] [emphasis added].

Those authors appear to be suggesting that Rugg-Gunn and colleagues claim that spot urine tests validly and reliably measure individuals' chronic fluoride exposure (duration of pregnancy – the meaningful measure). However, Rugg-Gunn et al. explicitly stated the opposite, noting that even 24-h urine samples (daily excretion) cannot measure chronic fluoride exposure in individuals. Rugg-Gunn et al. write:[18]

> Plots of daily urinary fluoride excretion against total daily fluoride intake suggest that daily urinary fluoride excretion is suitable for predicting fluoride intake **for groups of people, but not for individuals**. While fluoride concentrations in [blood] plasma, saliva and urine have some ability to predict fluoride exposure, **present data are insufficient to recommend utilizing fluoride concentrations in these body fluids as biomarkers of contemporary fluoride exposure for individuals**. Daily [24 h] fluoride excretion in urine can be considered a useful biomarker of contemporary fluoride exposure for groups of people, and normal values have been published. [emphasis added].

Aylward et al.[19] also reinforce the point that spot urine tests do not reliably measure chronic fluoride exposure in individuals, noting,

> Because of substantial within- and between-individual variation in urinary flow and creatinine excretion rates, as well as the rapid urinary elimination pharmacokinetics of fluoride, concentrations of fluoride in individual spot samples may vary substantially even when underlying exposures rates are consistent and within the exposure guidance values.

In other words, even though 24-h urine tests cannot tell us an individual's chronic exposure to fluoride, the MIREC fluoride-IQ authors who use the MIREC data attempt to claim that *three* maternal spot urine tests can reliably reveal the chronic fluoride exposure of a foetus to fluoride. These authors write,[16]

> To enhance our measurement, we therefore measured urinary fluoride at three time points, providing a more sensitive measurement of MUF [maternal urinary fluoride] concentration than if only one measurement were used. We only included participants who had valid fluoride measurements at each trimester in the analysis […]

This measurement 'enhancement' is, in fact, minimal. Pooling three samples reduces the random variation of single measurements, but does not make the measurement 'more sensitive', which would imply being able to detect smaller quantities. (Perhaps, the authors mean 'consistent', i.e. with lower variation). But even averaging three spot urine samples of the pregnant woman cannot reliably tell us the woman's chronic fluoride levels or intake. Further, by excluding women who did not supply three samples, the authors have limited the study population even further, with the possibility of selection bias (e.g. those who provided three urine samples might be more consistent in other behaviours compared to those who did not). That bias might confound any relationships with child IQ.

Even though Rugg-Gunn et al. and Alyward have made clear that neither spot urine nor 24-h urine can tell us how much fluoride an individual was exposed to, some MIREC fluoride-IQ authors surprisingly claim that spot maternal urine tests can be used to estimate foetal exposure to fluoride. This claim raises the second problem regarding the authors' third attempted measure of fluoride: The authors incorrectly claim that fluoride in urine is correlated to fluoride in blood. These authors reference a study by Thomas et al.[20] claiming, 'the Thomas (2016) study did find a moderate correlation ($r = .29$) between the two biomarkers [urine and blood] during early stages of pregnancy'.[17] But actually, Thomas et al. concluded that there is almost no correlation between fluoride measures in urine and in blood. Thomas et al. stated:[20]

> In general, **there was a lack of correlation between these two biomarkers [urine and blood]**, though a significant correlation was found in fluoride levels between urine and [blood] plasma of mothers sampled during **early** stages of pregnancy. Across the three stages of pregnancy, maternal urinary fluoride and plasma values (Figure 2) were not different and remained fairly stable as pregnancy progressed. As a summary measure of consistency in fluoride concentrations across the three stages of pregnancy from

> which we sampled biomarkers, the ICC [Intra-class correlation coefficient] for urine was 0.25 and for plasma was 0.39. [emphasis added].

In their 2016 article, Thomas et al.[20] report that the correlation coefficients *do not* show a correlation between the amount of fluoride in a pregnant woman's urine and in her blood. They assessed correlation coefficients relating fluoride levels in the woman's urine (creatinine-adjusted) and her blood plasma at two different stages of pregnancy. Among the participants, the correlations were 0.29 and −0.24 during early and late pregnancy respectively. These values are below 0.5—the recommended standard to indicate 'moderate' effects.[21] Furthermore, a multiple regression analysis did not show an association between the fluoride biomarkers of the pregnant woman's urine and blood plasma. In other words, the 2016 Thomas article describes low and variable, sometimes negative correlation of creatine-adjusted maternal urine fluoride with blood plasma fluoride, at least in Mexico City where fluoride supplementation occurs through fluoridated salt rather than water. It is unclear why the authors assert the opposite of what Thomas et al. state.

To summarize concerns about measuring foetal exposure to fluoride using spot maternal urine samples, there is a consensus in the scientific community that a spot maternal urine sample is not a valid biomarker of an individual's chronic exposure to fluoride.[22] Spot urine tests are not valid to quantify fluoride exposure in a pregnant woman or her foetus, no matter how precisely the researchers measured fluoride in the spot urine samples. Because the researchers report accessing only spot maternal urine tests in the MIREC database to assess foetal exposure (three in total) and there is low correlation of fluoride levels in urine and blood plasma, users of that database simply cannot reliably measure the pregnant woman's or the foetus' exposure to fluoride.

3.2 | Measurement of the outcome: IQ of children

The MIREC data claim to report the IQ of children using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, (WPPSI-III). But the IQ testing of the children in the MIREC sample is unreliable.

To measure the IQ of children in a comparable way, one must use standardized test administration. This testing approach is important especially because of the young age of the children—aged 3 to 4 years at the time of the IQ test. (A small subset of the children were aged 5–6 years when tested.) IQ testing of young children is notoriously difficult because the test must be administered and scored by an interviewing examiner, unlike the more straightforward written 'tests' that older children can complete on paper. Moreover, assessing such young children challenges even experienced examiners.[23] Little is published about sex differences in attention in preschool children, but they are found in slightly older children, so sex differences might affect test scoring.[24] In addition and irrespective of the age of the research subject, major sources of errors can occur in IQ testing. When different people administer the test, they introduce the possibility of differences in administration, scoring and interpretation across the population being studied. These issues of variability are well known. The National Institute of Environmental Health Sciences report, *Evaluating Features and Application of Neurodevelopmental Tests in Epidemiological Studies*, provides examples of factors that could present problems and introduce bias in the test results.[25] As Styck and Walsh report, 'examiner errors occur frequently and impact index and FSIQ [full scale IQ] scores', concluding that 'current estimates for the standard error of measurement of popular IQ tests may not adequately capture the variance due to the examiner'.[26]

So, for young children, it is vital to assess IQ using a consistent and reliable approach: Ideally, the same test administrator, with quality checks. Yet, the MIREC IQ data were created by a 'single staff person from each study site' according to Etzel et al.[27]; in other words, there were different MIREC IQ assessors in each of six cities. If examiners differed in the way in which they coded the children's behaviours into IQ, then this difference could lead to an apparent effect of fluoridation even if none existed. Thus, systematic variations among the six examiners might be a confounding variable. The examiners' backgrounds are described only as being 'research assistants', not formally trained psychometricians. According to Etzel et al., 'Study staff from each participating study site completed a 3-day training session that was led by a PhD-level psychologist (E.O.) and focused on specialized training of these assessment tools'.[27] According to some MIREC fluoride-IQ researchers,[17] regular site visits were made to observe these examiners, and test protocols were double scored. However, none of the MIREC fluoride-IQ articles describes the training process. A doctoral degree does not, of itself, provide the specialized training necessary to administer the WPPSI-III and it is not stated whether the psychologist who trained the administrators was an accredited, formally trained administrator of the WPPSI-III, as is desirable for test validity. Even the best testers will differ within themselves (if they retested the same subject) and between one another. Their accuracy may 'drift' over time. Analysis of accuracy would enable us to understand the variation, so we can understand how much difference in test score is meaningful. Therefore, validation of the IQ test scores would normally be expected in a research study. But none of MIREC fluoride-IQ articles present quality assurance statistics of the results, comparisons over time or among the study centres. For all these reasons, the MIREC IQ data do not permit anyone to know whether comparisons of IQ in fluoridated and non-fluoridated cities are meaningful.

Such failure to assure that the IQ assessments are valid is concerning. It appears that either the MIREC fluoride-IQ researchers are oblivious to the issues that cause variability in test results, or they have chosen not to address these issues—either in their articles or in their response to expressed concerns.[28,29] The issues of variability and therefore potential bias created by using different assessors of IQ in each city make it difficult to accept any claim of a small IQ decrement in children associated with fluoride exposure.

Indeed, if foetal fluoride exposure at fluoridation levels really did affect IQ, then the mean IQ of children in fluoridated cities should be systematically different from that in non-fluoridated cities. In the total sample of children, the mean IQ scores were 108.07 (SD = 13.31) and 108.21 (SD = 13.72) in non-fluoridated and fluoridated communities respectively. Yet, the children's IQ scores varied by 4–8 points among the six cities regardless of the fluoridation status.[28,30] This anomaly suggests that differences among cities in measurement or other factors such as maternal IQ are at least as large or larger than the effects of water fluoridation.

In the MIREC Green et al. article,[5] the authors reported in a table that average IQ was the same in fluoridated and unfluoridated cities but did not discuss the null finding. They engaged in *post hoc* analysis claiming differences between boys and girls, reporting this secondary analysis as the main effect. They allege that there is a 4-point difference between boys and girls, but given the measurement variation in scores for IQ testing, 4 points is not a large or even medium-sized effect.[31] Indeed, according to Ferguson[21] an IQ difference of over six points is required for the 'recommended minimum effect size representing a "practically" significant effect for social science data'.

Figure 3A in Green et al.[5] shows the relationship between the (disputed) estimate of maternal fluoride concentration and IQ for boys and girls. The figure reveals a very wide dispersion of fluoride levels, with most children being exposed to low levels of fluoride. The scores of the 10 or so boys exposed to the highest values of fluoride will have an undue influence on the regression coefficient. In other words, the presence of a few boys who were exposed to high levels of fluoride will lead to the relationship between fluoride concentration and IQ being overestimated for the group as a whole.

The Green et al.[5] article claims an association between fluoride exposure and IQ and purports to find only a 4-point difference in boys but not in girls. The random variance and bias due to variation in test administrators can account for far more than that difference.

By reporting an IQ point difference that was assessed using different IQ test administrators in different cities without careful validation, that is less than a third of the standard deviation of the test, and that varies independently of the city's fluoridation status, the MIREC database does not offer high-quality, reliable data about the children's IQ. Therefore, finding a decrease of four points in an IQ score only in boys (but not in girls) for every 1 mg/L increase in alleged fluoride concentration in urine is almost certainly a spurious finding.[32-34]

Measurement error has often been incorrectly considered to result only in a 'bias toward the null'. That is, errors in measurement make it less likely that one can observe a true association. However, in other situations, measurement error can result in a spurious overestimate of the true association.[35] That may be the case here. Other biases, such as measurement errors of outcome and covariates, confounding and selection bias, are also present in these MIREC fluoride-IQ articles.

3.3 | Lack of an appropriate conceptual model to assess causation

Addressing the complex question of the causal effect of fluoride on children's IQ requires models that incorporate knowledge and understanding of the causal mechanisms.[36] The MIREC fluoride-IQ articles apparently disregard several prenatal and postnatal factors that may influence children's IQ, such as maternal IQ, paternal IQ, gestational age, birth weight, breastfeeding, disease infections, traumatic events, exposure to environmental pollutants and social factors (e.g. attendance at daycare and kindergarten, and other social interactions). Conducting data analysis without an operational model that translates abstract concepts into measurable variables can oversimplify a complex problem.[37]

A conceptual model such as a directed acyclic graph can guide variable selection as well as indicate scenarios that might give rise to unanticipated 'backdoor pathways'.[38] In other MIREC articles, some of the MIREC fluoride-IQ authors used a simple version of a directed acyclic graph,[39,40] suggesting that the MIREC fluoride-IQ authors are aware of the value of the organizational tool but chose not to use it in all the articles they created.

Another major issue that raises questions about the validity of this set of articles is the absence of an operational model. The MIREC fluoride-IQ authors are not explicit about the question they are asking and the assumptions guiding their data analysis. Their analytical strategy relies on the selection of confounders based on *p*-values, a method widely acknowledged as not providing a reliable measure of evidence regarding a model or hypothesis.[41] This modelling strategy aligns more with prediction models rather than a causal inference model that specifies the role of each variable, including exposures, mediators, effect modifiers and confounders, which specification is necessary to address a causal question.

We did not undertake a formal quality assessment of these articles because we are not conducting a systematic review. Instead, we discuss the severe limitations that the MIREC fluoride-IQ authors have not addressed in their articles. Kumar et al. rated the Green et al. article as having a high risk of bias.[42] Kumar et al. stated,[42]

> Uncritical acceptance of fluoride-IQ studies, including non-probability sampling, inadequate attention to accurate measurement of exposure, covariates and outcomes, and inappropriate statistical procedures, has hindered methodological progress. Therefore, the authors urge a more scientifically robust effort to develop valid prenatal and postnatal exposure measures and to use interventional studies to investigate the fluoride-IQ hypothesis in populations with high fluoride (endemic) exposure.

As mentioned, the Green et al.[5] MIREC fluoride-IQ article reported in a table that the main overall effect was null. The question arises as to why the authors emphasize their *post hoc* analysis that claims to show a 4-point reduction for boys. This isolated secondary finding

lacks empirical corroboration, which is necessary for it to be regarded as causative. The authors themselves rightly note that such a finding 'requires more investigation'.

Several post-publication letters with respect to the Green et al. article specifically[32,34] and reviews of the MIREC fluoride-IQ articles generally[33,42-44] raise concerns regarding the overinterpretation of the findings resulting from their analytical approach. These concerns include inappropriate regression modelling based on a convenience sample of clusters of individuals and correlated observations, and inadequate attention to influential outlying observations. The MIREC fluoride-IQ articles in Table 1 show improper focus on subgroup analysis, and the failure to adjust significance levels given that the authors engaged in multiple testing. This 'data-dredging' approach ensures that at least some of the *p*-values will be 'significant' by chance. Such approaches might assist in exploratory analyses, but need replication before being accepted as evidence of an association – let alone cited as proof of causation, as some of the MIREC fluoride-IQ authors assert.[45,46]

3.4 | Other studies

Other published studies have addressed the same question: whether fluoridation affects foetal and child IQ. One replication study in Spain, which also used spot maternal urine as a proxy for foetal fluoride exposure, but different standard IQ tests, showed opposite effects: Fluoride led to a slight increase in boys' cognition, but not girls'.[47] Long-term cohort studies with larger samples and with IQ measurements at older ages, in New Zealand[48] and of military conscripts in Sweden[49] have shown no effect of fluoridation on cognitive development. A national cohort study of Australian children reported no impact of exposure to water fluoridation throughout life on measures of school-age executive functioning, emotional and behavioural development.[50]

Our critique is important because, among other reasons, members of the MIREC fluoride-IQ research group have self-cited their MIREC-based fluoride-IQ studies. For example, a recent report[11] of an alleged association between fluoride and cognition combined Danish data with data from two other studies, one of which was the MIREC study. The Danish data alone showed no association between fluoride and cognitive performance and, as our analysis has shown, the MIREC data cannot be used to claim an association between maternal fluoride exposure and diminished IQ. Consequently, this recent article[11] is also invalid.

4 | CONCLUSION

Researchers using the MIREC database claim that raised maternal fluoride exposure reduces children's IQ. They used what was available to them: spot urine tests of the pregnant women and IQ tests conducted on very young children by different assessors in six different cities. Although future studies might be designed to measure cognition in the MIREC cohort accurately, the flawed assessment of exposure to fluoride is insurmountable. Because the MIREC database offers neither valid data on maternal or foetal fluoride exposure, nor reliable measures of the IQ of the resulting children, the database cannot be used to make claims that fluoride exposure affects IQ.

AUTHOR CONTRIBUTIONS

Drs. Guichon and Dickinson created the draft which Drs. Rugg-Gunn and Cooper reviewed, including with specific attention to fluoride measurement (Dr. Andrew Rugg-Gunn) and intelligence measurement (Dr. Colin Cooper). All authors collaborated until satisfied with the final iteration.

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PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Where we quote words or ideas published in other journals, we cite the sources.

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REFERENCES

1. Centers for Disease Control and Prevention. Community water fluoridation. Accessed December 21, 2023. https://www.cdc.gov/fluoridation/index.html
2. Lowery G, Flinders M, Gibson BJ. When evidence alone is not enough: the problem, policy and politics of water fluoridation in England. *Evid Policy*. 2021;17(3):507-523.
3. Rushton G. *State college borough water authority board votes to stop fluoridation*. StateCollege.com. Published July 21, 2022. Accessed December 21, 2023. https://www.statecollege.com/articles/state-college/state-college-borough-water-authority-board-votes-to-stop-fluoridation/
4. Calendar for Judge Edward M. Chen, Courtroom 5, 17th Floor Courtroom Deputy: Vicky Ayala, Northern District of California. In Food & Water Watch vs EPA, Northern District of California, Motion to Lift Stay, Status Conference. Accessed December 21, 2023. https://apps.cand.uscourts.gov/CEO/cfd.aspx?7144
5. 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):940-948.

6. Oliveira BH, Cruz LR, Normando D, Cury JA. Fluoreto e inteligência: avaliação crítica de um estudo de coorte prospectivo. *Revista Científica do CRO-RJ (Rio de Janeiro Dental Journal)*. 2021;6(1):2-11.
7. Farmus, Linda, et al. Critical windows of fluoride neurotoxicity in Canadian children. *Environmental Research*. 2021;200:11315.
8. Till C, Green R, Flora D, et al. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. *Environ Int*. 2020;134:105315.
9. Goodman CV, Hall M, Green R, et al. Iodine status modifies the association between fluoride exposure in pregnancy and preschool boys' intelligence. *Nutrients*. 2022;14(14):2920.
10. Hall M, Lanphear B, Chevrier J, et al. Fluoride exposure and hypothyroidism in a Canadian pregnancy cohort. *Sci Total Environ*. 2023;869:161149.
11. Grandjean P, Meddis A, Nielsen F, et al. Dose dependence of prenatal fluoride exposure associations with cognitive performance at school age in three prospective studies. *Eur J Public Health*. 2024;34(1):143-149.
12. Arbuckle TE, Fraser WD, Fisher M, et al. Cohort profile: the maternal–infant research on environmental chemicals research platform. *Paediatr Perinat Epidemiol*. 2013;27(4):415-425.
13. Government of Canada. Chemicals management plan. Chemicals at a Glance. Accessed December 21, 2023. https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/chemicals-glance.html
14. Hill RJ, Davies PS. The validity of self-reported energy intake as determined using the doubly labelled water technique. *Br J Nutr*. 2001;85(4):415-430.
15. Riddell JK, Malin AJ, McCague H, Flora DB, Till C. Urinary fluoride levels among Canadians with and without community water fluoridation. *Int J Environ Res Public Health*. 2021;18(12):6203.
16. Till C, Green R, Grundy JG, 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.
17. Critical windows of fluoride neurotoxicity in Canadian children by Farmus and colleagues – In reply to Guichon et al. (2022) https://doi.org/10.1016/j.envres.2022.115201
18. Rugg-Gunn AJ, Villa AE, Buzalaf MR. Contemporary biological markers of exposure to fluoride. *Fluoride Oral Environ*. 2011;22:37-51.
19. Aylward LL, Hays SM, Vezina A, Deveau M, St-Amand A, Nong A. Biomonitoring equivalents for interpretation of urinary fluoride. *Regul Toxicol Pharmacol*. 2015;72(1):158-167.
20. Thomas DB, Basu N, Martinez-Mier EA, et al. Urinary and plasma fluoride levels in pregnant women from Mexico City. *Environ Res*. 2016;150:489-495.
21. Ferguson CJ. An effect size primer: a guide for clinicians and researchers. *Prof Psychol Res Pract*. 2009;40(5):532-538. doi:10.1037/a0015808
22. Baez RJ, Petersen PE, Marthaler TM, World Health Organization. *Basic Methods for Assessment of Renal Fluoride Excretion in Community Prevention Programmes for Oral Health*. World Health Organization; 2014 (This document was produced by a nine person working group of WHO, including Dr. Andrew Rugg-Gunn.).
23. Ford L, Kozey ML, Negreiros J. Cognitive assessment in early childhood: theoretical and practice perspectives. In: Flanagan DP, Harrison PL, eds. *Contemporary Intellectual Assessment: Theories, Tests, and Issues*. Vol 2022. 4th ed. The Guilford Press; 2012:585-622.
24. Efrat B, Orna T. Sex differences in the sustained attention of elementary school children. *BMC Psychol*. 2022;10(1):307.
25. White RF, Braun JM, Kopylev L, et al. NIEHS report on evaluating features and application of neurodevelopmental tests in epidemiological studies: NIEHS report 01. 2022; doi:10.22427/NIEHS-01
26. Styck KM, Walsh SM. Evaluating the prevalence and impact of examiner errors on the Wechsler scales of intelligence: a meta-analysis. *Psychol Assess*. 2016;28(1):3-17.
27. Etzel T, Muckle G, Arbuckle TE, et al. Prenatal urinary triclosan concentrations and child neurobehavior. *Environ Int*. 2018;114:152-159.
28. Guichon J, Nicolau B, Brandini M, Caron C, Mitchell I, D'Souza V. Letter to the editor regarding "Critical windows of fluoride neurotoxicity in Canadian children" by Farmus and colleagues. *Environ Res*. 2023:111315. doi:10.1016/j.envres.2021.111315
29. Guarino B. *Study raises questions about fluoride and children's IQ*. The Washington Post; 2019.
30. Green RR. *Prenatal Fluoride Exposure and Neurodevelopmental Outcomes in a National Birth Cohort*. York University. Published July, 2018. Accessed December 22, 2023. https://yorkspace.library.yorku.ca/server/api/core/bitstreams/c76e89ec-188c-4fb2-8b31-2738f926cc4c/content
31. Cohen J. A power primer. *Psychol Bull*. 1992;112(1):155-159.
32. Ritchie SJ, Morris AJ, McConway K. Association between maternal fluoride exposure and child IQ. *JAMA Pediatr*. 2020;174(2):213.
33. National Academies of Sciences, Engineering, and Medicine. Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Letter Report. 2021.
34. Baguley T, Jones O, Leahy J, et al. *Expert reaction to study looking at maternal exposure to fluoride and IQ in children*. Science Media Center. Published online August 19, 2019. Accessed December 22, 2023. https://www.sciencemediacentre.org/expert-reaction-to-study-looking-at-maternal-exposure-to-fluoride-and-iq-in-children/
35. Yland JJ, Wesselink AK, Lash TL, Fox MP. Misconceptions about the direction of bias from nondifferential misclassification. *Am J Epidemiol*. 2022;191(8):1485-1495.
36. Schuch HS, Nascimento GG, Demarco FF, Haag DG. Causal inference in dentistry: time to move forward. *Community Dent Oral Epidemiol*. 2023;51(1):62-66.
37. Celeste RK, Colvara BC, Rech RS, Reichenheim ME, Bastos JL. Challenges in operationalizing conceptual models in aetiological research. *Community Dent Oral Epidemiol*. 2023;51(1):58-61.
38. Digitale JC, Martin JN, Glymour MM. Tutorial on directed acyclic graphs. *J Clin Epidemiol*. 2022;142:264-267.
39. Goodman C, Hall M, Green R, et al. Maternal fluoride exposure, fertility and birth outcomes: the MIREC cohort. *Environ Adv*. 2022;7:100135.
40. Goodman CV, Till C, Green C, et al. Prenatal exposure to legacy PFAS and neurodevelopment in preschool-aged Canadian children: the MIREC cohort. *Neurotoxicol Teratol*. 2023;98:107181.
41. Karpen SC. P value problems. *Am J Pharm Educ*. 2017;81(9):6570.
42. Kumar JV, Moss ME, Liu H, Fisher-Owens S. Association between low fluoride exposure and children's intelligence: a meta-analysis relevant to community water fluoridation. *Public Health*. 2023;219:73-84.
43. Canadian Agency for Drugs and Technologies in Health. CADTH Rapid Response Report: Summary With Critical Appraisal Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects – A 2020 Update. 2020. Accessed February 24, 2023. https://www.ncbi.nlm.nih.gov/books/NBK567579/pdf/Bookshelf_NBK567579.pdf
44. Guth S, Hüser S, Roth A, et al. Contribution to the ongoing discussion on fluoride toxicity. *Arch Toxicol*. 2021;95:2571-2587.
45. Lanphear B, Till C, Birnbaum LS. "It is time to protect kids' developing brains from fluoride" Mounting evidence suggests fluoride may be hampering brain development and reducing kids' IQ. The US needs to rethink this exposure for pregnant women and children." and accompanying video, Environmental Health News, October 7, 2020. Accessed December 22, 2023. https://www.ehn.org/fluor

ide-and-childrens-health-2648120286/particle-7?rebelltitem=1#rebelltitem1

46. Lanphear B. Sworn Declaration of Bruce Lanphear, MD, MPH, United States District Court for the Northern District of California at San Francisco, Food & Water Watch, et al. vs. U.S. Environmental Protection Agency, Civ. No. 17-Cv-02162-Emc, May 20. 2020 https://drive.google.com/file/d/1ZaQ5lzo_aNgFyYjKnSJlJDo_azDbdrR_/view?usp=sharing
47. Ibarluzea J, Gallastegi M, Santa-Marina L, et al. Prenatal exposure to fluoride and neuropsychological development in early childhood: 1-to 4 years old children. *Environ Res*. 2022;207:112181.
48. Broadbent JM, Thomson WM, Ramrakha S, et al. Community water fluoridation and intelligence: prospective study in New Zealand. *Am J Public Health*. 2015;105(1):72-76.
49. Aggeborn L, Öhman M. The effects of fluoride in drinking water. *J Polit Econ*. 2021;129(2):465-491.
50. Do LG, Spencer AJ, Sawyer A, et al. Early childhood exposures to fluorides and child behavioral development and executive function: a population-based longitudinal study. *J Dent Res*. 2023;102(1):28-36.

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