December 15, 2018

Christopher J. Lynch, Ph.D.
Executive Secretary of the NIH Nutrition Research Task Force
National Institute of Diabetes and Digestive and Kidney Diseases
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Dear Dr. Lynch:

On behalf of the 3,400 individual and 103 institutional members of the American Association for Dental Research (AADR), thank you for the opportunity to comment on Request for Information (RFI): Soliciting Input on the Draft Strategic Plan for NIH Nutrition Research (NOT-DK-19-004). On April 13, 2017, AADR provided comments during the initial phase of this plan (http://www.iadr.org/Portals/69/docs/AADRComments_NutritionalResearchStrategicPlan.pdf). Because this plan will guide nutrition research for the next 10 years, AADR continues to advocate for the inclusion of themes, priorities and research activities that will advance dental, oral and craniofacial research and lead to improved overall health.

**General strengths of the draft strategic plan.** AADR commends the inclusion of Theme 2, “Assess the Role of Nutrition and Dietary Patterns in Development, Health and Disease across Life Stages,” which reflects AADR’s April 13, 2017 recommendation for research on the impact of sugar and overall diet quality on the development of dental caries. Examining the role of nutrition and dietary patterns in health across life stages should include research on life phase-specific conditions such as orofacial cleft and edentulism. AADR agrees with the inclusion of minority health, health disparities and women’s health as cross-cutting research areas as well as Theme 5 on implementation science to increase the use of effective nutrition interventions. AADR is pleased that the strategy includes collaboration among healthcare providers from multiple disciplines including dentistry. Finally, AADR supports the recommendation to train future researchers in large and diverse research teams.

**Noticeable omission of the oral microbiome.** There is sparse mention of the oral microbiome in this draft strategic plan. One could add the oral microbiome to almost any reference to the gut microbiome. AADR
recommends changing the term “gut microbiome” to “gastrointestinal-tract (GIT) microbiome” and clearly defining this term to include the oral microbiome.

Specific comments on the cross-cutting research areas and themes are described below. While the plan cannot specifically name all diseases, there are a few research areas of importance to the dental, oral and craniofacial research community that should be included or if not specifically mentioned in the plan, considered for future funding opportunities.

**Cross-cutting Research Areas – Minority Health and Health Disparities**

Analysis of the interrelationships between dietary intake, nutritional status and health leading to diet-related health disparities should be conducted for both men and women and should include the state of the subjects’ dentition, i.e., fully dentate, partially dentate or edentulous. This may be helpful in identifying dietary trends among the target groups.

**Theme 1: Investigate Nutritional Biochemistry, Physiology, and the Microbiome**

1-3 Investigations should not only identify diet, host and gut microbiome interrelationships but should also consider diet, host and oral microbiome interrelationships and the interrelationships between the oral and gut microbiomes. A more holistic approach evaluating influences on the gut and oral microbiome are essential to understanding dietary influences on the microbiome of humans. Oral microbiome research should be fully integrated throughout this theme.

1-3a Add as a future research activity: Investigate the role of nutrition in caries control.

**Theme 2: Assess the Role of Nutrition and Dietary Patterns in Development, Health, and Disease across Life Stages?**

2-1 Add as future research activities:

- Examine, at a more granular level, the impact of individual nutrient excesses or deficiencies and related contextual factors on congenital anomalies.
- Examine the impact of mother and child oral health status on subsequent health and disease later in life, as part of the “Developmental Origins of Health and Disease” (DOHaD) hypothesis.

2-2a Add as future research activity: Determine how nutrition in the first 24 months of life impacts lifelong oral health status.

2-2b Add as future research activity: Determine how human milk versus formula composition impact the oral health of infants and the oral microbiome.

2-3 Add as future research activities:

- Explore the influence of dietary patterns during early childhood and adolescence on oral health and disease, particularly the impact of early exposure to varying amounts of sugar and its’ impact on dietary preferences and dietary habits associated with oral disease throughout life.
- Conduct studies that test various dietary interventions during childhood and adolescence to determine their potential impact on oral health.
- Evaluate how dietary patterns affect oral health in children and adolescents.

2.5a Add as a future research activity: The impact of calorie restriction and circadian misalignment on oral health with further investigation into the effect on overall health.

2.5b Add as a future research activity: Leverage natural policy experiments (e.g. taxing of sugar sweetened beverages) to evaluate the extent to which policies impact nutrition, oral and overall health outcomes.

Theme 3: Explore Individual Variability in Response to Diet Interventions to Inform Nutrition Science, Improve Health, and Prevent Disease

3-1 Add as a future research activity: Explore connections between oral health, obesity and diet.

3.2 Add as future research activities:

- Research on the dentition and nutrition of nursing home residents.
- Research on the dentition and nutrition of both men and women with eating disorders, particularly long-term oral health effects and studies that stratify bulimics based on treatment type and eating disorder type.

Theme 4: Enhance Clinical Nutrition Research to Improve Health Outcomes in Patients

4-1 AADR was pleased that the plan recognizes that “missing teeth, orofacial pain, salivary dysfunction, and oral complications during cancer treatment” (scientific priority 4-1) can impact nutritional intake and the prioritization of elucidating how these conditions can alter dietary intake and vice versa. This will provide an important opportunity to explore the connection between oral and overall health.

Add as a future research activity: Determine how nutritional approaches can influence the control of oral diseases, including caries.

4.5 Add as a future research activity: Research on nutritional support for infants with orofacial clefts.

Insert new Scientific Priority, between 4.4 and 4.5, “Pragmatic research to optimize breastfeeding to reduce disparities, particularly among vulnerable infants.”

Breastfeeding should be incorporated in this plan beyond how it affects preterm infants. Examples of future research activities include:

- Establish best practices for the process of transitioning to breastfeeding and overcoming barriers to successful breastfeeding in populations known to have disparities in breastfeeding (e.g. infants with cleft lip only, limited English proficiency mothers).
- Identification of strategies to optimize the feeding experience and that set up the mother-infant dyad to successfully transition to exclusive breast milk feeding among infants who receive supplementation at birth during hospitalization.
- Identify and address key barriers to breastfeeding in primiparas (women who have given birth for the first time).
Theme 5: Advance Implementation Science to Increase the Use of Effective Nutrition Interventions

5-1 AADR applauds the inclusion of industry practices as one of many multi-level influences on dietary pattern.

Theme 6: Develop and Refine Research Methods and Tools

6-1 AADR agrees with the need for biomarkers that can confirm self-reported dietary intake and with the inclusion of the development of oral bio-devices as a future research activity under scientific priority 6-5.

6-1b Add as a future research activity: Research to improve understanding of the relationship between urine fluoride and total fluoride intake.

AADR is one of many organizations that support community water fluoridation as an effective and evidence-based population-level intervention for the prevention of dental caries. Numerous studies have affirmed the safety of community water fluoridation (https://www.iadr.org/AADR/About-Us/Policy-Statements/Science-Policy/Community-Water-Fluoridation). Understanding the health effects of total fluoride intake (i.e., fluoride from dietary, environmental and other sources) is an active area of research, but measuring total fluoride intake is still difficult. For example, a recent study in Mexico City, where fluoride is added to salt, found an association between prenatal fluoride exposure and symptoms of ADHD. However, the value of the study was limited because it was “not possible to attribute the fluoride exposure to any particular source” (see Appendix, “Review of ‘Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6–12 years of age in Mexico City’”).

Some researchers inaccurately use fluoridated drinking water levels as a proxy when there are many other sources of fluoride. As a result, some studies imply a link between water fluoridation and adverse systemic health effects. Another study that found an association between fluoride exposure and thyroid function was also limited because it did not account for sources of fluoride other than drinking water (see Appendix, “Review of ‘Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status’”). More research is needed to understand the relationship between total fluoride intake and urine fluoride concentrations, including in pregnant women (see Appendix, “Review of ‘Community water fluoridation and urinary fluoride concentrations in a national sample of pregnant women in Canada’”). Research conducted under scientific priority 6-7, “Encourage the use of Controlled Human Feeding Studies,” may also increase knowledge in this area.

Theme 7: Support Training to Build an Outstanding Nutrition Research Workforce

7.1 Expand this scientific priority to include training on the interrelationship between the oral microbiome and diet.

7.2 Add as research activities:
• Educational research on how to teach DDS/MDs to provide nutritional counseling.
• Evaluation of the effectiveness of the current curricula.
• Oral health clinical nutrition research.

Once again, AADR appreciates the opportunity to provide input on the latest phase of development of the nutrition research strategic plan. AADR looks forward to the finalized draft and stands ready to work with NIH for the promotion and dissemination of the final plan. If you have any questions or need further information please contact AADR Director of Science Policy and Government Affairs, Dr. Seun Ajiboye, at sajiboye@aadr.org.

Sincerely,

Christopher H. Fox, DMD, DMSc
Chief Executive Officer

Maria Emanuel Ryan, DDS, PhD
President

Appendix

1. Review of “Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6–12 years of age in Mexico City”
2. Review of “Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status”
3. Review of “Community water fluoridation and urinary fluoride concentrations in a national sample of pregnant women in Canada”
SYNOPSIS

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

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Link to this article: Available from: https://ehp.niehs.nih.gov/doi/10.1289/EHP655

Key messages

- Research assessing adverse health effects of water fluoridation has gained attention given concern around the use of fluoride as a public health intervention to improve dental health. This article has assessed attention-deficit/hyperactivity disorder (ADHD) symptoms in 6-12 year olds as an outcome of prenatal fluoride exposure. It is the second study from the same cohort of pregnant women in Mexico, which earlier assessed the effect of prenatal fluoride exposure on cognitive outcomes in children at 4 and 6–12 years of age.¹

- Using creatinine adjusted maternal urinary fluoride (MUFcr; mean(SD)-0.85(0.33) mg/L) to assess prenatal fluoride exposure, and validated scales administered on mothers and children to assess ADHD in children, the study found that a 0.5 mg/L increase in MUFcr corresponded with increases of several measures of ADHD using the Conners' Rating Scales-Revised (CRS-R) (test based on mothers’ reporting). Although statistically significant, these changes were within the normal range and would not be considered clinically significant. Authors found no significant associations between MUFcr and Conners’ Continuous Performance Test (CPT-II) measurements (test administered on children to measure ADHD).
• Methodologically, the study is better than previous studies in the field and incorporates individual level, rather than ecological, exposure assessment. However, not all potential confounders were fully addressed and these remain possible explanations for the association found.

• The study population in Mexico City does not receive fluoridated drinking water although fluoride is added to salt in Mexico. As per the Canadian study, published on the same date (October 10, 2017), MUF levels of pregnant women living in fluoridated regions of Canada (mean(SD) MUFcr - 0.87(0.50) mg/L) are comparable to mean MUFcr levels of pregnant women in this study; therefore, findings may be relevant in the Ontario context.

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

Appraisal

Study Design
• This prospective cohort study used longitudinal birth cohort (Early Life Exposures to Environmental Toxicants (ELEMENT) data in Mexico, following children from the prenatal period through to school age. This study assessed the relationship between prenatal fluoride exposure and ADHD in 6-12 year olds. The MUFcr (the predictor) was collected by spot urine samples. To assess ADHD behaviours, the Conners' Rating Scales-Revised (CRS-R) was completed by mothers, and the Conners' Continuous Performance Test (CPT-II) was administered to their children aged 6-12.

• The environmental sources of fluoride for this population included fluoridated salt (250 ppm) and naturally-occurring fluoride in drinking water (estimated range: 0.15-1.38 mg/L). Mexico City does not fluoridate its drinking water. Mothers were recruited during the first trimester of pregnancy across two birth cohort studies during the periods 1997-1999 (cohort ‘2A’) and 2001-2003 (cohort ‘3’). Cohort 2A was an observational birth cohort and cohort 3 was a randomized
double-blind placebo-controlled trial in which subjects were either randomized to the calcium supplement (Cohort 3 – Ca +) or to placebo (Cohort 3 – placebo). There were differences in the distribution of covariates between the two study cohorts (described in the limitation section).

**Main findings**

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

- As per Table 1 of the article, the means and 95% CI values for the four CRS-R indices for study participants are as follows:
  - DSM-IV Inattention - 53.89 (52.48, 55.30)
  - DSM-IV ADHD Total - 55.61 (54.26, 56.97)
  - Cognitive Problems and Inattention - 54.62 (53.14, 56.10)
  - ADHD Index - 54.30 (52.88, 55.71)

- Overall, mean ± SD scores across all of the CRS-R scales fell within the average range (i.e., mean T=50 ± 10, which is 1 SD). The authors found that a 0.5 mg/L increase in MUFcr corresponded with approximately a 2.5 point increase across the four indices, which remains within normal boundaries. In other words, although the confidence intervals for each of the four outcomes above indicate the changes are statistically significant, the changes would not be clinically significant. That said, it is important to conduct more studies in the future, with robust methodologies, to further explore this association.

- Authors observed a possible ceiling effect of the exposure to CRS-R; this ceiling effect would essentially mean that after a particular threshold of exposure, no further increase in outcome can be observed. However, evidence for this effect is not consistent for all of the outcomes. Also, to the extent that non-linear effects are present, the coefficients given in Table 2 would not apply across the full range of MUFcr.

- Authors found no significant associations between maternal urinary fluoride and the performance of children on an objective test (the CPT-II) or on symptom scales assessing hyperactivity with MUF. The CPT-II measured errors of omission, commission, and reaction times. The mean scores of all three dimensions of the CPT-II were significantly different for children from cohort 2A versus those from cohort 3. Whether this is due to differences in the
period of recruitment or other factors is not clear. It does raise questions about the merits of a combined analysis of the cohorts and the internal validity of findings.

- It is interesting that the authors choose to use gamma regression to model the data; the residual plot from the linear regression would be helpful in assessing the appropriateness of gamma regression. One would have greater confidence in the associations found if other methods of analysis had also been used and gave similar results. This is particularly true in light of the borderline statistical significance of some of the associations.

- Approximately 10% of the study participants fell in the clinically significant range (i.e. T-score ≥70 on the Index scores). The authors do not comment on whether their results are unusual or typical with respect to what has been found when using this screening questionnaire in other settings. The prevalence of ADHD in US children aged 8-15 is 8.7%, with a higher prevalence in those with lower socio-economic status, so these results may not be unusual.

**Strengths**

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

- Maternal urinary fluoride concentrations were adjusted for creatinine to account for variations in urine dilution.

- Attention outcomes were assessed using the Spanish version of the Conners' Rating Scales-Revised (CRS-R), a validated screening tool for ADHD. In addition, the Conners' Continuous Performance Test was administered on children to assess sustained attention and inhibitory control.

- The study adjusted for some covariates such as gestational age, birth weight, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. non-smoker), marital status (married vs. others), and education.

**Limitations**

- The study population was comprised of two cohorts (referred to as “Cohort 2A” and “Cohort 3”) that were both recruited from hospitals in Mexico City that serve low-to-moderate income populations. It is not necessarily representative of the general population.

- The two cohorts were recruited at different time periods, under different study designs. There were differences in the distribution of covariates between the two study cohorts. For example, as per the authors' previous study, participants in cohort 2A had higher mean bone lead levels (p-value 0.001) than participants in cohort 3. This study also shows differences between
children’s ages between cohorts at outcome assessment (p<0.01). Further, the CPT-II results for all three dimensions were significantly different between the two cohorts: omission errors (p=0.024); commission errors (p=0.007); and reaction time (0.016).

- This study did not assess source of fluoride exposure (e.g., consumption of foods high in fluoride or swallowing of toothpaste) contributing to total fluoride exposure. Therefore although the study showed an association with a biomarker of fluoride exposure it is not possible to attribute the fluoride exposure to any particular source.

- The authors used gamma regression for their analysis. While this choice is defensible, it would give greater confidence in the results if results for other regression models were used and gave similar results. This is particularly important given the marginal statistical significance of some of the associations found. A more detailed discussion of the analysis and the residuals would have been helpful.

- The curvilinear relationships found between fluoride and outcomes such as ‘cognitive problems and inattention’ are unusual. They depart from more common ‘dose-response’ relationships found in studies of environmental risk factors and are difficult to explain with respect to underlying mechanism. Although some adjustment for cohort was done during the analysis, the relationship reported in the study may reflect different relationships in the two cohorts.

- There was an attempt to adjust for maternal lead in this study, by measuring and adjusting for maternal bone lead levels of mothers where data were available. Bone lead is an excellent measure of long-term exposure to lead, but for a study such as this it would be preferable to have measured umbilical cord blood lead or maternal blood lead during pregnancy given that the interest is in circulating lead that would have the potential to cross the placenta and negatively affect neurological development in utero. Given the environmental levels of lead that would be present during the study period, and the well-established link between lead and neurological outcomes in children, there is potential for unmeasured confounding. The study also lacks data on other environmental exposures that could potentially confound the association between fluoride and cognitive performance; for example, persistent organic pollutants, iodine and arsenic. The potential for confounding from other environmental exposures is a serious limitation with respect to interpreting the associations found with maternal urinary fluoride.

- Only 6.5% of women had urinary fluoride level data from each trimester of pregnancy. The majority, 57%, had only one urine sample. This has potential for exposure misclassification. The MUF levels vary over pregnancy, increasing from trimester 1 to trimester 3. Combining MUF values from different trimesters has a potential to affect the validity of the exposure variable. A study by Malin et al., published on the same date as this study (October 10, 2018) and conducted in Canada, used three urine samples, from each trimester, for all study participants, which is a better way of assessing the exposure.
• Spot samples may reflect acute, rather than ongoing fluoride exposure. It is not clear if any sample with severely high values (outliers) were excluded from analysis or not.

• There is no mention if assessors or participants in the study were blinded to the outcome. If not, then there is a potential for confirmation bias.4

• Covariates:
  • The study did not take into consideration any paternal covariates, such as father’s mental health,5 education and smoking status.
  • Participants’ marital status or mental health status was assessed only during the first trimester of pregnancy. This information was not updated at the time of ADHD testing, as it can change over time, and existing literature suggests that mothers with depression5,6 or single parent can report higher ADHD scores for their children.
  • The HOME score, an important predictor of home environment, was administered only to a subset of participants and therefore was not included in the adjusted model but was only a part of the sensitivity analyses.
  • Secular trends also need to be taken into consideration. In the last decade or so reporting and treatment of ADHD is on the rise.7

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

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

Relevance
The effects found in this study were found at the population or group level; they would not be discernable in individuals, as such they do not appear to have clinical relevance.

This study has limitations and by itself does not establish a link between fluoride intake during pregnancy and subsequent ADHD in children. However, it does add to a growing body of research studies suggesting possible associations between relatively low levels of fluoride exposure and neurocognitive outcomes. Careful monitoring of future studies in this area is warranted.

As such, a number of studies in recent years have been conducted to assess the association between fluoridated water and adverse health effects, if any. Public Health Ontario (PHO) has recently contributed to the evidence in this regard by reviewing the relevant literature published from 2010 to May 2017, and synthesizing it in an evidence report.

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

References


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


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


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<tr>
<th>Bashash – Responses to criteria</th>
<th>Yes</th>
<th>No</th>
<th>Other (CD, NR, NA)*</th>
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<tr>
<td>1. Was the research question or objective in this paper clearly stated?</td>
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<td>2. Was the study population clearly specified and defined?</td>
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<td>3. Was the participation rate of eligible persons at least 50%?</td>
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<td>4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?</td>
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<td>Note: two cohorts from different time periods, cohorts not the same</td>
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<td>5. Was a sample size justification, power description, or variance and effect estimates provided?</td>
<td>X</td>
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<td>Note: they provide estimates of variance in the form of CI for their regression analysis</td>
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<td>6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?</td>
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<td>7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?</td>
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<td>8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?</td>
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<td>9. Were the exposure measures (independent variables) clearly defined,</td>
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Review of: *Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6–12 years of age in Mexico City* 10
valid, reliable, and implemented consistently across all study participants?

Note: did not use urine sample from all three trimesters (mean value of all 3 trimesters would be a more valid measure of exposure); it is understandable in surveys it’s difficult to get 24-hour sample of urine but spot sample used not the best way to measure

10. Was the exposure(s) assessed more than once over time?

Note: assessed at multiple time points in only a small portion of the pregnant women sample, and did not include as part of the model; ideal would have been collecting in all 3 trimesters and accounting for it and only a very small portion (6.5% of total sample/14 participants had data for all 3 trimesters) (57% provided a sample for trimester 1)

11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

X

12. Were the outcome assessors blinded to the exposure status of participants?

Note: participants were not blinded

X

13. Was loss to follow-up after baseline 20% or less?

Note: 234 complete data at 6-12 year assessment, out of total denominator 512 mother-child pairs

X

14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Note: should have accounted for additional confounders including other fluoride exposures including toothpaste, varnish, supplements, other toxins, blood lead levels (as opposed to bone lead levels which are more long-term exposure

X

Public Health Ontario acknowledges the financial support of the Ontario Government.
Review of “Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status”

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Request reviewed by: Ray Copes, MD, Chief, Environmental and Occupational Health, and Heather Manson, MD, Chief, Health Promotion, Chronic Disease and Injury Prevention
Date: 10/10/2018
Contact information: sonica.singhal@oahpp.ca

Key messages

- This article adds to knowledge about the relationship between thyroid stimulating hormone (TSH) levels, urinary iodine and urinary fluoride as found in a representative sample of Canadians from the Canadian Health Measures Survey (CHMS).

- This study, by Malin et al. specifically determined if urinary iodine status modifies the effect of fluoride exposure on thyroid stimulating hormone (TSH) levels among moderately to severely iodine deficient adults. Authors state that 1 mg/L increase in specific gravity adjusted urinary fluoride (UFSG) was associated with a 0.35 mIU/L increase in TSH (95% CI: 0.06, 0.64) among adults with iodine deficiency. These results are not clinically significant. The normal range for TSH, as given by the authors, is 0.55 – 4.78 mIU/L. An increase of 0.35 mIU/L in the average or 90th percentile would still be within the normal range.

- This study has some weaknesses in exposure assessment; for example, there is no information on other forms of fluoride exposure apart from water. Tap water fluoride concentrations for those in the study had a mean of 0.22 mg/L, the 10th percentile was 0.00 mg/L and the 90th percentile was 0.6 mg/L. Assessment of iodine exposure is not addressed.

- Single tailed p values were used for the interaction between urinary iodine and urinary fluoride. The use of 2 tail p-value is more justifiable. Additional studies that address these weaknesses would be helpful in clarifying interactions between iodine and fluoride on thyroid function.
Background

- Malin et al.’s article, based on Canadian data, was published online on October 10th 2018; the same day two other papers related to fluoride, one from Canada and one from Mexico were released. There were a number of media releases following these publications. Community water fluoridation has been a source of controversy in some communities. Health units have requested that Public Health Ontario provide a review of these studies to assist in addressing inquiries from the public, media and others.

Appraisal

Study Design

- This cross-sectional study used data from Cycle 3 (2012-2013) of the Canadian Health Measures Survey to assess whether the relationship between fluoride exposure and thyroid function is modified by iodine status among adults, age 18 and above. Fluoride and iodine levels were measured in urine samples. Thyroid gland functioning was assessed by serum levels of Thyroid Stimulating Hormone (TSH). (Reference range provided by the authors was 0.55 – 4.78 mIU/L.)

- The study population (2,671) was divided into two groups, one with moderate/severe iodine deficiency (urinary iodine levels ≤ 0.38 µmol/L) and the other without deficiency (urinary iodine levels > 0.38 and ≤ 2.37 µmol/L). Based on WHO criteria, authors appear to have grouped iodine more than adequate, adequate and mildly iodine deficient individuals together and contrasted them with those who have moderate and severe iodine deficiency. The authors excluded individuals who were iodine excess.

Main findings

- The mean TSH among all individuals in the study was 1.79 mIU/L, 10th percentile, 0.79 mIU/L; and 90th percentile, 2.87 mIU/L. Among iodine deficient adults, the mean TSH level was 1.66 mIU/L, the 10th percentile was 0.83 mIU/L and the 90th percentile, 2.41 mIU/L.

- The authors state that 1 mg/L increase in urinary fluoride corrected for specific gravity (UFSG)was associated with a 0.35 mIU/L increase in TSH (95% CI: 0.06, 0.64) among adults in the iodine deficiency group. No relationship was found between UFSG and TSH in adults in the non-iodine deficient group. These results do not seem to be clinically significant. The reference or normal range for TSH, as given by the authors, is 0.55 – 4.78 mIU/L. An increase of 0.35 mIU/L in the average or 90th percentile would still be within the normal range.

- Among adults in the iodine deficient group, mean urinary iodine was 0.25 µmol/L, the UFSG was 1.06 mg/L and tap water fluoride was 0.12 mg/L. Among adults in the non-iodine deficient...
group, mean urinary iodine was 0.99 µmol/L, the UFSG was 0.91 mg/L and tap water fluoride was 0.25 mg/L. It is evident that water is not the only source of fluoride exposure and iodine deficient adults might have been exposed to other sources of fluoride; however, information on other fluoride exposures, such as tooth paste, black tea, sea food, fluoride varnish, have not been collected or adjusted for. Sources of iodine exposure are not addressed. This is a major shortcoming as dietary sources including dairy products would be expected to be major contributors. Consumers of dairy products (e.g. milk) may consume less tap water and vice versa producing an inverse relationship between urinary fluoride and urinary iodine.

Strengths

- The first Canadian study to assess if urinary iodine status modifies the effect of fluoride exposure on thyroid functioning.
- The study sample of 2,671 from the Canadian Health Measures Survey was population based and representative of Canadian population.
- The study used biomarkers for measuring both the exposure and the effect: urinary fluoride; urinary iodine; and serum TSH.
- Urinary fluoride concentrations were adjusted for specific gravity to account for variations in urine dilution.
- The inclusion and exclusion criteria were applied uniformly to all study participants.

Limitations

- Fluoride exposures apart from tap water were not considered in the study. Sources of iodine exposure and their potential effect on fluoride exposure were not considered.
- According to WHO guidelines, the authors appear to have grouped participants with mild iodine deficiency with those having adequate and more than adequate iodine intakes. Those with excess iodine intakes were excluded from the study.
- The interaction between UF$_{5g}$ and urinary iodine was significant (p=0.03, one tailed). A two tailed test of significance for the interaction may be more appropriate. The p values are influenced by the choice of a two tailed vs one tailed test.
- In the overall analysis UF$_{5g}$ was not a predictor of TSH. The increase in TSH associated with UF$_{5g}$ was confined to the group defined as iodine deficient by the authors.
- While some of the findings attain statistical significance, none of the findings appear to be of clinical significance.

Review of: Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status
Reliability

- The authors are from Mount Sinai, New York; and York University, Toronto.
- The 2016 impact factor for the Environmental International was 7.08.
- Authors reported that they had no conflicts of interest.
- This research was supported by funds to the Canadian Research Data Centre Network (CRDCN) from the Social Sciences and Humanities Research Council (SSHRC), the Canadian Institutes of Health Research (CIHR), the Canadian Foundation for Innovation (CFI), and Statistics Canada.
- Reporting issues:
  - Iodine excess individuals were excluded from the study. According to WHO criteria, the authors appear to have grouped iodine more than adequate, adequate and mildly iodine deficient individuals together and contrasted them with those who have moderate and severe iodine deficiency.

Relevance

None of the associations reported in the study appear to be clinically significant.

Ontario Applicability

The study was based on Canadian data, including study participants who resided in Ontario.

References

1. World Health Organization, 2013, Urinary iodine concentrations for determining iodine status in populations
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Review of: Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status
Appendix A


<table>
<thead>
<tr>
<th>Malin - Responses to criteria</th>
<th>Yes</th>
<th>No</th>
<th>Other (CD, NR, NA)*</th>
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<tbody>
<tr>
<td>1. Was the research question or objective in this paper clearly stated?</td>
<td>X</td>
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<tr>
<td>2. Was the study population clearly specified and defined?</td>
<td>X</td>
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<tr>
<td>3. Was the participation rate of eligible persons at least 50%? (2950 of total surveyed were asked to provide sample, and 2671 provided sample = 90.5%)</td>
<td>X</td>
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<tr>
<td>4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?</td>
<td>X</td>
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<td>Note: is cross-sectional, all one time period, CHMS has strong methodology</td>
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<td>5. Was a sample size justification, power description, or variance and effect estimates provided?</td>
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<td>Note: variance estimates in the form of 95% CI; however, noted that they used a one-tailed t-test without rationale about why a one-tailed t-test was used as opposed to two-tailed t-test. This is particularly noteworthy since they did not use the one-tailed t-test for all of the estimates.</td>
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<td>6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?</td>
<td>X</td>
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<td>Note: cross-sectional</td>
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<tr>
<td>7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?</td>
<td>X</td>
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<tr>
<td>8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?</td>
<td>X</td>
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</tbody>
</table>

Review of: Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? X

10. Was the exposure(s) assessed more than once over time? X

11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? X

12. Were the outcome assessors blinded to the exposure status of participants? X – can’t tell, no description

13. Was loss to follow-up after baseline 20% or less? X – NA; cross-sectional

14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? X

Public Health Ontario acknowledges the financial support of the Ontario Government.

Review of: *Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status*
SYNOPSIS

Review of “Community water fluoridation and urinary fluoride concentrations in a national sample of pregnant women in Canada”

Requestor: Paul Sharma, OAPHD
Request prepared by: Elaina MacIntyre, PhD, Acting Manager, Toxicology and Exposure Assessment, Environmental and Occupational Health, and Sonica Singhal, BDS, PhD, Oral Health Scientist, Health Promotion, Chronic Disease and Injury Prevention
Request reviewed by: Ray Copes, MD, Chief, Environmental and Occupational Health, and Heather Manson, MD, Chief, Health Promotion, Chronic Disease and Injury Prevention
Date: 10/10/2018
Contact information: elaina.macintyre@oahpp.ca

Key messages

- This study describes the relationship between fluoride concentrations in drinking water and urinary fluoride concentrations in a cohort of Canadian women during pregnancy.

- Women who lived in communities that supplied fluoridated water had higher levels of urinary fluoride, as compared with women who lived in communities that did not fluoridate their drinking water. On average, there was a five-fold difference in water fluoride concentrations, and a two-fold difference in urinary fluoride concentrations, between fluoridated and non-fluoridated communities.

- The concentration of fluoride in drinking water explained 24-26% of the variation in maternal urinary fluoride concentrations (unadjusted R²). The substantial variation in maternal urinary fluoride concentrations, particularly among women who had the same concentration of drinking water fluoride, suggests that Canadian women are exposed to significant amounts of fluoride from sources other than drinking water, although drinking water is an important source for women who live in communities that add fluoride to drinking water and who consume tap water.
Background

- The article by Till et. al., published in Environmental Health Perspectives on October 10 2018, describes the relationship between fluoride concentrations in drinking water and urinary fluoride concentrations in a cohort of Canadian women during pregnancy.

- Data were collected through the national Maternal-Infant Research on Environmental Chemicals (MIREC) research project. The objective of this project is to “obtain national biomonitoring data on pregnant women and their infants and to examine potential adverse health effects of prenatal exposure to environmental chemicals on pregnancy and infant health”. *

- There is currently an emerging area of research on the topic of prenatal fluoride exposure and health outcomes in children. This article adds to our growing knowledge in this area by characterizing maternal urinary fluoride concentrations during pregnancy in a cohort of Canadian women.

Appraisal

Study Design

- During 2008-2011, the MIREC study recruited 2,001 women from prenatal clinics during their first trimester of pregnancy across 10 Canadian cities (Vancouver, Edmonton, Winnipeg, Toronto, Hamilton, Sudbury, Kingston, Ottawa, Montreal, and Halifax). The following inclusion criteria were used at study entry: ability to communicate in English/French, over the age of 18 years, less than 14 weeks gestation (ie. first trimester). Women were excluded if they used alcohol or drugs during pregnancy, had medical complications, or there was a known fetal abnormality.

- Spot urine samples were taken once during each trimester of pregnancy and stored under appropriate environmental conditions. Urine samples were analyzed for fluoride at the Indiana University School of Dentistry. The limit of detection was 0.02 mg/L. Maternal urinary fluoride (MUF) concentrations were adjusted to account for urine dilution using two methods: urinary creatinine and specific gravity. Two study participants were excluded because of unusually high urine fluoride that may have reflected recent dental treatment rather than long term exposure. There were 1,566 women with urine spot samples for each trimester of pregnancy.

- Reports from municipal drinking water systems were used to estimate fluoride concentrations in tap water. Drinking water data were linked to the residence of mothers during the first trimester of pregnancy, based on forward sortation area (the first 3 digits of the residential postal code). Fluoride concentrations measured at the drinking water treatment plant were used to calculate

* For more information please see: http://www.mirec-canada.ca/en/about/study-overview/
an average concentration over 9 months using the 3 quarterly results that most closely mirrored the duration of pregnancy. If a city had more than one drinking water treatment plant with a common distribution system then an average was calculated across the multiple treatment plants for each forward sortation area. Fluoride intake from drinking water and tea consumption was estimated using survey questions. Women who did not drink tap water were excluded. There were 1,359 women with drinking water fluoride concentration data.

- The analyses of drinking water and MUF included 1,135 women (672 in cities with community-wide fluoridation (CWF) and 463 in cities without CWF).

- This study had two research questions:
  1. Are maternal urinary fluoride concentrations during pregnancy associated with socio-demographic factors, tea consumption habits, and/or water fluoride concentrations?
  2. How do different methods that adjust for urinary dilution affect the within-person reliability of MUF concentrations, and the relationship of MUF concentrations to water fluoride concentration?

**Main findings**

- For the seven Canadian cities that fluoridate their drinking water, fluoride concentrations ranged from 0.41-0.87 mg/L, as measured by municipal drinking water system operators (mean 0.61 mg/L; standard deviation (SD) 0.11 mg/L). This is significantly different from the range of 0.04-0.20 mg/L that was measured in drinking water systems that do not add fluoride (mean 0.12 mg/L; SD 0.06 mg/L) (table 2).

- Fluoride concentrations in drinking water were approximately five times higher in fluoridated versus non-fluoridated communities (mean 0.61 mg/L versus mean 0.12 mg/L); while MUF concentrations were almost two times higher in fluoridated versus non-fluoridated communities (mean 0.71 mg/L versus mean 0.41 mg/L) (table 2). The authors concluded that a 0.5 mg/L increase in drinking water fluoride concentration [the difference between fluoridated and non-fluoridated drinking water] would result in a 73-82% increase in MUF.

- Using linear regression, the concentration of fluoride in drinking water explained 24-26% of the variation in MUF concentrations (unadjusted R²). After adjustment for available covariates, fluoride concentration in drinking water was positively associated with specific gravity-adjusted MUF (B=0.48, 95%CI:0.43,0.53) and explained 22% of the variation in MUF concentrations (table 4).

- There was considerable variation in MUF among women who had the same concentration of drinking water fluoride (figure 3 & table 2). For example, the range of MUF concentrations adjusted using specific gravity for women living in fluoridated communities was 0.10-3.12 mg/L (mean 0.71 mg/L; standard deviation 0.38 mg/L) while the range for women living in non-fluoridated communities was 0.08-2.78 mg/L (mean 0.41 mg/L; standard deviation 0.28 mg/L).
This suggests that Canadian women are exposed to significant amounts of fluoride from sources other than drinking water.

**Strengths**

- To date, this is the largest and most relevant study to characterize maternal urinary fluoride during pregnancy. This is a life stage where a developing fetus may be at increased susceptibility to environmental factors, and where we generally have very little data. The study included 1,566 pregnant women in the analyses of urinary fluoride and 1,135 pregnant women in the analyses of fluoride in drinking water (672 women in CWF; 463 women in non-CWF).

- The study collected urine spot samples at three time points during pregnancy, one for each trimester. This allowed the authors to examine trends in urinary fluoride concentrations throughout pregnancy. Their finding of increased fluoride concentrations in urine as pregnancy progressed is consistent with prior research.

- The study used two approaches to adjust for dilution in urine samples: specific gravity and creatinine. Although the use of multiple measures for exposure can sometimes be a concern due to the potential of multiple testing, in this study the approach was warranted given that there is no established standard to adjust for urinary dilution when measuring urinary fluoride. The study findings add to our understanding in this area and the high correlation that the authors found between adjustment methods (r=0.91, p<0.001) may help inform future research in this area.

- The study adjusted for women’s age, pre-pregnancy BMI, education, income level, water and tea consumption.

**Limitations**

- Although this is a large Canadian study, the population is not representative of pregnant women in the general population. The study population was entirely urban and tended to be Caucasian (86%), Canadian born (81%), married/common-law (96%), college/university educated (85%), and employed (86%).

- Urinary fluoride is a good measure of fluoride intake, but the sampling method should be chosen carefully due to the half-life of fluoride in urine (approximately 5-9 hours). The spot samples that were used to collect urine during each trimester of pregnancy may have been influenced by diurnal variation in MUF.

- Fluoride concentrations in drinking water were not measured at the home (ie. point of use). This raises the potential of misclassification because it is possible that fluoride concentrations at the drinking water treatment centre were different from those at the study participant’s home. Lack of adjustment for residential mobility during pregnancy (estimated at 11% of the study population) may have also contributed to misclassification.
• The authors calculated intraclass correlation coefficients (ICCs) as a measure of reliability for their MUF measures. The ICCs ranged between 0.37-0.40 and were presented at ‘modest’ in the paper, but there is some debate about the interpretation of ICCs in the literature and a previous study concluded that ICC values less than 0.50 should be considered poor.¹

• Finally, exposure to other sources of fluoride used to prevent tooth decay were not assessed. The most important is use of fluoridated tooth paste (the concentration of fluoride in tooth paste, amount of usage, and the frequency of tooth brushing). Other potential sources of exposure not addressed in the study include consumption of food grown using fluoridated water, beverages manufactured using fluoridated water, and seafood (e.g., shrimp, crab, shell fish). A more comprehensive assessment of fluoride exposure would likely have produced models with greater predictive value.

Reliability

• The authors of this paper are based at numerous reputable organizations through Canada and the United States. No author declared competing financial interests.

• MIREC is a longitudinal birth cohort study that receives funding through Health Canada under Canada’s Chemical Management Plan, the Canadian Institutes for Health Research, and the Ontario Ministry of the Environment.

• Environmental Health Perspectives (EHP) is an open access journal published with support from the U.S. National Institute of Environmental Health Sciences. Based on the 2018 Journal Citation Reports, EHP currently has an impact factor of 8.31 and ranks 5th among public, environmental and occupational health journals.

Relevance

This is the first Canadian cohort study to assess the relationship between drinking water fluoride concentrations and maternal urinary fluoride concentrations during pregnancy.

Ontario Applicability

Participants of the MIREC study lived in one of ten Canadian cities, and five of these cities were in Ontario (Kingston, Toronto, Hamilton, Ottawa, Sudbury). Results from this study will be useful when assessing the generalizability (or external validity) of future research examining the potential association between prenatal fluoride exposure and health outcomes in children.

References

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Appendix A


<table>
<thead>
<tr>
<th>Till et. al. (2018) – Responses to criteria</th>
<th>Yes</th>
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</thead>
<tbody>
<tr>
<td>1. Was the research question or objective in this paper clearly stated?</td>
<td>X</td>
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<td>X</td>
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<td>3. Was the participation rate of eligible persons at least 50%?</td>
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<tr>
<td>Note: 1,566 of 2,001 study participants from MIREC = 78%</td>
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<tr>
<td>4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?</td>
<td>X</td>
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<tr>
<td>5. Was a sample size justification, power description, or variance and effect estimates provided?</td>
<td>X</td>
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<tr>
<td>Note: 95% confidence intervals were provided</td>
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<tr>
<td>6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?</td>
<td>X</td>
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<tr>
<td>Note: Concentrations of fluoride in water were assessed retrospectively</td>
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<td>7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?</td>
<td>X</td>
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<tr>
<td>10. Was the exposure(s) assessed more than once over time?</td>
<td>X</td>
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</tbody>
</table>
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?  

12. Were the outcome assessors blinded to the exposure status of participants?  
   **Note:** Researchers would have known the fluoridation status (CWF or non-CWF) for each participant by their city of residence

13. Was loss to follow-up after baseline 20% or less?

14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?  
   **Note:** Fluoride sources other than drinking water and tea were not measured.

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