CADTH

CADTH TECHNOLOGY REVIEW

Community Water Fluoridation Programs: A Health Technology Assessment — Review of Dental Caries and Other Health Outcomes

PROSPERO Registration Number: CRD42017080057

Service Line: CADTH Technology Review
Issue: 12
Publication Date: February 2019
Report Length: 478 Pages

Cite as: Community Water Fluoridation Programs: A Health Technology Assessment — Review of Dental Caires and Other Health Outcomes. Ottawa: CADTH; 2019 Feb. (CADTH technology review; no. 12).

ISSN: 2369-7385

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Contact **requests@cadth.ca** with inquiries about this notice or legal matters relating to CADTH services.

Table of Contents

Tables

Abbreviations

AI	adequate intake
ANOVA	analysis of variance
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
CWF	community water fluoridation
DBP	diastolic blood pressure
defs	decayed, extracted, and filled deciduous tooth surfaces
deft	decayed, extracted, and filled deciduous teeth
DEFT	decayed, extracted, and filled permanent teeth
dfs	decayed and filled deciduous tooth surfaces
DFS	decayed and filled permanent tooth surfaces
dft	decayed and filled deciduous teeth
dmfs	decayed, missing, and filled deciduous tooth surfaces
DMFS	decayed, missing, and filled permanent tooth surfaces
dmft	decayed, missing, and filled deciduous teeth
DMFT	decayed, missing, and filled permanent teeth
GP	general practitioner
HTA	health technology assessment
IMD	index of multiple deprivation
IQ	intelligence quotient
IRR	incidence rate ratio
LAFW	lifetime access to fluoridated water
MAC	maximum acceptable concentration
MD	mean difference
MR	mean ratio
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NOF	naturally occurring fluoride
NS	not significant
OR	odds ratio
PHE	Public Health England
ppm	parts per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QA	quality assessment
RCT	randomized controlled trial
SBP	systolic blood pressure
SE	standard error
SES	socio-economic status
SR	systematic review
TSH	thyroid-stimulating hormone
T3	total triiodothyronine
T4	total thyroxine
UL	upper limit

Protocol Amendments

Amendment	Page
In the research questions 1, 2, and 3, the terms “non-fluoridated drinking water (fluoride level < 0.4 ppm)” or “non-fluoridated communities (fluoride level < 0.4 ppm)” has been changed to “low community water fluoride level of < 0.4 ppm.” The change was made in response to a stakeholder’s feedback.	12
In Table 1, study design, the following edits and additions were made for the purpose of clarity. • Primary studies of any design included within the NHMRC 2016 and McLaren 2016 reviews, in addition to those published after the latest search date of each review, including randomized controlled trials or comparative observational studies including concurrent or historical cohort studies, case-control studies, interrupted time series, cross-sectional studies, ecological studies, and before-and-after studies. • For Question 1: To be eligible, studies must have conducted multivariable analysis to control for confounding variables. • For questions 2 and 3: Primary studies of any design were eligible, whether confounding was controlled for or not.	16
Details on the assessment of the body of evidence were added after protocol publication. Evidence by outcome was evaluated based on the number of studies addressing each outcome, the quality of those studies, and the applicability of those studies’ findings to the Canadian context.	18

NHMRC = National Health and Medical Research Council; ppm = parts per million.

Introduction

Dental caries is a common public health problem in Canada,[1] and it affects about 57% of children aged six to 11 years and 59% of adolescents aged 12 to 18 years.[2] It has been estimated that the prevalence of coronal caries and the prevalence of root caries for Canadian adults aged 19 years and older is 96% and 20.3%, respectively.[2] Dental caries can result in pain, infection, premature tooth loss, and misaligned teeth.[3] Untreated dental caries in children are associated with poor overall growth, iron deficiency, behaviour problems, low self-esteem, and a reduction in school attendance and performance.[4-9] In pregnant women, periodontal diseases are risk factors for preterm low birth weight.[10,11] By adulthood, about 96% of Canadians have experienced dental caries.[2] In 2018, the cost of dental services was estimated to be approximately $17 billion in Canada, about $461 per Canadian, based on total national health expenditure estimated from both the private sector ($15.2 billion) and public sector ($1.8 billion).[12] Poor oral health is experienced by Canadians who cannot access regular dental care, including lower income families with no insurance, seniors in long-term care, new immigrants, and Indigenous peoples.[2,13]

Fluoride is a negative ion (F^-) of the element fluorine (F_2).[14] The term fluoride also refers to compounds containing F^-, such as sodium fluoride (NaF), calcium fluoride (CaF_2), fluorosilicic acid (H_2SiF_6), or sodium fluorosilicate (Na_2SiF_6).[14] In water, these compounds dissociate to release F^-.[14] Fluoride compounds exist in soil, air, plants, animals, and water.[15] Epidemiological studies in the 1930s and 1940s found that people living in areas with high naturally occurring fluoride levels in water had lower incidence of dental caries (i.e., cavities and tooth decay), a chronic and progressive disease of the mineralized and soft tissue of the teeth. This finding led to the controlled addition of fluoride to community drinking water with low fluoride levels in order to prevent dental caries.[16,17] In 1945, Brantford, Ontario, was the first city in Canada and the third city in the world to implement drinking water fluoridation.[18,19]

Fluoride helps to prevent dental caries both systemically (pre-eruptive or before the teeth emerge) and topically (post-eruptive or on the tooth surface).[20,21] The systemic effect occurs through the incorporation of ingested fluoride into enamel during tooth formation, which strengthens the teeth, making them more resistant to decay.[21-23] The major sources of systemic fluoride are fluoridated water and foods and beverages prepared in areas with fluoridated water.[24,25] Fluoride from other sources such as toothpaste, mouth rinses, gels, varnishes, or foams provides a topical effect (unless swallowed) through direct contact with exposed tooth surface; this increases tooth resistance to decay against bacterial acid attack by inhibiting tooth de-mineralization, facilitating tooth remineralization, and inhibiting the activity of bacteria in plaque.[26] As well, after being absorbed systemically, a small portion of fluoride is excreted into the saliva where it provides a topical effect from the continuous bathing of saliva over the teeth.[27] Evidence has suggested that CWF is associated with a decrease in dental caries, a decline in numbers of hospital attendances for general anesthesia and tooth extractions, and a reduction in the cost of dental treatment in children.[28-34]

Daily intake levels of fluoride in humans vary depending on many factors, these include sources of fluoride (water, foods or beverages, or dental products), levels of fluoride in water or foods, the amount of water or food consumed, and individual characteristics and habits.[14] About 75% to 90% of ingested fluoride is absorbed through the gastrointestinal tract, and up to 75% of the absorbed fluoride is deposited in calcified tissues (such as bones and teeth) in the form of fluorapatite within 24 hours.[35,36] The rest is excreted primarily in the urine, with small amounts excreted in perspiration, saliva, breast milk, and feces.[35,36] In 2007, a dietary survey of the Canadian population estimated that the average intake of fluoride in children aged one to four years old in fluoridated and non-fluoridated communities was 0.026 mg/kg/day and 0.016 mg/kg/day, respectively.[14] The average dietary intake of fluoride in adults 20 years and older ranged from 0.038 mg/kg/day to 0.048 mg/kg/day in fluoridated communities, and ranged from 0.024 mg/kg/day to 0.033 mg/kg/day in non-fluoridated communities.[14] Based on the average daily dietary fluoride intakes in fluoridated areas (i.e., 0.7 to 1.1 ppm) in Canada and US, the recommended adequate intake (AI) of fluoride from all sources that is sufficient to prevent dental caries is 0.05 mg/kg/day, irrespective of age groups, sex, and pregnancy status.[37,38] The tolerable upper limit (UL) value for infants through children aged eight years is 0.10 mg/kg/day.[37] The UL for children older than eight years and for adults including pregnant women is 10 mg/day.[37]

According to the 2010 Health Canada *Guidelines for Drinking Water Quality*, the maximum acceptable concentration (MAC) of fluoride in drinking water is 1.5 ppm (parts per million or mg/L), while the optimal level of fluoride in drinking water is recommended to be 0.7 ppm (reduced from the previous range of 0.8 ppm to 1.0 ppm) for providing optimal dental health benefits and minimizing dental fluorosis.[15] MAC was determined with moderate dental fluorosis as the end point of concern.[15] Thus, community water fluoridation (CWF) in Canada is the process of controlling fluoride levels (by adding or removing fluoride) in the public water supply to reach the recommended optimal level of 0.7 ppm and to not exceed the maximum acceptable concentration of 1.5 ppm.[15] Most sources of drinking water in Canada have low levels of naturally occurring fluoride.[15] According to a Canadian survey conducted between 1984 and 1989, the average, provincial, naturally occurring fluoride levels in drinking water ranged from less than 0.05 ppm in British Columbia and Prince Edward Island, to 0.21 ppm in Yukon.[15] The provincial and territorial data on drinking water in 2005 provided by the Federal-Provincial-Territorial Committee on Drinking Water showed that the average fluoride concentrations in fluoridated drinking water across Canada ranged between 0.46 ppm and 1.1 ppm.[15] As of 2017, about 38.7% of Canadians were exposed to CWF for the protection of dental caries.[39] The decision to fluoridate drinking water is not regulated at the federal, provincial, or territorial levels, but rather the decision is made at the municipal level and is often taken by means of a community vote (i.e., by referendum or plebiscite).[14]

While public and dental health agencies and organizations, and about 60% of Canadians, view CWF as an effective and equitable means of improving and protecting the dental health of populations, there continues to be opposition, resistance, and skepticism about CWF, especially in terms of human and environmental health.[40-42] There are a variety of different perspectives on CWF, some of which centre on the scientific evidence of dental benefit,[42,43] while others include the availability of alternative oral public health programs or interventions that avoid perceived concerns of CWF.[43,44] Alternative publicly funded oral public health programs, such as school-based topical fluoride varnishes, though available, are not consistent across Canadian jurisdictions.[45-47] Importantly, the available programs are not universal in nature and mainly target high-risk populations.[45,46] Furthermore, public health programming is often targeted toward youth, excluding the adult and elderly populations. CWF, in contrast, is an intervention that reaches a broader population, so long as persons drink from municipal water supplies. Still, others cite potentially harmful side effects of fluoridation, for example, fluorosis, thyroid function, lowered average intelligence quotient (IQ) in populations, and negative environmental impact[14,48] as motivation for water fluoridation cessation. Additional concerns include possible relationships between industry and fluoridation.[14,48] Finally, an unsettled tension exists around the ethics of CWF in terms of distribution of benefits to all persons who consume fluoridated tap water, removing (or making very difficult) the ability to “choose” fluoridation.[43,49-51]

It is within this context that some municipalities are choosing to cease water fluoridation, leading to its decline.[39] Notably, large Canadian cities such as Calgary, Quebec City, Windsor, Moncton, and Saint John have discontinued their water fluoridation programs in recent years.[52-54] Other municipalities have also discontinued CWF across provinces and territories since 2012.[39] Although the total percentage of Canadians with access to CWF has increased from 2012 (37.4%) to 2017 (38.7%), some provinces and territories have shown a significant decline in fluoridated water system coverage.[39] As of 2017, the provinces and territories with the fewest municipalities with CWF systems include British Columbia, Quebec, New Brunswick, Newfoundland and Labrador, and Yukon.[39] The impact of the CWF cessation on dental health is unclear.

A request has been submitted to CADTH for a health technology assessment (HTA) that would comprehensively review the multi-disciplinary evidence related to CWF. The review is not intended to be a comprehensive assessment of all interventions for caries prevention. In contrast to other public health programs (such as school programs) water fluoridation, where available, has the potential to reach a broader population. Other alternatives, such as fluoridated milk or fluoridated salt, are not available in Canada. The HTA focuses exclusively on CWF and does not examine the effectiveness of other sources of fluoride, including fluoridated dental products, fluoridated salts, and fluoride supplements. Furthermore, we do not compare the effectiveness of CWF with these other sources of fluoride.

Policy Question

This HTA is intended to provide guidance to policy- and decision-makers at the municipal levels to help orient discussions and decisions about water fluoridation in Canada. This HTA seeks to address the following policy question: Should community water fluoridation be encouraged and maintained in Canada? The analytic framework informing this Health Technology Assessment (HTA) is presented in Appendix 1.

Objectives

The aim of this HTA is to inform the policy question through an assessment of the effectiveness and safety,[55] economic considerations,[56] implementation issues,[57] environmental impact,[58] and ethical considerations[59] for CWF. An analysis of the evidence related to these considerations comprises different chapters of the HTA, each with specific and different research questions and methodologies. The following report presents the Review of Dental Caries and Other Health Outcomes. Other sections have been published separately.

Research Questions

The HTA addressed the following research questions:

Review of Dental Caries and Other Health Outcomes

1. What is the effectiveness of community water fluoridation (fluoride level between 0.4 ppm and 1.5 ppm) compared with non-fluoridated drinking water (fluoride level < 0.4 ppm) in the prevention of dental caries in children and adults?
2. What are the effects of community water fluoridation cessation (fluoride level < 0.4 ppm) on dental caries in children and adults compared with continued community water fluoridation (fluoride level between 0.4 ppm and 1.5 ppm), the period before

cessation of water fluoridation (fluoride level between 0.4 ppm and 1.5 ppm), or non-fluoridated communities (fluoride level < 0.4 ppm)?

3. What are the negative effects of community water fluoridation (at a given fluoride level) compared with non-fluoridated drinking water (fluoride level < 0.4 ppm) or fluoridation at different levels on human health outcomes?

Economic Analysis

4. From a societal perspective, what is the budget impact of introducing water fluoridation in a Canadian municipality without an existing community water fluoridation program?
5. From a societal perspective, what is the budget impact of ceasing water fluoridation in a Canadian municipality that currently has a community water fluoridation program?

Implementation Issues

6. What are the main challenges, considerations, and enablers related to implementing or maintaining community water fluoridation programs in Canada?
7. What are the main challenges, considerations, and enablers related to the cessation of community water fluoridation programs in Canada?

Environmental Assessment

8. What are the potential environmental (toxicological) risks associated with community water fluoridation?

Ethical Considerations

9. What are the major ethical issues raised by the implementation of community water fluoridation?
10. What are the major ethical issues raised by the cessation of community water fluoridation?
11. What are the major ethical issues raised by the legal, social, and cultural considerations to consider for implementation and cessation?

This review of dental caries and other health outcomes addressed research questions 1 to 3.

A detailed protocol was prepared, a priori; reviewed by stakeholders external to CADTH; and registered with the PROSPERO database (CRD42017080057). All amendments are detailed in the Amendments Table at the beginning of this report.

Review of Dental Caries and Other Health Outcomes

Review Design

To reduce redundancy in research and leverage existing published research, updates to two previously published systematic reviews (SRs)[52,60] identified through our initial systematic scoping were conducted. While other related reviews had been published in the past decades,[61-66] in accordance with recent guidance documents, these two reviews were identified as the most recent, comprehensive, and relevant to our policy and research questions.[67] Further, their methodological quality was considered sufficient to warrant an update as compared with a de novo review (e.g., high confidence in review findings based on an assessment using AMSTAR2),[68] and details of methods and results were reported transparently and comprehensively as to facilitate the updating process. Both the review by Jack et al.[60] and the review by McLaren and Singhal[52] satisfied 13 of 16 items of the AMSTAR 2 checklist[68] (Appendix 2).

To address the research questions related to the effects of CWF (questions 1 and 3), an update of the 2016 Australian National Health and Medical Research Council (NHMRC) review by Jack et al.[60] was conducted. To address the research question related to the impacts of CWF cessation on dental caries (Question 2), the 2016 SR by McLaren and Singhal was updated.[52]

The NHMRC review process included two main parts. The first part of the review, an evaluation of the dental effects of water fluoridation, consisted of an overview of reviews and an SR of primary studies on the effects of water fluoridation on dental caries, and a critical appraisal of the evidence on the role of water fluoridation in the development of dental fluorosis included in a 2015 Cochrane review.[62] The second part of the review consisted of an SR of other (non-dental) health effects of water fluoridation. The 2016 NHMRC review was an update of a 2007 NHMRC review, which included publications from 1996 onward.[61] The time frame for the literature search strategy of the 2016 NHMRC review for dental caries (Question 1) was between October 1, 2006, and November 12, 2015, and for other health outcomes of water fluoridation (Question 3) was between October 1, 2006, and October 14, 2014.

McLaren and Singhal conducted an SR of primary studies that explored the impact of CWF cessation on measures of caries prevalence and severity.[52] The search period of the SR by McLaren and Singhal 2016[52] was from inception of databases to September 29, 2014.

Therefore, to update both reviews, a search for eligible primary studies was conducted from January 1, 2014 to December 2018, during which only new studies, which were not included in the reviews by Jack et al.[60] and MacLaren and Singhal,[52] were examined. Appendix 3 presents flow diagrams of sources of evidence with literature search timeframes of each SR.

Methods

Standardized Reporting

The report of findings related to impacts and effects was prepared in consideration of relevant reporting guidelines for SRs (i.e., Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]).[69]

Literature Search Strategy

The literature search was performed by an information specialist, using a peer-reviewed search strategy. The search strategy is presented in Appendix 4.

Published literature was identified by searching a relevant selection of CADTH subscription databases: MEDLINE (1946–) with in-process records and daily updates, Embase (1974–), the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Cochrane Methodology Register, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database via Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO, PubMed, and Scopus. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords.

The search strategies developed for the NHMRC 2016 review[60] relevant to research questions 1 and 3, and the search strategy developed for the SR by McLaren and Singhal 2016[52] relevant to Question 2, were merged and restructured, and additional subject headings and keywords were incorporated to produce a single broad search strategy. This single strategy was used to identify literature relevant to all three research questions. The main search concepts were fluoridation and fluoride in water. To keep the search broad, search concepts for dental caries, cessation, and health outcomes were not integrated into the search strategy. While the original searches for NHMRC 2016[60] and McLaren and Singhal 2016[52] included multiple databases; the databases used for the search in this update review were limited to those recommended in the Cochrane Handbook[70] and supplemented with other databases to which CADTH has access.

Retrieval was limited to documents added to the databases beginning in January 1, 2014, to capture studies after the literature searches for NHMRC 2016[60] and McLaren and Singhal 2016[52] had been conducted. Conference abstracts were excluded from the search results. No methodological filters or language limits were applied.

Regular alerts were established to update the searches until the publication of the final report. Regular search updates were performed on databases that did not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review were incorporated into the analysis if they were identified prior to the completion of the stakeholder feedback period of the final report. Any studies that were identified after the stakeholder feedback period were described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, economics-related resources, public perspective groups, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials.

These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Study Eligibility

Eligibility criteria for inclusion of studies in this report are outlined in Table 1.

Table 1: Selection Criteria for Review of Dental Caries and Other Health Outcomes

Population	Human populations of any age Subgroups: • Age (e.g., 0 years to 9 years, 10 years to 17 years, 18 years and older, and seniors [≥ 65 years])[a] • Geographic location (e.g., remote, rural, and urban)[a] Socio-economic status (e.g., high, mid, and low in terms of education or household income)[a]
Intervention or Exposure	Q1: Natural or added water fluoridation (fluoride level 0.4 ppm to 1.5 ppm)[b] Q2: Cessation of water fluoridation (fluoride level < 0.4 ppm) Q3: Water fluoridation at any level[c]
Comparator	Q1: Low fluoride level of < 0.4 ppm Q2: Continued water fluoridation (fluoride level 0.4 ppm to 1.5 ppm), before cessation of water fluoridation, or low community fluoride level of < 0.4 ppm Q3: Low water fluoride level of < 0.4 ppm, or different fluoride levels in drinking water
Outcomes	**Review of dental caries (Q1 and Q2):** Any measure of dental outcomes including but not limited to: • mean dmft/s or DMFT/S • mean dfs or DFS • caries prevalence (%dmft/s > 0 or %DMFT/S > 0) • proportion of caries-free (%dmft/s = 0 or %DMFT/S = 0) • hospital admissions for caries-related dental surgery under general anesthesia. **Review of other health outcomes (Q3):** Any measure of adverse health outcomes associated with water fluoridation, including but not limited to: • dental fluorosis • skeletal fluorosis • bone development and bone fracture • thyroid function • cancer • neurodevelopment • mortality • others.
Time Frame	January 1, 2014, to December 2018
Study Designs	• Primary studies of any design included within the NHMRC 2016 and McLaren 2016 reviews, in addition to those published after the latest search date of each review, including randomized controlled trials or comparative observational studies, including concurrent or historical cohort studies, case-control studies, interrupted time series, cross-sectional studies, ecological studies, and before-and-after studies. • For Question 1: To be eligible, studies must have conducted multivariable analysis to control for confounding variables. • For questions 2 and 3: Primary studies of any design were eligible, whether confounding was controlled for or not.

dfs = decayed and filled deciduous tooth surfaces; DFS = decayed and filled permanent tooth surfaces; dmfs = decayed, missing, and filled deciduous tooth surfaces; DMFS = decayed, missing, and filled permanent tooth surfaces; DMFT = decayed, missing, and filled permanent teeth; dmft = decayed, missing, and filled deciduous teeth; NHMRC = National Health and Medical Research Council; ppm = parts per million.

[a] As defined by the included studies.

[b] The average of fluoride concentrations in the fluoridated drinking water across Canada ranged between 0.46 ppm and 1.1 ppm. The fluoride level of 0.4 ppm is chosen to mark the cut-off between non-fluoridated and fluoridated water. This level is in line with that set in the NHMRC 2016 review and other previous systematic reviews.

[c] Fluoride at any level was applied for the intervention of Question 3 with the intention to capture all adverse health outcomes potentially associated with water fluoridation.

Full-text published or unpublished studies in English or French that met the criteria outlined in Table 1 were included. Conference abstracts, duplicates publications of the same study, narrative reviews, letters, editorials, laboratory studies, and technical reports were excluded.

For questions related to the effectiveness of CWF and the impact of CWF cessation on dental caries (i.e., questions 1 and 2), studies were excluded if they assessed the impact of a fluoride levels in the community drinking water of greater than 1.5 ppm, based on Health Canada guidance on the maximum acceptable level in drinking water;[15] or if the effects of fluoride originated from sources other than drinking water, such as supplements, toothpaste, mouth rinse, salt, milk, diet, soil, air, etc. Participants of any age, in any jurisdiction, who resided in a fluoridated or non-fluoridated community, in conjunction with or without the use of other sources of fluorides (e.g., fluoridated toothpaste) were included. In addition to participants' age, there was no limit regarding geographic location, socio-economic status (SES), and ethnicity.

For the question related to the effectiveness of CWF for the prevention of dental caries (Question 1), a water fluoridated community (added fluoride or naturally fluoridated) was compared with a low community fluoride level of < 0.4 ppm or with the same community before the introduction of water fluoridation. In addition, studies were also included if they compared participants' percentage exposures to CWF; for instance, a study was considered when comparing 100% (or any percentage) life time exposure with 0% (or any percentage lower than 100%) lifetime exposure to water fluoridation. The effect of CWF was not compared with other fluoridated products, as they were considered confounding variables. Other confounding variables of interest included oral health habits (i.e., toothbrushing, flossing, mouthwash, etc.), diet, SES, and the presence of other public health programming. As in the exclusion criteria of the NHMRC 2016 review,[60] studies that did not conduct multivariable analysis to control for confounding variables were excluded. Given the widespread use and availability of fluoridated toothpaste in both fluoridated and non-fluoridated communities, the effect of water fluoridation was considered to be above and beyond the effect of fluoridated toothpaste. In addition to the confounding variables previously listed, the presence of other public health interventions, such as school-based varnish programs, was also taken into consideration.

For the question related to the impacts of CWF cessation on dental caries (Question 2), a community where water fluoridation had been discontinued was compared with a continually fluoridated community, a community with low fluoride level of < 0.4 ppm, or the same community at a period before cessation of water fluoridation.

For the question related to the effects of fluoridated water on dental fluorosis and human health outcomes other than dental caries (Question 3), a community where people were exposed to any level of fluoride in drinking water was compared with a community with a fluoride level of < 0.4 ppm or a community of different concentrations of fluoride in drinking water.

Due to limited evidence for the impacts of CWF cessation on dental caries (Question 2) and other health outcomes (Question 3), studies were included whether or not confounding variables were controlled for. Also, in Question 3, the level of fluoride in water was open to any level of comparison in order to capture evidence of all potential health outcomes that may be associated with high fluoride levels.

For outcomes, any measure of dental caries and adverse health outcomes as a result of fluoridated water exposure or non-exposure was considered. For the purpose of updating the evidence in the literature, comparative primary studies of any study design were considered.

Study Selection

Two reviewers independently screened titles and abstracts of all citations retrieved from the literature search relevant to research questions 1 to 3, followed by an independent review of the full-text of potentially relevant articles, based on the pre-determined selection criteria outlined in Table 1. The two reviewers then compared their included and excluded studies from their full-text review and resolved any disagreements through discussion until consensus was reached.

Data Extraction

Data extraction for included studies was conducted using standardized data abstraction forms similar to those in the NHMRC 2016 report,[60] which were customized for each research question. The forms were presented in the CADTH protocol.[71]

Two reviewers piloted the data extraction form on the same three randomly selected studies. Following calibration, data from each included study were extracted by one reviewer and verified by the second reviewer. Disagreements were resolved through discussion until consensus was reached.

Quality Assessment of Included Studies

For all newly identified eligible studies included in this update, two National Institute for Health and Care Excellence (NICE) checklists, which were designed for public health intervention studies, were used to assess study quality.[72] One NICE checklist was used to assess the quality of quantitative intervention studies, such as randomized controlled trials, case-control studies, cohort studies, controlled before-and-after studies, and interrupted time series.[72] The other NICE checklist was used to assess the quality of quantitative studies reporting correlations and associations, such as cross-sectional studies and ecological studies.[72] The quality assessment (QA) checklists for primary studies were presented in the CADTH protocol.[71] The quality of all studies included in the NHMRC and McLaren 2016 reviews are reported as assessed by the authors of those reviews.

Two reviewers piloted the assessment of the study quality, in duplicate, on three randomly selected studies. Following the calibration, the quality of the remaining studies was independently assessed. Disagreements between reviewers regarding QA were resolved through discussion and consensus.

Assessment of the Body of Evidence

Evidence by outcome was evaluated based on the number of studies addressing each outcome and the applicability of those studies' findings to the Canadian context.

The findings of each study from both the updated review and CADTH review were assessed and categorized as high, partial, or limited applicability to the Canadian context based on the comparison of water fluoride level and socio-economic parameters. Applicability was defined as follows:

- High: Studies conducted in Canada.
- Partial: Studies conducted in countries, other than Canada, having community water fluoride levels similar to the current Canadian levels, and with comparable socio-

  economic parameters and health care system. Many developed countries in the Western region with similar fluoride levels in the water compared with Canada were considered to be partially applicable to the Canadian context.
- Limited: Studies not in the first two categories.

The assessments were made by one reviewer during the data extraction phase and were checked by a second reviewer; disagreements were resolved through consensus.

The wording used in the evidence evaluation for each outcome was categorized and defined as follows:

- Consistent evidence: All or most studies (greater than three studies) are applicable (high or partial) to the Canadian context, and provide a body of evidence that consistently shows an association or no association between water fluoridation and an outcome.
- Limited evidence: Two or three studies that are applicable to the Canadian context (high or partial) and consistently show an association or no association between water fluoridation and an outcome.
- Insufficient evidence: Evidence from a single study, mixed evidence, or evidence from studies, which are not applicable to the Canadian context.

Data Analysis and Reporting

Most studies identified in the SRs conducted by NHMRC 2016[60] and McLaren and Singhal 2016[52] were of ecological and cross-sectional design, which were highly heterogeneous and affected by multiple confounding variables. Studies identified in this updated review were also of similar study designs. A narrative synthesis of the results of the updated SRs and primary studies was conducted alongside a descriptive analysis of the study characteristics, the study quality, and study results.

The findings are presented by outcome, starting with the findings of the NHMRC[60] 2016 and McLaren and Singhal 2016[52] reviews, followed by the results for the primary studies identified in the updated literature search. Summary tables were made to include the findings of the original SRs together with those primary studies identified in this review. For the interpretation of the results, the evidence of each outcome is presented together with the quality appraisal and the applicability of the included studies to the Canadian context. The quality of each study was assessed and classified as high, acceptable, or low based on the internal validity of the study results (i.e., how well did the study minimize sources of bias by adjusting for potential confounders?) and the external validity (i.e., generalizability of the findings to the source population). Applicability was judged by the review authors as high, partial, or limited based on the comparability with the Canadian context, including the levels of fluoride in fluoridated and non-fluoridated water, socio-economic factors, and similarity to dental and health care systems in Canada.

Results

Quantity of Research Available

The updated literature search for this review yielded a total of 3,395 citations, from which 163 were identified as potentially relevant and retrieved for full-text scrutiny. Twenty-three reports were retrieved from other sources (i.e., grey literature, hand search, and search alerts). Of these 186 potentially eligible reports, a total of 60 were found to be eligible and included across the three research questions, subsequently described.

The report selection process is outlined in Appendix 5 using a PRISMA diagram.

Research Question 1

The NHMRC 2016 review[60] was an update of the previous review, NHMRC 2007[61] on the efficacy and safety of water fluoridation. For the effects of water fluoridation on dental caries the NHMRC 2016 literature search identified 25 citations, of which three were SRs and 22 were primary studies. One of the SRs identified was the Cochrane 2015 review conducted by Iheozor-Ejiofor et al.,[62] which sought to update a previous SR by McDonagh et al. (2000)[64] on public water fluoridation.

Seventeen additional studies were identified as eligible through the search update (Appendix 6).

Research Question 2

The McLaren and Singhal 2016 review[52] included 15 studies, 12 of which had results on the effects of cessation of CWF on dental caries. Of the other three studies, two used a single post-cessation cross-sectional design (not a pre-post or longitudinal design) and one did not include dental caries assessment.

An additional four studies relevant to this research question were identified through the search update (Appendix 6).

Research Question 3

For the effect of water fluoride in the development of dental fluorosis, the NHMRC 2016 review did not conduct an SR, but instead reported and critically appraised the evidence from the SR by McDonagh et al. (2000)[64] and the Cochrane 2015 review.[62] For the effect of water fluoridation on other health outcomes, the authors of the NHMRC 2016 review conducted a literature search to identify primary studies (and not SRs). Forty-one primary studies were identified reporting on 19 outcomes.

An additional 41 studies were identified through the current search update (Appendix 6).

Lists of included and excluded citations identified from the updated search for all three research questions — with details describing the rationale for those excluded — are presented in Appendix 6 and Appendix 7, respectively.

Characteristics of Included Studies

Summary tables of the characteristics of the included studies are presented in Appendix 8. The characteristics of each study are described with the presentation of the study findings.

Outcomes and Measures in Included Studies

Details describing the outcomes and measures within the included studies can be found in Appendix 9. Detailed descriptions of the outcomes and measures are presented in the study findings.

Quality of Included Studies

Details for the QA of the included studies are presented in Appendix 9, and overall assessments for the study quality as it applies to the outcome are found in the first column of each summary table in each section. Of the 17 newly identified included studies for Research Question 1, three were ecological studies that were assessed to be of acceptable quality, six were ecological studies assessed to be of low quality, one was a cross-sectional study assessed to be of acceptable quality, and seven were cross-sectional studies assessed to be of low quality. Common issues across studies included patient recruitment (risk of selection bias) and lack of generalizability to the Canadian context. The NHMRC 2016 review included three SRs (one of high quality and two of low quality) and 25 primary studies (19 of acceptable quality and six of low quality).

Of the four newly identified, pre-post studies for Research Question 2, three were deemed to be of acceptable quality and one was deemed to be of low quality. The McLaren and Singhal 2016 review classified studies as having moderate methodological quality or better, versus not, based on six bias domains. Nine of the 12 analyzed studies were rated as having moderate quality or better, based on having high or uncertain risk of bias on three or fewer of the six bias domains.

From the 41 newly identified studies for Research Question 3, three were case-control studies (one assessed as of acceptable quality and two assessed to be of low quality), seven ecological studies (four assessed to be of acceptable and three assessed to be of low quality), and 31 cross-sectional studies assessed to be of low quality. For dental fluorosis, the NHMRC 2016 review reported the findings of the Cochrane 2015 review by Iheozor-Ejiofor et al.[62] along with the those of McDonagh 2000 and NHMRC 2007.[61] Studies included in the Cochrane review were assessed as high risk of bias and those included in the McDonagh 2000 and NHMRC 2007 reviews were assessed as low quality. For other health outcomes, the NHMRC 2016 review included 41 studies, one was assessed as high quality, 14 were of acceptable quality, and the remaining studies were of low quality.

Quality of the Evidence

Evidence evaluation for each outcome is presented in the summary of review findings.

Study Findings

Research Question 1: Effectiveness of Community Water Fluoridation in the Prevention of Dental Caries in Children and Adults

1. Dental Caries

a) Deciduous Teeth

Mean Number of Decayed, Missing, and Filled Deciduous Teeth

Results for mean decayed, missing, and filled deciduous teeth (dmft) are presented in Table 2.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified two SRs and three ecological studies (two from Australia and one from England).

The SR by Iheozor-Ejiofor et al. (2015) was assessed as high quality and pooled the results for mean dmft from nine studies (all were assessed to be of high risk of bias) for children aged 3 to 12 years living in fluoridated areas versus low or non-fluoridated areas. Mean dmft was significantly lower in fluoridated areas than in the low or non-fluoridated areas (mean difference [MD] = –1.81; 95% confidence interval [CI], –2.31 to –1.31). With a median dmft of 5.1 in low or non-fluoridated areas, a 35% (1.81/5.1) reduction in dmft was estimated in children being exposed to CWF.

The SR by Rugg-Gunn and Do (2012) was assessed as low methodological quality. It compared mean dmft or mean decayed and filled deciduous teeth (dft) in children aged 3 to 12 years being exposed to CWF versus non-CWF. The non-pooled results from 21 studies (no QA reported) showed that the median per cent reduction in dmft and dft in fluoridated areas was 44% (values ranging from 29% to 68%) and 47% (values ranging from 34% to 59%), respectively, compared with non-fluoridated areas.

The ecological study assessed to be of acceptable quality by Armfield (2013) compared the mean dmft of children aged 5 to 10 years from four Australian states, who had > 50% lifetime exposure to fluoridated water and the mean dmft of those with 0% to 50% life time exposure to fluoridated water. The results showed a significant inverse association between mean dmft and percentage lifetime exposure to fluoridated water (beta coefficient = –0.66; 95% CI, –0.77 to -0.54; $P < 0.001$) after adjustment for age, gender, household income, parental education, remoteness, toothbrushing frequency, and sugary drink consumption.

The ecological study assessed as of acceptable quality by Blinkhorn et al. (2015) compared the mean dmft of children aged 5 to 7 years who resided in areas that had been fluoridated for about 40 years with the mean dmft of children in non-fluoridated areas in Australia. Measurements were taken in 2008, 2010, and 2012. In all three measurements, mean dmft was significantly higher in non-fluoridated areas than in fluoridated areas (mean dmft ratio [i.e., the ratio of mean dmft without and with fluoridation] was 2.06, 2.81, and 2.23, respectively), after adjustment for age, gender, Indigenous status, cardholder status, maternal country of birth, parental education, toothbrushing behaviour, and sugary drink consumption.

The ecological study conducted by Public Health England (PHE) (2014) assessed as of acceptable quality compared the mean d3mft (the "3" denotes obvious decay into the dentine) of children aged five years living in areas supplied with and without fluoridated drinking water. Mean d3mft was found significantly lower in fluoridated areas than in the non-fluoridated areas (MD = –0.37; 95% CI, –0.48 to –0.27; $P < 0.001$), after adjustment for deprivation and ethnicity.

Evidence From the Updated Literature Search

The updated literature search identified two additional cross-sectional studies.

One cross-sectional study assessed to be of acceptable quality by Arrow (2016)[73] found that children aged 5 to 10 years living in non-fluoridated areas in Australia had a 62% higher risk of deciduous tooth decay compared with those living in the fluoridated areas (rate ratio [RR] = 1.62; 95% CI, 1.18 to 2.22; $P = 0.003$) after adjustment for age, gender, sealants, Aboriginal identity, SES, interval between dental checkup, region, inflammation.

Another cross-sectional study assessed to be of low quality by Blinkhorn et al. (2015)[74] compared the mean dmft of children aged 5 to 7 years living in three areas in Australia (fluoridated, pre-fluoridated, and non-fluoridated areas). Compared with fluoridated areas, children living in pre-fluoridated (incidence rate ratio [IRR] = 1.38; 95% CI, 1.14 to 1.67;

$P < 0.001$) and non-fluoridated areas (IRR = 1.53; 95% CI, 1.23 to 1.89; $P < 0.001$) had a significantly higher risk of dental caries, after adjustment for age, gender, Indigenous status, cardholder status, and mother's country of birth.

Summary

Two SRs (one assessed to be of high quality and one assessed to be of low quality) and three ecological studies identified by the 2016 NHMRC review and assessed to be of acceptable quality all showed that the mean dmft among children living in fluoridated areas was significantly lower than those living in the low or non-fluoridated areas. The updated literature search identified two additional cross-sectional studies, one assessed to be of acceptable quality[73] and one assessed to be of low quality,[74] which also showed that children living in pre-fluoridated or non-fluoridated areas had a significantly higher risk of dental caries compared with those living in fluoridated areas. Confounding variables were adjusted in the analyses of the primary studies. The findings of all primary studies were assessed to be partially applicable to the Canadian context. Overall, there was consistent evidence for an association between water fluoridation and the reduction in the number of dmft in children.

Table 2: Mean Decayed and Filled Deciduous Teeth

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Two SRs and Three Ecological Studies					
Iheozor-Ejiofor et al. (2015) UK; Canada SR High	Children aged 3 to 12 years 9 studies (high risk of bias) N = 44,268	• CWF (≥ 0.4 ppm) • Non-CWF (< 0.4 ppm)	Mean dmft of the non-CWF group ranged from 1.21 to 7.8 (median: 5.1) 35% (1.81/5.1) reduction in mean dmft in children being exposed to CWF	MD = –1.81; 95% CI, –2.31 to –1.31	Mean dmft was significantly lower in fluoridated areas than in the non-fluoridated areas.
Rugg-Gunn and Do (2012) Australia; UK SR Low	Children aged 3 to 12 years 21 studies (no QA) N = NR	• CWF (F level NR) • Non-CWF (F level NR)	Median % reduction (range): • dmft: 44% (29% to 68%) • dft: 47% (34% to 59%)	NR	Mean dmft or dft was lower in fluoridated areas than in the non-fluoridated areas.
Armfield (2013) Australia Ecological Acceptable	Children aged 5 to 10 years N = 16,857 for total 5 to 16 years	Lifetime exposure to fluoridated water • > 50% • 0 to 50%	NR	Beta coefficient = –0.66 (95% CI, –0.77 to –0.54); *P* < 0.001 (Adjustment for age, gender, household income, parental education, remoteness, toothbrushing frequency, and sugary drink consumption)	There was a significant inverse association between mean dmft and percentage lifetime exposure to fluoridated water. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Blinkhorn et al. (2015) Australia Ecological Acceptable	Children aged 5 to 7 years N = 2,129 (2008) N = 2,284 (2010) N = 2,267 (2012)	• CWF for over 40 years (F level NR) • Non-CWF (F level NR)	Mean dmft (95% CI) CWF 2008: 1.40 (1.22 to 1.58) 2010: 0.96 (0.83 to 1.09) 2012: 0.69 (0.57 to 0.81) Non-CWF 2008: 2.09 (1.84 to 2.35) 2010: 2.06 (1.79 to 2.33) 2012: 1.21 (1.03 to 1.39)	MR (95% CI) 2008: 2.06 (1.48 to 2.85) 2010: 2.81 (2.16 to 3.64) 2012: 2.23 (1.66 to 2.98) CWF as ref (Adjustment for age, gender, Indigenous status, cardholder status, maternal country of birth, parental education, toothbrushing behaviour, and sugary drink consumption)	Mean dmft was significantly lower in fluoridated areas than in the non-fluoridated areas. (*Partial*)
PHE (2014) England Ecological Acceptable	Children aged 5 years N = NR	• CWF (0.8 ppm to 1.0 ppm) • Non-CWF (F level NR)	NR	MD = –0.37; 95% CI, –0.48 to –0.27; *P* < 0.001 (Adjustment for deprivation and ethnicity)	Mean d3mft[b] was significantly lower in fluoridated areas than in the non-fluoridated areas. (*Partial*)
Evidence From the Updated Literature Search: Two Cross-Sectional Studies					
Arrow (2016)[73] Australia Cross-sectional Acceptable	Children aged 5 to 10 years N = 6,318	• CWF (F level NR) • Non-CWF (F level NR)	Mean dmft (95% CI) • CWF: 1.39 (1.33 to 1.45) • Non-CWF: 1.86 (1.59 to 2.12)	RR = 1.62; 95% CI ,1.18 to 2.22; *P* = 0.003 CWF as ref (Adjustment for age, gender, sealants, Aboriginal identity, SES, interval between dental checkup, region, and inflammation)	Children living in the non-fluoridated areas had a 62% higher risk of deciduous tooth decay compared with those living in the fluoridated areas. (*Partial*)
Blinkhorn et al. (2015)[74] Australia Cross-sectional	Children aged 5 to 7 years old living in three areas N = 2,129	• CWF (F level NR) • Pre-CWF (F level NR) • Non-CWF (F level	Mean dmft (95% CI) • CWF: 1.40 (1.22 to 1.58) • Pre-CWF: 2.02 (1.80 to 2.23)**	IRR (95% CI) • CWF: ref • Pre-CWF: 1.38 (1.14 to 1.67)**	Children living in the pre-fluoridated and non-fluoridated areas had significantly higher risk of dental caries compared

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Low		NR)	- Non-CWF: 2.09 (1.84 to 2.35)** ***P* < 0.001 compared with fluoridated	- Non-CWF: 1.53 (1.23 to 1.89)** ***P* < 0.001 (Adjustment for age, gender, Indigenous status, cardholder status, and mother's country of birth)	with those living in the fluoridated areas. (*Partial*)

CI = confidence interval; CWF = community water fluoridation; dft = decayed and filled deciduous teeth; dmft = decayed, missing, and filled deciduous teeth; F = fluoride; IRR = incidence rate ratio; MD = mean difference; MR = mean ratio; NHMRC = National Health and Medical Research Council; NR = not reported; PHE = Public Health England; ppm = parts per million; QA = quality assessment; Ref = reference; RR = rate ratio; SD = standard deviation; SE = standard error; SES = socio-economic status; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] The "3" in d3mft denotes obvious decay into dentine.

Mean Number of Decayed, Missing, and Filled Deciduous Tooth Surfaces (dmfs)

Results for mean decayed, missing, and filled deciduous tooth surfaces (dmfs) are presented in Table 3.

Evidence From the 2016 NHMRC Review

One SR and four primary studies (one prospective cohort study and three ecological studies) were identified.

The SR by Rugg-Gunn and Do (2012) was rated as low quality and compared mean dmfs or mean decayed and filled deciduous tooth surfaces (dfs) in children aged 5 to 11 years being exposed to CWF versus non-CWF. The non-pooled data from nine studies (no QA conducted) showed that the median per cent reduction in dmfs and dfs in fluoridated areas was 33% (values ranging from 14% to 66%).

The prospective cohort study by Wang et al. (2012), rated to be of acceptable quality, found that children aged five years in Iowa, USA, with higher fluoride intake from drinking water had significantly fewer dental caries ($P < 0.05$), measured by the number of tooth surfaces with frank cavitated or filled caries experiences (denoted as d2ft). Adjustments were made for age, gender, and toothbrushing frequency, but actual effect estimates were not reported.

The ecological study by Do et al. (2014), rated to be of acceptable quality, compared the mean dmfs among children aged 8 to 10 years in New South Wales, Australia, who had different percentages of lifetime exposure to fluoridated water (i.e., 100%, > 0 to 99% and 0%). Compared with 0% exposure, children who had 100% lifetime exposure (mean dmfs ratio = 0.65; 95% CI, 0.54 to 0.78) or > 0 to 99% lifetime exposure (mean dmfs ratio = 0.66; 95% CI, 0.53 to 0.82) to fluoridated water had significantly lower mean dmfs, after adjustment for household income, parental education, dietary fluoride supplement use, age, and gender.

The ecological study by Do and Spencer (2015), rated to be of acceptable quality, compared mean dmfs among children aged 5 to 8 years in Queensland, Australia, who were exposed to CWF and non-CWF. After adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride tooth paste, age of first dental visit, sugary drink consumption, and school type, mean dmfs was significantly lower in fluoridated areas than in the non-fluoridated areas (mean dmfs ratio = 0.61; 95% CI, 0.44 to 0.82).

The ecological study rated to be of low quality by Do et al. (2011) studied the relationship between mean dmfs and drinking water fluoride level in schoolchildren aged 6 to 11 years in Vietnam. The children were divided into three groups based on water fluoride level: > 0.5 ppm, 0.3 ppm to 0.5 ppm, and < 0.3 ppm. After adjustment for age, gender, age toothbrushing started, age toothpaste use started, brushing frequency, household income, dental visit, residential status, parental education, and area, there was a significant inverse association between mean dmfs and fluoride level in drinking water (beta coefficient [standard error (SE)] = –2.99 [1.12]; $P = 0.008$).

Evidence From the Updated Literature Search

The updated literature search identified no additional studies.

Summary

One SR (assessed to be of low quality) and four primary studies (one cohort and two ecological studies assessed to be of acceptable quality; one ecological study assessed to be of low quality) identified by the 2016 NHMRC review all showed that the mean dmfs among children living in fluoridated areas was significantly lower than those living in the low or non-fluoridated areas. Confounding variables were adjusted in the analyses of primary studies. The findings of three primary studies (one conducted in the US and two conducted in Australia) were assessed to be partially applicable to the Canadian context, and one (conducted in Vietnam) was assessed to have limited applicability. No additional study was identified from the updated literature search. Overall, there was consistent evidence for an association between water fluoridation and the reduction in the number of dmfs in children.

Table 3: Mean Decayed, Missing, and Filled Deciduous Tooth Surfaces

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One SR and Four Observational Studies (One Prospective Cohort Study and Three Ecological Studies)					
Rugg-Gunn and Do (2012) Australia; UK SR Low	Children aged 5 to 11 years 9 studies (No QA) N = NR	• CWF (F level NR) • Non-CWF (F level NR)	Median % reduction in dmfs or dfs (range) = 33% (14 to 66)	NR	Mean dmfs or dfs was lower in fluoridated areas than in the non-fluoridated areas.
Wang et al. (2012) USA Prospective cohort Acceptable	Children aged 5 years N = 575	Fluoride intake from water	Children with higher fluoride from drinking water had significant fewer dental caries measured as d2fs (*P* < 0.05)	NR (Adjustment for age, gender, and toothbrushing frequency)	Children with higher fluoride intake from drinking water had significantly fewer d2fs. (*Partial*)
Do et al. (2014) Australia Ecological Acceptable	Children aged 8 to 10 years N = 1,406	Lifetime exposure to fluoridated water • 100% • > 0% to 99% • 0%	Mean dmfs • 100%: 2.38 • > 0% to 99%: 2.30 • 0%: 3.82	MR (95% CI) • 100%: 0.65 (0.54 to 0.78) • > 0% to 99%: 0.66 (0.53 to 0.82) 0% exposure as ref (Adjustment for household income, parental education, dietary fluoride supplement use, age, and gender)	Mean dmfs was significantly lower in children who had 100% or > 0% to 99% lifetime exposure to fluoridated water compared with 0% exposure. (*Partial*)
Do and Spencer (2015) Australia Ecological Acceptable	Children aged 5 to 8 years N = 2,214	• CWF (F level NR) • Non-CWF (F level NR)	Mean dmfs (95% CI) CWF: 2.75 (2.16 to 3.34) Non-CWF: 4.31 (3.79 to 4.84)	MR = 0.61; 95% CI, 0.44 to 0.82 Non-CWF as ref (Adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement	Mean dmfs was significantly lower in fluoridated areas than in the non-fluoridated areas. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
				use, age of first use of fluoride tooth paste, age of first dental visit, sugar drink consumption, and school type)	
Do et al. (2011) Vietnam Ecological Low	Children aged 6 to 11 years N = 2,748	NOF in water: • > 0.5 ppm • 0.3 ppm to 0.5 ppm • < 0.3 ppm	NR	Beta coefficient (SE) = –2.99 (1.12); *P* = 0.008 (Adjustment for age, gender, age toothbrushing started, age tooth paste use started, brushing frequency, household income, dental visit, residential status, parental education, and area)	There was a significant inverse association between mean dmfs and fluoride level in drinking water. (*Limited*)
Evidence From the Updated Literature Search: No Study Identified					

CI = confidence interval; CWF = community water fluoridation; d2fs = number of tooth surfaces with frank cavitated or filled caries experiences; dfs = decayed and filled deciduous tooth surfaces; dmfs = decayed, missing, and filled deciduous tooth surfaces; F = fluoride; MR = mean ratio; NOF = naturally occurring fluoride; NR = not reported; ppm = parts per million; QA = quality assessment; ref = reference; SE = standard error; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Dental Caries Prevalence and Proportion of Caries-Free of Deciduous Teeth

Results for dental caries prevalence and proportion of caries-free deciduous teeth are presented in Table 4. Caries prevalence is the proportion of participants with dmft/s or decayed, missing, and filled permanent teeth and tooth surfaces (DMFT/S) scores greater than zero. They are often reported as %dmft/s > 0 or ≥ 1 and %DMFT/S > 0 or ≥ 1. Proportion of caries-free is the proportion of participants with dmft/s or DMFT/S scores of zero (%dmft/s = 0 or %DMFT/S = 0). Caries prevalence can also be calculated from the proportion of caries-free (caries prevalence = 1- [proportion caries-free]).

Evidence From the 2016 NHMRC Review

One SR, assessed to be of high quality, and seven ecological studies (six assessed to be of acceptable quality and one assessed to be of low quality) were identified. The SR reported findings as a proportion of caries-free and seven ecological studies reported results as caries prevalence.

The high quality SR by Iheozor-Ejiofor et al. (2015) included 10 studies classified as having a high risk of bias, compared the proportion of caries-free of deciduous teeth among children aged 3 to 12 years between CWF and non-CWF areas. Pooled results showed that the proportion of caries-free children for deciduous dentition was significantly higher in the fluoridated areas than in low or non-fluoridated areas (MD = 0.15; 95% CI, 0.11 to 0.19).

The ecological study of acceptable quality by Blinkhorn et al. (2015) examined caries prevalence of children aged 5 to 7 years in three areas in Australia. Areas with water fluoridation for over 40 years were compared with those with no water fluoridation. Measurements were taken in 2008, 2010, and 2012. In all three measurements, caries prevalence of deciduous teeth was significantly lower in CWF areas than non-CWF areas (i.e., odds ratio [OR] was 0.34, 0.41, and 0.51, respectively), after adjustment for age, gender, Indigenous status, cardholder status, maternal country of birth, parental education, toothbrushing behaviour, and sugary drink consumption.

The ecological study of acceptable quality by PHE (2014) reported caries prevalence of deciduous teeth in five-year-old children. After adjustment for deprivation and ethnicity, caries prevalence was 28% lower in children in CWF areas compared with those in non-CWF areas (% difference in odds = –28%; 95% CI, –35 to –21).

The ecological study of acceptable quality by Do and Spencer (2007) compared the relationship between proportion of lifetime exposure to fluoridated water from birth to three years old and caries prevalence in children aged 5 to 8 years in Australia. Higher proportion of lifetime exposure to fluoridated water (i.e., > 50% and > 0% to 50%) had significantly lower caries prevalence compared with 0% exposure, after adjustment for confounders.

The ecological study of low quality conducted by the Centres for Disease Control and Prevention (2011) investigated the caries prevalence of children aged 4 to 11 years living in CWF villages and non-CWF villages in Alaska. Compared with non-fluoridated areas, caries prevalence of deciduous teeth was significantly lower in fluoridated areas (OR = 0.29; 95% CI, 0.23 to 0.36) after adjustment for soda pop consumption and frequency of toothbrushing.

The ecological study of acceptable quality by Do et al. (2014) found that children aged 8 to 10 years in New South Wales, Australia, who had 100% lifetime exposure to fluoridated water had significantly lower caries prevalence compared with those never exposed to fluoridated water (0%). After adjustment for household income, parental education, dietary fluoride supplement use, age, and gender, the prevalence ratio was 0.83 (95% CI, 0.70 to

0.99). Children who had > 0% to 99% lifetime exposure to fluoridated water also had lower caries prevalence compared with those with 0% exposure, but the difference was not statistically significant.

The ecological study of acceptable quality by Do et al. (2015) found that children aged 5 to 8 years in Queensland, Australia, who lived in non-CWF areas had significantly higher caries prevalence compared with those living CWF areas. The prevalence ratio was 1.29 (95% CI,1.11 to 1.50), after adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride toothpaste, age of first dental visit, sugar drink consumption, and school type.

The ecological study of acceptable quality by Postma et al. (2008) investigated the relationship between public drinking water supply fluoride levels and caries prevalence in children aged 36 to 71 months in South Africa. The drinking water fluoride levels were classified as < 0.1 ppm, 0.10 ppm to 0.29 ppm, 0.30 ppm to 0.60 ppm, and > 0.60 ppm. Compared with < 0.1 ppm, caries prevalence of deciduous teeth was significantly lower in higher water fluoride level areas, after adjustment for age, gender, locality, ethnicity, and income.

Evidence From the Updated Literature Search

The updated literature search identified two additional studies both assessed to be of low quality; one ecological study by Crouchley and Trevithick (2016)[75] and one cross-sectional study by Blinkhorn et al. (2015).[74]

The ecological study by Crouchley and Trevithick (2016)[75] examined the association between exposure to fluoridated water and caries prevalence among children aged 5 to 9 years in Western Australia. The study found that caries prevalence in children living in non-CWF areas was higher in all age groups compared with those living in CWF areas. After adjustment for age, sex, Aboriginal status, and having a record of an initial examination at a dental treatment centre, children living in non-CWF areas were found to have 1.5 times the odds of having one or more dmft compared with those living in CWF areas (OR = 1.54; 95% CI, 1.35 to 1.75; $P = 0.000$).

The cross-sectional study by Blinkhorn et al. (2015)[74] compared the proportion of caries-free of children aged 5 to 7 years living in three communities (CWF, pre-CWF, and non-CWF) in New South Wales, Australia. It was found that children living in pre-CWF and non-CWF areas had a significantly lower proportion of caries-free compared with those living in CWF areas. After adjustment for age, gender, Indigenous status, cardholder status, and mother’s country of birth, children living in the pre-CWF and non-CWF areas had 1.62 and 1.86 times greater odds of having one or more dmft compared with those living in CWF areas, respectively.

Summary

One SR assessed as high quality, seven ecological studies (six assessed to be of acceptable quality, and one assessed to be of low quality) identified by the 2016 NHMRC review showed that water fluoridation significantly reduced caries prevalence compared with no water fluoridation. Two additional studies (one ecological study and one cross-sectional study assessed to be of low quality) identified from the updated literature search also showed similar results. Analyses in all primary studies were adjusted for confounding variables. The findings of all primary studies were assessed to be partially applicable to the Canadian context. Overall, there was consistent evidence for an association between water fluoridation and the reduction in caries prevalence and an increase in the proportion of caries-free deciduous teeth in children.

Table 4: Dental Caries Prevalence and Proportion of Caries-Free of Deciduous Teeth

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One SR and Seven Ecological Studies					
Iheozor-Ejiofor et al. (2015) UK; Canada SR High	Children aged 3 to 12 years 10 studies (high risk of bias) N = 39,966	• CWF (≥ 0.4 ppm) • Non-CWF (< 0.4 ppm)	Proportion of caries-free in non-CWF ranged from 0.06 to 0.67 (median 0.22)	MD = 0.15; 95% CI, 0.11 to 0.19	The proportion of caries-free children for deciduous dentition was significantly higher in the fluoridated areas than non-fluoridated areas.
Blinkhorn et al. (2015) Australia Ecological Acceptable	Children aged 5 to 7 years N = 2,129 (2008) N = 2,284 (2010) N = 2,267 (2012)	• CWF for over 40 years (F level NR) • Non-CWF (F level NR)	Caries prevalence CWF 2008: 37.4% 2010: 31.8% 2012: 24.2% Non-CWF 2008: 51.4% 2010: 44.6% 2012: 32.7%	OR (95% CI) 2008: 0.34 (0.23 to 0.49) 2010: 0.41 (0.32 to 0.54) 2012: 0.51 (0.39 to 0.67) Non-CWF as ref (Adjustment for age, gender, Indigenous status, cardholder status, maternal country of birth, parental education, toothbrushing behaviour, and sugary drink consumption)	Caries prevalence of deciduous teeth was significantly lower in fluoridated areas than non-fluoridated areas. (*Partial*)
PHE (2014) England Ecological Acceptable	Children aged 5 years N = NR	• CWF (0.8 ppm to 1.0 ppm) • Non-CWF (F level NR)	NR	% difference in odds = –28%; 95% CI, –35 to –21 (Adjustment for deprivation and ethnicity)	Caries prevalence of deciduous teeth was significantly lower in fluoridated areas than non-fluoridated areas (*Partial*)
Do and Spencer (2007) Australia Ecological Acceptable	Children aged 5 to 8 years N = 667	Lifetime exposure to fluoridated water (from birth to 3 years old) • > 50% • > 0% to 50% • 0%	Caries prevalence • > 50%: 25.5% • > 0% to 50%: 30.1% • 0%: 45.8%	OR • > 50%: 0.4 (95 % CI, 0.2 to 0.7) • > 0 to 50%: 0.5 (95% CI, 0.3 to 0.9) 0% lifetime exposure as ref	Caries prevalence of deciduous teeth was significantly lower in higher proportion of lifetime exposure to fluoridated water. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
				(Adjustment for age in month at 6-year examination, gender, birth cohort, fluoride supplements, infant formula, household income, age toothpaste use started, brushing frequency, amount of tooth paste use, after brushing routine, eating and licking toothpaste habit, and parental education)	
CDC (2011) USA Ecological Low	Children aged 4 to 11 years N = 348 (whole population 4 to 15 years)	• CWF (F level NR) • Non-CWF (F level NR)	Caries prevalence CWF • 4 to 5 years: 67% • 6 to 8 years: 73% • 9 to 11 years: 68% Non-CWF • 4 to 5 years: 100% • 6 to 8 years: 97% • 9 to 11 years: 71%	OR = 0.29; 95% CI, 0.23 to 0.36 Non-CWF as ref (Adjustment for soda pop consumption and frequency of toothbrushing)	Caries prevalence of deciduous teeth was significantly reduced in fluoridated areas than non-fluoridated areas. (*Partial*)
Do et al. (2014) Australia Ecological Acceptable	Children aged 8 to 10 years N = 1,406	Lifetime exposure to fluoridated water • 100% • > 0% to 99% • 0%	Caries prevalence (SE) • 100%: 32.6% (1.4) • > 0% to 99%: 31.5% (2.3) • 0%: 39.0% (2.6)	PR (95% CI) • 100%: 0.83 (0.70 to 0.99) • > 0% to 99%: 0.81 (0.65 to 1.01) 0% exposure as ref (Adjustment for household income, parental education, dietary fluoride supplement use, age, and gender)	100% lifetime exposure to fluoridated water associated with a significant reduction in caries prevalence. (*Partial*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>[a])</th></tr>
<tr><td>Do et al. (2015)
Australia
Ecological
Acceptable</td><td>Children aged 5 to 8 years
N = 2,214</td><td>CWF (F level NR)
Non-CWF (F level NR)</td><td>Caries prevalence (95% CI)
CWF: 36.9% (58.7 to 67.4)
Non-CWF: 47.7% (44.3 to 51.1)</td><td>PR = 1.29; 95% CI, 1.11 to 1.50

CWF as ref

(Adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride toothpaste, age of first dental visit, sugary drink consumption, and school type)</td><td>Children living in non-CWF areas had significantly higher caries prevalence compared with CWF areas. (<i>Partial</i>)</td></tr>
<tr><td>Postma et al. (2008)
South Africa
Ecological
Acceptable</td><td>Children aged 36 to 71 months
N = 5,822</td><td>Fluoride level in public water supply:
> 0.60 ppm
0.30 ppm to 0.60 ppm
0.10 ppm to 0.29 ppm
< 0.10 ppm</td><td>NR</td><td>OR (95% CI)
> 0.60 ppm: 0.40 (0.25 to 0.63)
0.30 ppm to 0.60 ppm: 0.62 (0.44 to 0.87)
0.10 ppm to 0.29 ppm: 0.80 (0.64 to 0.99)
< 0.10 ppm as ref

(Adjustment for age, gender, locality, ethnicity, and income)</td><td>Caries prevalence of deciduous teeth was significantly lower in fluoridated areas than non-fluoridated areas. (<i>Partial</i>)</td></tr>
<tr><td colspan="6">Evidence From Updated Literature Search: One Ecological Study and One Cross-Sectional Study</td></tr>
<tr><td>Crouchley and Trevithick (2016)[75]
Australia
Ecological
Low</td><td>Children aged 5 to 9 years
N = 7,220</td><td>CWF (F level NR)
Non-CWF (F level NR)</td><td>Caries prevalence<table><tr><th>Age (year)</th><th>CWF</th><th>Non-CWF</th></tr><tr><td>5</td><td>28.7%</td><td>40.3%</td></tr><tr><td>6</td><td>35.3%</td><td>44.0%</td></tr><tr><td>7</td><td>43.6%</td><td>55.5%</td></tr><tr><td>8</td><td>48.1%</td><td>55.9%</td></tr><tr><td>9</td><td>50.5%</td><td>56.7%</td></tr></table></td><td>OR = 1.54; 95 % CI, 1.35 to 1.75; <i>P</i> = 0.000

CWF as ref
(Adjustment for age, sex, Aboriginal status, and having a record of an initial examination at a dental treatment centre)</td><td>Children living in non-CWF areas had 1.5 times the odds of having one or more dmft compared with those living in CWF areas. (<i>Partial</i>)</td></tr>
</table>

Study Country Design Quality	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
Blinkhorn et al. (2015)[74] Australia Cross-sectional Low	Children aged 5 to 7 years old living in three areas N = 2,129	• CWF (F level NR) • Pre-CWF (F level NR) • Non-CWF (F level NR)	Proportion of caries-free • CWF: 62.6% (95% CI, 59.2 to 65.9) • Pre-CWF: 50.8% (95% CI, 47.3 to 54.3)** • Non-CWF: 48.6% (95% CI, 44.3 to 52.9)** **P < 0.001 compared with fluoridated	Caries experience OR (95% CI) • CWF: ref • Pre-CWF: 1.62 (1.31 to 2.01)** • Non-CWF: 1.86 (1.46 to 2.37)** **P < 0.001 (Adjustment for age, gender, Indigenous status, cardholder status, and mother's country of birth)	Children living in the pre-fluoridated and non-fluoridated areas had significantly higher risk of dental caries compared with those living in the fluoridated areas. (*Partial*)

CDC = Centers for Disease Control and Prevention; CI = confidence interval; CWF = community water fluoridation; dmft = decayed, missing, or filled deciduous teeth; F = fluoride; MD = mean difference; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; PHE = Public Health England; ppm = parts per million; PR = prevalence ratio; ref = reference;; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

b. Permanent Teeth

Mean Number of Decayed, Missing, and Filled Permanent Teeth

Results for mean DMFT are presented in Table 5.

Evidence From the 2016 NHMRC Review

Three SRs (one assessed to be of high quality and two as low quality) and six ecological studies (five assessed as acceptable and one as low quality) were identified.

The SR by Iheozor-Ejiofor et al. (2015), which was rated as high quality, included 10 studies with a high risk of bias. The pooled analysis showed that fluoridated water significantly reduced mean DMFT for children 8 to 11 years old (MD = –1.16; 95% CI, –0.72 to –1.61) compared with low or non-fluoridated areas. With a median DMFT of 4.4 in non-fluoridated areas, a 26% (1.16/4.4) reduction in DMFT in children being exposed to CWF was estimated.

The SR by Rugg-Gunn and Do (2012), which was rated as low quality, compared mean DMFT in participants aged 8 to 51 years being exposed to CWF versus non-CWF. The non-pooled results from 37 studies (no QA reported) showed that the median per cent reduction in DMFT in fluoridated areas was 37% (values ranging from 5% to 85%) compared with non-fluoridated areas.

The SR by Griffin et al. (2007), which was rated as low quality, included nine studies (no QA reported), which all showed that fluoridated water significantly reduced mean DMFT compared with non-fluoridated water in adults ≥ 20 years old ($P < 0.001$). Pooled analysis of seven comparable studies (evaluating lifetime residents of fluoridated or non-fluoridated communities) yielded a RR of 0.65 (95% CI, 0.49 to 0.87).

The ecological study of acceptable quality by Armfield (2013) compared the mean DMFT among children aged 11 to 16 years from four Australian states who had > 50% lifetime exposure to fluoridated water and those with 0 to 50% life time exposure to fluoridated water. The results showed a significant inverse association; there was a lower mean DMFT associated with a higher lifetime exposure to fluoridated water (beta coefficient = –0.10; 95% CI, –0.20 to 0.00; $P < 0.05$), after adjustment for age, gender, household income, parental education, remoteness, toothbrushing frequency, and sugary drink consumption.

The ecological study of low quality by Da Silva et al. (2015) examined the relationship between fluoridated water supply and mean DMFT in children 12 years old in Brazil. The study found that exposure to water fluoridation was associated with a significant reduction in mean DMFT (beta coefficient = –0.613; 95% CI, –1.030 to –0.196; $P = 0.006$) after adjustment for economic deprivation and sociosanitary (a composite measure incorporating rates of urbanization, proper sanitation, and illiteracy).

The ecological study of acceptable quality by Slade (2013) examined the relationship between lifetime exposure to fluoridated water (≥ 75% and < 25%) and mean DMFT among participants aged ≥ 15 years in Australia. The participants were divided into two cohorts: born before 1960 (before fluoridation was widespread) and born between 1960 and 1990 (when fluoridation became more common). The study found that ≥ 75% lifetime exposure to fluoridated water was associated with fewer DMFT in the pre-1960 cohort (beta coefficient = –2.58; 95% CI, –4.05 to –1.11) and in the 1960-1990 cohort (beta coefficient = –1.14; 95% CI, –2.09 to –0.19) when compared with those with < 25% lifetime exposure. Adjusted confounding variables included Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride toothpaste, age of first dental visit, sugary drink consumption, and school type.

The ecological study conducted by PHE (2014), assessed to be of acceptable quality, compared the mean D3MFT (the “3” denotes obvious decay into the dentine) of children aged 12 years living in areas with and without CWF in England. Mean D3MFT was found to be significantly lower in fluoridated areas than in the non-fluoridated areas (MD = –0.19; 95% CI, –0.27 to –0.11; *P* < 0.001) after adjustment for deprivation (i.e., poverty) and ethnicity.

The ecological study of acceptable quality by Skinner et al. (2014) included children aged 14 to 15 years in New South Wales, Australia. Compared with non-fluoridated areas, mean DMFT was significantly lower in fluoridated areas (mean ratio [MR] = 0.58; 95% CI, 0.44 to 0.75) after adjustment for income, mother’s education level, sugary drink consumption, having a dental visit in the previous year, age, and gender.

The ecological study of acceptable quality by Haysom et al. (2015) included participants aged 13 to 21 years in New South Wales, Australia. The study also showed that mean DMFT was significantly lower in fluoridated areas than in non-fluoridated areas. Mean DMFT ratio was 1.77 (95% CI, 1.11 to 2.83), after adjustment for Aboriginal status, age, gender, history of out-of-home care, socio-economic disadvantage, remoteness, time incarcerated, snacks more than twice a week, preferring sweetened drinks, toothbrushing frequency, toothache or problems with teeth or gums, self-reported status of teeth, dental service previous year, and location of dental provider in the previous year.

Evidence From the Updated Literature Search

The updated literature search identified two ecological studies (one assessed to be of acceptable quality and one of low quality) and three cross-sectional studies (one assessed to be of acceptable quality and two of low quality).

The ecological study of acceptable quality by Aggeborn and Öhman (2017)[76] from Sweden studied the effect of fluoride exposure through the drinking water throughout life on dental health in individuals aged 16 years and older who were born between 1985 and 1992. Sweden has naturally occurring fluoridated water with fluoride levels in the community water kept below 1.5 ppm. Regression analysis showed that, for dental repair, the percentage of teeth filled would decrease by approximately 0.6 percentage points if fluoride increased by 1 ppm, after adjustment for sex, marital status, parent’s education, parent’s income, father’s cognitive and non-cognitive ability, parent immigrant, and cohort mean education (at birth, at school start, at 16 years age).

The ecological study of low quality by Crocombe et al. (2016)[77] examined the relationship between exposure to fluoridated water and dental caries experience of adults living outside Australian capital cities and those living in the capital cities. Adults living in the capital cities had a mean lifetime exposure of 59.1%, while those living outside capital cities had a mean lifetime exposure of 42.3%. Mean DMFT of those living in the capital cities was significantly lower than those living outside capital cities (12.9 versus 14.3; *P* = 0.02). After adjustment for sociodemographic characteristics, preventive dental behaviour, and access to dental care parameters, there was a significant positive relationship between caries experience (DMFT) and living outside capital cities (beta coefficient = 0.8; *P* = 0.01). The study did not capture differences in rural areas and different levels of remoteness. With additional adjustment of lifetime fluoride exposure, significant difference between regions was no longer observed for DMFT.

The cross-sectional study of low quality by Kim et al. (2017)[78] investigated the association between CWF programs and dental caries prevention on permanent teeth in children aged 6, 8 and 11 years in South Korea. The study found that children aged 8 and 11 years in the CWF areas had significantly lower mean DMFT compared with those in the non-CWF areas (0.15 versus 0.56, P <0.001; and 0.86 versus 1.43, P < 0.001; respectively), after adjustment for sex, monthly family income, household educational level, Family Affluence Scale score, and number of sealed teeth. For children aged six, there was no difference in mean DMFT in CWF versus non-CWF areas. The authors argued that the DMFT index could not be accurately used to express to oral health status of this age group because of mixed dentition, and the permanent teeth of six-year-old children had not been exposed long enough to fluoride to observe the benefit of CWF. Children in both areas widely used fluoridated toothpaste.

The cross-sectional study of acceptable quality by Arrow (2016)[73] compared mean DMFT among children aged six to 15 years in Western Australia. The study found that children living in the non-fluoridated areas had over a 100% increase in permanent tooth decay compared with those living in the fluoridated areas (RR = 2.13; 95% CI,1.52 to 2.96; P < 0.001), after adjustment for age, gender, sealants, Aboriginal identity, SES, interval between dental checkup, region, and inflammation.

The cross-sectional study of low quality by Peres et al. (2016)[79] investigated whether lifetime access to fluoridated water (LAFW) is associated with dental caries experience among adults aged 20 to 59 years in Brazil. LAFW was divided into three groups: > 75%, 50% to 75%, and < 50%. The study found that lowest LAFW (< 50%) had a significantly higher rate of DMFT compared with more than 75% lifetime water fluoridation exposure (RR = 1.39; 95% CI, 1.05 to 1.85). The study included a small sample size and a high risk of selection bias, but the findings were adjusted for sex, age, education, income, SES, pattern of dental attendance, and smoking.

Summary

Three SRs (one assessed to be of high quality and two assessed to be of low quality) and six ecological studies (five assessed as acceptable quality and one assessed as low quality) identified by the 2016 NHMRC review showed that mean DMFT among children and adults living in fluoridated areas was significantly lower than those living in non-fluoridated areas. The updated literature search identified five additional studies (one ecological and one cross-sectional studies assessed as of acceptable quality, and one ecological and two cross-sectional studies assessed as of low quality), which showed similar results. Various confounding variables were adjusted and controlled in the analyses of all primary studies. The findings of all primary studies, except one from Brazil,[79] were assessed to be partially applicable to the Canadian context. Overall, there was consistent evidence that water fluoridation reduced caries in permanent teeth (measured using DMFT) in both children and adults.

Table 5: Mean Decayed, Missing, and Filled Permanent Teeth

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Three SRs and Six Ecological Studies					
Iheozor-Ejiofor et al. (2015) UK; Canada SR High	Children aged 8 to 11 years 10 studies (high risk of bias) N = 78,764	• CWF (≥ 0.4 ppm) • Non-CWF (< 0.4 ppm)	Mean DMFT of the non-CWF group ranged from 0.71 to 5.5 (median = 4.4) 26% (1.16/4.4) reduction in mean dmft in children being exposed to CWF	MD = –1.16; 95% CI, –1.61 to –0.72	Mean DMFT was significantly lower in fluoridated areas than in the non-fluoridated areas.
Rugg-Gunn and Do (2012) Australia; UK SR Low	Participants aged 8 to 51years 37 studies (No QA) N = NR	• CWF (F level NR) • Non-CWF (F level NR)	Median % reduction (range) = 37% (5 to 85)	NR	Mean DMFT was lower in fluoridated areas than in the non-fluoridated areas.
Griffin et al. (2007) USA SR Low	Adults aged ≥ 20 years 9 studies (No QA) N = 7,853	• CWF (F level NR) • Non-CWF (F level NR)	NR	RR = 0.65; 95% CI, 0.49 to 0.87	Adults had significantly lower mean DMFT in fluoridated water areas than non-fluoridated areas.
Armfield (2013) Australia Ecological Acceptable	Children aged 11 to 16 years N = 16,857 for total 5 to 16 years	Lifetime exposure to fluoridated water • > 50% • 0 to 50%	NR	Beta coefficient = –0.10; 95% CI, –0.20 to 0.00; $P < 0.05$ (Adjustment for age, gender, household income, parental education, remoteness, toothbrushing frequency, and sugary drink consumption)	There was a significant inverse association between mean DMFT and percentage lifetime exposure to fluoridated water. (*Partial*)
Da Silva et al. (2015) Brazil Ecological Low	Children aged 12 years N = NR	Fluoridated water supply (F level NR)	NR	Beta coefficient = –0.613; 95% CI,–1.030 to –0.196; $P = 0.006$ (Adjustment for economic deprivation and sociosanitary [a composite measure incorporating	Exposure to water fluoridation was associated with a significant reduction in mean DMFT. (*Limited*)

Study Country Design Quality	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
				rates of urbanization, proper sanitation and illiteracy])	
Slade (2013) Australia Ecological Acceptable	Participants aged ≥ 15 years N = 3,779 Two cohorts: • Pre-1960: N = 2,270 • 1960 to 1990: N = 1,509	Lifetime exposure to fluoridated water • ≥ 75% • < 25%	NR	Beta coefficient (95% CI) • Pre-1960 cohort: –2.58 (–4.05 to–1.11) • 1960 to 1990 cohort: –1.14 (–2.09 to –0.19) < 25% exposure as ref (Adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride toothpaste, age of first dental visit, sugary drink consumption, and school type)	Greater or equal to 75% lifetime exposure was associated with significantly fewer DMFT in both cohorts. (*Partial*)
PHE (2014) England Ecological Acceptable	Children aged 12 years N = NR	• CWF (0.8 to 1.0 ppm) • Non-CWF (F level NR)	NR	MD = –0.19; 95% CI, –0.27 to –0.11; *P* < 0.001 (Adjustment for deprivation and ethnicity)	Mean of D3MFT[b] was significantly lower in fluoridated areas than non-fluoridated areas. (*Partial*)
Skinner et al. (2014) Australia Ecological Acceptable	Children aged 14 to 15 years N = 1,199	• CWF (F level NR) • Non-CWF (F level NR)	NR	MR = 0.58; 95% CI, 0.44 to 0.75 Non-CWF as ref (Adjustment for income, mother’s education level, sugary drink consumption, dental visit last year, age, and gender)	Mean DMFT was significantly lower in fluoridated areas than non-fluoridated areas. (*Partial*)
Haysom et al. (2015) Australia Ecological Acceptable	Participants aged 13 to 21 years N = 361	• CWF (F level NR) • Non-CWF (F level NR)	NR	MR = 1.77; 95% CI, 1.11 to 2.83 CWF as ref	Mean DMFT was significantly higher in non-fluoridated areas than fluoridated areas. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
				(Adjustment for Aboriginal status, age, gender, history out-of-home care, socio-economic disadvantage, remoteness, time incarcerated, snacks more than twice a week, preferred sweetened drinks, toothbrushing frequency, toothache or problems with teeth or gums, self-reported status of teeth, dental service previous year, and location of dental provider in the previous year)	
Evidence From Updated Literature Search: Two Ecological Studies and Three Cross-Sectional Studies					
Aggeborn and Öhman (2017)[76] Sweden Ecological Acceptable	Participants aged ≥ 16 years N = national population	NOF ≤ 1.5 ppm	NR	Dental repair (Tooth filled [FT]) Beta coefficient (SE) = –0.0583 (0.0155); *P* < 0.01 Expressed in 0.1 ppm fluoride (Adjustment for sex, marital status, parent's education, parent's income, father's cognitive and non-cognitive ability, parent immigrant, cohort mean education [at birth, at school start, at 16 years of age])	For dental repair, a tooth filled would decrease by approximately 0.6 percentage points if fluoride increased by 1 ppm. (*Partial*)
Kim et al. (2017)[78] South Korea Cross-sectional Low	Elementary schoolchildren aged 6, 8, and 11 years N = 1,411	• CWF (F level NR) • Non-CWF (F level NR)	Mean DMFT (SE) 6 years • CWF: 0.13 (0.03) • Non-CWF: 0.13 (0.04); *P* = 0.940	NR	Children aged 8 and 11 years in the CWF areas had significantly lower mean DMFT compared with those in the non-CWF areas. For children aged 6 years, there was no

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
			8 years • CWF: 0.15 (0.06) • Non-CWF: 0.56 (0.06); *P* < 0.001 11 years • CWF: 0.86 (0.10) • Non-CWF: 1.43 (0.10); *P* < 0.001 (Adjustment for sex, monthly family income, householder educational level, FAS score, and number of sealed teeth)		difference in mean DMFT in CWF versus non-CWF areas. (*Partial*)
Arrow (2016)[73] Australia Cross-sectional Acceptable	Children aged 6 to 15 years N = 8,377	• CWF (F level NR) • Non-CWF (F level NR)	Mean DMFT (95% CI) • CWF: 0.49 (0.46 to 0.52) • Non-CWF: 0.82 (0.67 to 0.96)	RR = 2.13; 95% CI,1.52 to 2.96; *P* < 0.001 CWF as ref (Adjustment for age, gender, sealants, Aboriginal identity, SES, interval between dental checkup, region, and inflammation)	Children living in the non-fluoridated areas had over 100% increase in permanent tooth decay compared with those living in the fluoridated areas. (*Partial*)
Crocombe et al. (2016)[77] Australia Ecological Low	Participants aged ≥ 15 years N = 3,770	• Capital cities (mean lifetime exposure = 59.1%) • Outside capital cities (mean lifetime exposure = 42.3%)	Mean DMFT • Capital: 12.9 • Outside: 14.3; *P* = 0.02	Beta coefficient • Capital: ref • Outside: 0.8; *P* = 0.01 (adjustment for age, income, education, time brushed, and access to dental care) Beta coefficient • Capital: ref • Outside: 0.6; *P* = 0.09	After adjustment sociodemographic characteristics, preventive dental behaviour, and access to dental care parameters, there was a significant positive relationship between caries experience (DMFT) and living outside capital city. (*Partial*) With additional adjustment of lifetime fluoride exposure,

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
				(Adjustment for age, income, education, time brushed, access to dental care, and lifetime fluoride exposure)	significant difference between regions was no longer observed for DMFT. (*Partial*)
Peres et al. (2016)[79] Brazil Cross-sectional Low	Adults aged 20 to 59 years N = 209	LAFW • > 75% • 50% to 75% • < 50%	NR	RR (95% CI) • > 75%: ref (1) • 50% to 75%: 1.11 (0.85 to 1.44) • < 50%: 1.39 (1.05 to 1.85) (Adjustment for sex, age, education, income, SES, pattern of dental attendance, and smoking)	Lowest LAFW (< 50%) had a significantly higher rate of DMFT compared with more than 75% lifetime water fluoridation exposure. (*Limited*)

CI = confidence interval; CWF = community water fluoridation; dmft = decayed, missing, or filled deciduous teeth; DMFT = decayed, missing, and filled permanent teeth; F = fluoride; FAS = Family Affluence Scale; LAFW = lifetime access to fluoridated water; MD = mean difference; MR = mean ratio; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; PHE = Public Health England; ppm = parts per million; QA = quality assessment; ref = reference; RR = rate ratio; SES = socio-economic status; SE = standard error; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] The “3” in D3MFT denotes obvious decay into dentine.

Mean Number of Decayed, Missing, and Filled Permanent Tooth Surfaces

Results for mean decayed, missing, and filled permanent tooth surfaces (DMFS) are presented in Table 6.

Evidence From the 2016 NHMRC Review

One SR assessed to be of low quality and four ecological studies (three assessed to be of acceptable quality and one of low quality) were identified.

The SR of Rugg-Gunn and Do (2012), which was rated as low quality, included 14 studies (no QA reported) and assessed the mean DMFS among participants aged 5 to 35 years. Non-pooled results showed that the median percentage of caries reduction in populations exposed to water fluoridation was 29% (values ranging from 0% to 50%) compared with those not exposed to water fluoridation.

The ecological study, which was rated to be of acceptable quality, by Do and Spencer (2015) compared mean DMFS among children aged 9 to 14 years in Queensland, Australia, who were exposed to CWF and non-CWF. After adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride tooth paste, age of first dental visit, sugar drink consumption, and school type, mean DMFS was significantly lower in children residing in fluoridated areas compared with those in the non-fluoridated areas (mean DMFS ratio = 0.63; 95% CI, 0.47 to 0.85).

The ecological study by Do et al. (2014), which was rated to be of acceptable quality, examined the mean DMFS among children aged 8 to 12 years in New South Wales, Australia. Exposure to water fluoridation from birth to three years of age was classified as 100%, > 0% to 99% and 0%. The study found that mean DMFS was significantly lower in children who had 100% lifetime exposure to fluoridated water compared with 0% exposure. After adjustment for household income, parental education, dietary fluoride supplement use, age and gender, the MR was 0.76 (95% CI, 0.62 to 0.94). However, the decrease in mean DMFS among children who had 0% to 99% lifetime exposure compared with 0% exposure did not reach statistical significance (MR = 0.84; 95% CI, 0.66 to 1.07).

The ecological study by Do et al. (2011), which was rated to be of low quality, studied the relationship between mean DMFS and drinking water fluoride level in schoolchildren aged six to 17 years in Vietnam. The children were divided into three groups based on water fluoride level: < 0.3 ppm, 0.3 ppm to 0.5 ppm, and > 0.5 ppm. After adjustment for household income parental education, dietary fluoride supplement use, age, and gender, there was a non-significant inverse relationship between mean DMFS and fluoride level in drinking water (beta coefficient = –0.34; *P* = 0.330).

The ecological study by Slade (2013), which was rated to be of acceptable quality, examined the relationship between lifetime exposure to fluoridated water (≥ 75% and < 25%) and mean decayed and filled permanent tooth surfaces (DFS) among participants aged ≥ 15 years in Australia. The participants were divided into two cohorts: born before 1960 (before fluoridation was widespread) and born between 1960 and 1990 (after fluoridation became more common). The study found that ≥ 75% LAFW was associated with fewer DFS in the pre-1960 cohort (beta coefficient = –11.10; 95% CI, –15.47 to –6.72) and in the 1960-1990 cohort (beta coefficient = –3.44; 95% CI, –5.28 to –1.60) when compared with those with < 25% lifetime exposure. Confounding variables that were adjusted for in the analyses were Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride toothpaste, age of first dental visit, sugary drink consumption, and school type.

Evidence From the Updated Literature Search

The updated literature search identified one ecological study, which was rated as of acceptable quality, by Do et al. (2017)[80] and two cross-sectional studies, which were rated as of low quality, by Kim et al. (2017)[78] and by Spencer et al. (2017).[81]

The ecological study of acceptable quality by Do et al. (2017)[80] examined the association between per cent LAFW and caries experience (measured as DMFS) within and across age groups of participants aged 15 to 91 years in Australia. Four age groups were set out: 15 to 34 years, 35 to 44 years, 45 to 54 years, and 55 years and older. Each age group was then divided into quartiles based on lifetime access to the equivalent of 1.0 ppm fluoride in drinking water. Results in Table 6 showed the comparison between the lowest and highest quartile. Compared with the lowest quartile, highest exposure to the fluoridated water in the young (15 to 34 years) and middle-aged adults (35 to 44 years) was associated with significantly lower mean DMFS. No association was found for those 45 to 54 years and 55 and older. Adjusted confounding variables were age, sex, residential location, dental visit pattern, toothbrushing frequency, household income, and oral hygiene.

The cross-sectional study of low quality by Kim et al. (2017)[78] investigated the association between CWF programs and dental caries prevention on permanent teeth in children aged 6, 8 and 11 years in South Korea. The study found that children aged 8 and 11 years in the CWF areas had significantly lower mean DMFS compared with those in the non-CWF areas (0.22 versus 0.79, *P* <0.001; and 1.31 versus 2.20, *P* < 0.001; respectively), after adjustment for sex, monthly family income, householder educational level, Family Affluence Scale score, and number of sealed teeth. Same results were obtained for pit-and-fissure DMFS and smooth surface DMFS. There was no significant difference in mean DMFS in children aged six in areas with and without CWF. In this study, children in both areas widely used fluoridated toothpaste.

The cross-sectional study of low quality by Spencer et al. (2017)[81] analyzed the preventive effect of access to fluoridated water on dental caries among young adults in South Australia. This was a follow-up substudy of a cohort of South Australian schoolchildren, who had been previously 5 to 17 years old, and were 20 to 35 years old at the follow-up. Participants were divided into three groups based on periods of access to fluoridated water; i.e., early in life (from birth to 1991), across maturation to young adulthood (1991 to 2006), and full lifetime (from birth to 2006). Within each group, exposure to fluoridated water was classified as 100% LAFW, 75% to 99% LAFW, and 0 to 74% LAFW. When age, sex, parents' education, education of self as a young adult, and toothbrushing as a child and as a young adult were adjusted in the negative binomial regression model, among those who had full-time access to water fluoridation (i.e., birth to 2006), the lowest exposure to fluoridated water (i.e., 0% to 74% LAFW) showed a significantly higher DMFS count compared with 100% LAFW (RR = 1.26; 95% CI, 1.01 to 1.57).

Summary

One SR rated to be of low quality and four ecological studies rated to be of acceptable quality identified by the 2016 NHMRC review showed that mean DMFS or DFS count was lower in children and adults living in fluoridated areas compared with those in non-fluoridated areas. The updated literature search identified three additional studies; one ecological study rated to be of acceptable quality and two cross-sectional studies rated to be of low quality. All three studies showed that exposure to water fluoridation was associated with a lower DMFS count within certain age groups. Likely confounding variables were adjusted in all analyses. All primary studies, except one by Do et al. (2011) conducted in Vietnam, were assessed to be partially applicable to the Canadian context. Overall, there was consistent evidence that water fluoridation reduced caries in permanent teeth (measured using DMFS) in both children and younger adults.

Table 6: Mean Decayed, Missing, and Filled Permanent Tooth Surfaces

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One SR and Four Ecological Studies					
Rugg-Gunn and Do (2012) Australia; UK SR Low	Participants aged 5 to 35 years 14 studies (No QA) N = NR	• CWF (F level NR) • Non-CWF (F level NR)	Median % reduction (range) = 29% (0 to 50)	NR	Mean DMFS was lower in fluoridated areas than in the non-fluoridated areas.
Do and Spencer (2015) Australia Ecological Acceptable	Children aged 9 to 14 years N = 3,186	• CWF (F level NR) • Non-CWF (F level NR)	Mean DMFS (95% CI) CWF: 0.82 (0.65 to 0.99) Non-CWF: 1.51 (1.31 to 1.71)	MR = 0.63;95% CI, 0.47 to 0.85 Non-CWF as ref (Adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride tooth paste, age of first dental visit, sugar drink consumption, and school type)	Mean DMFS was significantly lower in fluoridated areas than in the non-fluoridated areas. (*Partial*)
Do et al. (2014) Australia Ecological Acceptable	Children aged 8 to 12 years N = 2,611	Lifetime exposure to fluoridated water • 100% • > 0% to 99% • 0%	Mean DMFS (SE) • 100%: 0.59 (0.04) • > 0% to 99%: 0.63 (0.09) • 0%: 0.91 (0.1)	MR (95% CI) • 100%: 0.76 (0.62 to 0.94) • > 0% to 99%: 0.84 (0.66 to 1.07) 0% exposure as ref (Adjustment for household income, parental education, dietary fluoride supplement use, age, and gender)	Mean DMFS was significantly lower in children who had 100% lifetime exposure to fluoridated water compared with 0% exposure. (*Partial*)
Do et al. (2011) Vietnam	Children aged 6 to 17 years	NOF in water: • > 0.5 ppm	NR	Beta coefficient = –0.34; *P* = 0.330	There was a non-significant inverse relationship between

Study Country Design Quality	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
Ecological Low	N = 2,748	• 0.3 ppm to 0.5 ppm • < 0.3 ppm		(Adjustment for household income parental education, dietary fluoride supplement use, age, and gender)	mean DMFS and fluoride level in drinking water. (*Limited*)
Slade (2013) Australia Ecological Acceptable	Participants aged ≥ 15 years N = 3,779 Two cohorts: • Pre-1960: N = 2,270 • 1960 to 1990: N = 1,509	Lifetime exposure to fluoridated water • ≥ 75% • < 25%	NR	Beta coefficient (95% CI) • Pre-1960 cohort: –11.10 (–15.47 to –6.72) • 1960 to 1990 cohort: –3.44 (–5.28 to –1.60) < 25% exposure as ref (Adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride toothpaste, age of first dental visit, sugary drink consumption, and school type)	Greater or equal to 75% lifetime exposure was associated with significantly fewer DFS in both cohorts. (*Partial*)
Evidence From Updated Literature Search: One Ecological Study and Two Cross-Sectional Studies					
Do et al. (2017)[80] Australia Ecological Acceptable	Data of individuals aged 15 to 91 years from the Australian National Survey of Adult Oral Health 2004-2006 N = 4,090	% LAFW (life time access to the equivalent of 1.0 ppm fluoride in drinking water) 15 to 34 years • 0% to 20% • 100% 35 to 44 years • 0% to <26%	NR	MR (95% CI) 15 to 34 years • 0% to 20%: ref • 100%: 0.67 (0.48 to 0.92) 35 to 44 years • 0% to < 26%: ref • 100%: 0.78 (0.66 to 0.93)	Water fluoridation was significantly associated with lower caries experience (measured as DMFS) in young and middle-aged adults. No association was found for those 45 to 54 years and 55 years and older. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
		- 100% 45 to 54 years - 0% to <34% - 78% to 89% 55+ years - 0% to <23% - 61% to 73%		45 to 54 years - 0% to < 34%: ref - 78% to 89%: 0.93 (0.82 to 1.04) 55+ years - 0% to < 23%: ref - 61% to 73%: 1.00 (0.93 to 1.08) (Adjustment for age, sex, residential location, dental visit pattern, toothbrushing frequency, household income, and oral hygiene)	
Kim et al. (2017)[78] South Korea Cross-sectional Low	Elementary schoolchildren aged 6, 8, and 11 years old N = 1,411	- CWF (F level NR) - Non-CWF (F level NR)	Mean DMFS (SE) 6 years - CWF: 0.19 (0.05) - Non-CWF: 0.16 (0.06); *P* = 0.769 8 years - CWF: 0.22 (0.08) - Non-CWF: 0.79 (0.09); *P* < 0.001 11 years - CWF: 1.31 (0.17) - Non-CWF: 2.20 (0.17); *P* < 0.001 (Adjustment for sex, monthly family income, householder	NR	Children aged 8 and 11 years in the CWF areas had significantly lower mean DMFS compared with those in the non-CWF areas. The same results were obtained for pit-and-fissure DMFS and smooth surface DMFS. There was no significant difference in mean DMFS in children aged 6 in areas with and without CWF. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
			educational level, FAS score, and number of sealed teeth)		
Spencer et al. (2017)[81] Australia Cross-sectional Low	Follow-up sub-studies of a cohort of South Australian schoolchildren who had previously been aged 5 to 17 years. Those retained at the follow-up were aged 20 to 35 years N = 1,220	% LAFW • 0% to 74% • 75% to 99% • 100% Three periods of access to fluoridated water • Birth to 1991 (early in life) • 1991 to 2006 (across maturation to young adulthood) • Birth to 2006 (full lifetime)	NR	RR (95% CI) % LAFW (Birth to 1991) • 0% to 74%: 1.20 (0.99 to 1.45) • 75% to 99%: 0.96 (0.67 to 1.32) • 100%: ref % LAFW (1991 to 2006) • 0% to 74%: 1.22 (0.93 to 1.54) • 75% to 99%: 0.85 (0.60 to 1.19) • 100%: ref % LAFW (Birth to 2006) • 0% to 74%: 1.26 (1.01 to 1.57) • 75% to 99%: 1.06 (0.85 to 1.32) • 100%: ref (Adjustment for age, sex, parents' education, education of self as a young adult, toothbrushing as a child and as a young adult)	In adjusted model, only the lowest access to fluoridated water (0% to 74% LAFW) in full lifetime access to water fluoridation (birth to 2006) showed significantly higher count of DMFS than 100% LAFW. No association was found for LAFW between 75% and 99%. (*Partial*)

CI = confidence interval; CWF = community water fluoridation; DFS = decayed and filled permanent tooth surfaces; DMFS = decayed, missing, and filled permanent tooth surfaces; F = fluoride; FAS = family affluence scale; LAFW = lifetime access to fluoridated water; MR = mean ratio; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; ppm = parts per million; QA = quality assessment; ref = reference; RR = rate ratio; SE = standard error; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Caries Prevalence and Proportions of Caries-Free of Permanent Teeth

Results for dental caries prevalence and proportion of caries-free of permanent teeth are presented in Table 7.

Evidence From the 2016 NHMRC Review

One SR assessed to be of high quality and 10 ecological studies (seven assessed to be of acceptable quality and three of low quality) were identified.

The SR by Iheozor-Ejiofor et al. (2015), which was rated as high quality, included nine studies at high risk of bias. Pooled analysis showed that water fluoridation was associated with an increase of 14.0% (95% CI, 5% to 23%) in the proportion of caries-free of permanent teeth in children aged 5 to 17 years, as compared with no water fluoridation.

The ecological study of acceptable quality by Lee and Han (2015) studied the dental caries prevalence among children aged eight, ten, and 12 years, who participated in the South Korean Oral Health Survey in 2003, 2006, and 2010. After adjustment for gender, fluoride sealant, and region, the study found no significant differences in dental caries prevalence between CWF and non-CWF in all three surveys.

The ecological study of acceptable quality conducted by PHE (2014) investigated the effect of fluoridation on the prevalence of dental caries (measured as D3MFT; “3” denotes obvious decay into dentine) in 12-year-old children. After adjustment for deprivation and ethnicity, caries prevalence in permanent teeth was significantly lower in fluoridated areas than non-fluoridated areas (% difference in odds = –21%; 95% CI, –29 to –12).

The ecological study of acceptable quality by Skinner et al. (2014) compared caries prevalence in permanent teeth among children aged 14 to 15 years living in CWF and non-CWF areas. After adjustment for household income, mother’s education level, sugary drink consumption, dental visit last year, and toothbrushing frequency, the study found that the odds of having any caries in the fluoridated areas was significantly less than in the non-fluoridated areas (OR = 0.59; 95% CI, 0.37 to 0.94).

The ecological study of acceptable quality by Freire et al. (2013) examined caries prevalence among children aged 12 years in the Brazilian Oral Health Survey 2010. After adjustment for gender, skin colour, household income, residences connected to water supply, and median income municipality, the study found that caries prevalence in permanent teeth was significantly lower among children living in the fluoridated areas than in the non-fluoridated areas (prevalence ratio = 0.90; 95% CI, 0.83 to 0.97).

The ecological study of acceptable quality by Haysom et al. (2015) studied caries prevalence among participants aged 13 to 21 years who were in custody in juvenile justice centres in New South Wales, Australia. After adjustment for Aboriginal status, age, gender, history out-of-home care, socio-economic disadvantage, remoteness, time incarcerated, snacks more than twice a week, preferred sweetened drinks, toothbrushing frequency, toothache or problems with teeth or gums, self-reported status of teeth, dental service previous year, and location of dental provider in the previous year, it was found that participants who were exposed to CWF had significantly lower odds of having any caries compared with those not exposed to CWF (OR = 0.30; 95% CI, 0.10 to 0.86).

The ecological study of low quality by McGrady et al. (2012) included children aged 11 to 13 years living in two cities (one had and one did not have a fluoridated water supply) in the

UK. After adjustment for age at examination and index of multiple deprivation (IMD), prevalence of dental caries (measured as %D4-6MFT [lesions extended into dentine] > 0) was significantly lower in the city with a fluoridated water supply (OR = 0.54; 95% CI, 0.43 to 0.67) compared with the city without fluoridated water.

The ecological study of low quality conducted by the Centres for Disease Control and Prevention (2011) investigated the caries prevalence of children aged 6 to 15 years living in the CWF villages and non-CWF villages in Alaska. Compared with non-fluoridated areas, caries prevalence of permanent teeth was significantly lower in fluoridated areas (OR = 0.6; 95% CI, 0.5 to 0.7), after adjustment for soda drink consumption and frequency of toothbrushing.

The ecological study of acceptable quality by Do et al. (2014) examined caries prevalence in children aged 8 to 12 years in New South Wales, Australia, who had lifetime exposure to fluoridated water of various degrees; i.e., 100%, > 0% to 99%, and 0%. The study found no significant decrease in caries prevalence associated with water fluoridation, after adjustment for household income, parental education, dietary fluoride supplement use, age, and gender. The prevalence ratios (95% CI) were 0.84 (0.67 to 1.07) and 0.81 (0.62 to 1.06) for 100% and 0 to 99% lifetime exposure, respectively, compared with 0% lifetime exposure.

The ecological study of acceptable quality by Do et al. (2015) compared caries prevalence among children aged 9 to 14 years in Queensland, Australia, living in CWF and non-CWF areas. The study found that children living in non-CWF areas had significantly higher caries prevalence compared with CWF areas (prevalence ratio = 1.49; 95% CI,1.01 to 2.21), after adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age of first use of fluoride toothpaste, age of first dental visit, sugary drink consumption, and school type.

The ecological study of low quality by Da Silva et al. (2015) studied the relationship between water fluoridation and proportion of caries-free permanent teeth among children aged 12 years in Brazil. After adjusting for economic deprivation and sociosanitary (a composite measure incorporating rates of urbanization, proper sanitation, and illiteracy), no association between exposure to water fluoridation and caries-free permanent teeth was found (beta coefficient = 6.750; 95% CI, –1.131 to 14.63; *P* = 0.09).

Evidence From the Updated Literature Search

The updated literature search identified two additional ecological studies[75,82] both assessed to be of low quality, reporting the prevalence of dental caries in permanent teeth.

The ecological study low quality by Aguiar et al. (2017)[82] examined the effect of CWF and non-CWF on the prevalence of different components of caries experience (decayed teeth ≥ 1, missing teeth ≥ 1, and filled teeth ≥ 1 teeth) among participants aged 15 to 19 years in Brazil. After adjustment for age, gender, equivalent household income, time since last dental visit (years), interviewee’s education (years of schooling), per capita gross domestic product, and population size, the study found that the odds of decayed (OR = 1.42; 95% CI, 1.08 to 1.86) and missing teeth (OR = 1.57; 95% CI, 1.16 to 2.14) were significantly higher in non-CWF compared with CWF areas but were not for filled teeth (OR = 0.85; 95% CI, 0.64 to 1.13).

The ecological study of low quality by Crouchley and Trevithick (2016)[75] included children aged 6 to 12 years in fluoridated and non-fluoridated areas in Australia. Caries prevalence in children of all age groups (6 to 12 years) was less in CWF areas than non-CWF areas. After adjustment for age, sex, Aboriginal status, and having a record of an initial examination at a dental treatment centre, the study found that children living in non-CWF areas had 1.6 times the odds of having one or more DMFT compared with those living in CWF areas (OR = 1.62; 95% C1, 1.33 to 1.98; $P < 0.001$).

Summary

Of the 10 ecological studies (eight assessed to be of acceptable quality and two of low quality) identified by the 2016 NHMRC, seven showed a significant decrease in caries prevalence in permanent teeth associated with water fluoridation in children, after adjustment for various confounding variables. Three studies did not show a significant decrease in caries prevalence in permanent teeth among children living in CWF areas. The updated literature search identified two additional ecological studies of low quality, which showed a significant increase in caries prevalence in permanent teeth associated with non-CWF in children and adolescents. The findings of 10 out of 12 primary studies were assessed to be partially applicable to the Canadian context, while two were assessed to be of limited applicability. Overall, there was consistent evidence that water fluoridation at the current Canadian levels reduced caries prevalence and increased the proportion of caries-free permanent teeth in children and adolescents.

Table 7: Dental Caries Prevalence and Proportion of Caries-Free of Permanent Teeth

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One SR and 10 Ecological Studies					
Iheozor-Ejiofor et al. (2015) UK; Canada SR High	Children aged 5 to 17 years 9 studies (high risk of bias) N = 63,538	• CWF (≥ 0.4 ppm) • Non-CWF (< 0.4 ppm)	Proportion of caries-free in non-CWF ranged from 0.01 ppm to 0.67 (median 0.14)	MD = 0.14; 95% CI, 0.05 to 0.23	The proportion of caries-free children for permanent dentition was significantly higher in the fluoridated areas than non-fluoridated areas.
Lee and Han (2015) South Korea Ecological Acceptable	Children aged 8, 10, and 12 years N = 23,059	• CWF (F level NR) • Non-CWF (F level NR)	NR	Caries prevalence OR (95% CI) 2003 • 8 years: 1.30 (0.81 to 2.11) • 10 years: 0.92 (0.57 to 1.50) • 12 years: 0.74 (0.42 to 1.30) 2006 • 8 years: 1.41 (0.47 to 4.25) • 10 years: 1.18 (0.64 to 2.20) • 12 years: 0.87 (0.44 to 1.74) 2010 • 8 years: 0.80 (0.57 to 1.14) • 10 years: 1.04 (0.70 to 1.54) • 12 years: 0.92 (0.69 to 1.22) Non-CWF as ref (Adjustment for gender, fluoride sealant, and region)	No significant differences in dental caries prevalence between CWF and no CWF in 2003, 2006, and 2010 survey. (*Partial*)
PHE (2014) England Ecological Acceptable	Children aged 12 years N = NR	• CWF (0.8 ppm to 1.0 ppm) • Non-CWF (F level NR)	NR	% difference in odds –21%; 95% CI, –29% to –12%	Caries prevalence in permanent teeth was significantly lower in fluoridated areas than non-

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings** **(*Applicability*[a])**
				(Adjustment for deprivation and ethnicity)	fluoridated areas. (*Partial*)
Skinner et al. (2014) Australia Ecological Acceptable	Children aged 14 to 15 years N = 1,199	• CWF (F level NR) • Non-CWF (F level NR)	NR	Caries prevalence OR = 0.59; 95% CI, 0.37 to 0.94 Non-CWF as ref (Adjustment for income, mother's education level, sugary drink consumption, dental visit last year, and brushing frequency)	The odds of having any caries in the fluoridated areas were significantly less than in the non-fluoridated areas. (*Partial*)
Freire et al. (2013) Brazil Ecological Acceptable	Children aged 12 years N = 7,247	• CWF (F level NR) • Non-CWF (F level NR)	Caries prevalence • CWF: 53.9% • Non-CWF: 67.8%	PR = 0.90; 95% CI, 0.83 to 0.97 Non-CWF as ref (Adjustment for gender, skin colour, household income, residences connected to water supply, and median income municipality)	Caries prevalence in permanent teeth was significantly lower among children living in the fluoridated areas than in the non-fluoridated areas. (*Partial*)
Haysom et al. (2015) Australia Ecological Acceptable	Participants aged 13 to 21 years N = 294	• CWF (F level NR) • Non-CWF (F level NR)	NR	Caries prevalence OR = 0.30; 95% CI, 0.10 to 0.86 Non-CWF as ref (Adjustment for Aboriginal status, age, gender, history out-of-home care, socio-economic disadvantage, remoteness, time incarcerated, snacks more than twice a week, preferred sweetened drinks, toothbrushing frequency, toothache or problems with teeth or gums, self-reported	The odds of having any caries in the fluoridated areas were significantly less than in the non-fluoridated areas. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
				status of teeth, dental service previous year, and location of dental provider in the previous year)	
McGrady et al. (2012) UK Ecological Low	Children aged 11 to 13 years N = 1,783	• CWF (1 ppm) • Non-CWF (F level NR)	NR	Caries prevalence OR = 0.54; 95% CI, 0.43 to 0.67 Non-CWF as ref (Adjustment for age at examination and index of multiple deprivation)	The odds of having any caries in the fluoridated areas were significantly less than in the non-fluoridated areas. (*Partial*)
CDC (2011) USA Ecological Low	Children aged 6 to 15 years N = 348 (whole population 4 to 15 years)	• CWF (F level NR) • Non-CWF (F level NR)	Caries prevalence CWF • 4 to 5 years: 0% • 6 to 8 years: 31% • 9 to 11 years: 65% • 12 to 15 years: 91% Non-CWF • 4 to 5 years: 0% • 6 to 8 years: 57% • 9 to 11 years: 86% • 12 to 15 years: 91%	OR = 0.6; 95% CI, 0.5 to 0.7 Non-CWF as ref (Adjustment for soda pop consumption and frequency of toothbrushing)	Caries prevalence in permanent teeth was significantly reduced in fluoridated areas than non-fluoridated areas. (*Partial*)
Do et al. (2014) Australia Ecological Acceptable	Children aged 8 to 12 years N = 1,984	Lifetime exposure to fluoridated water • 100% • > 0% to 99% • 0%	Caries prevalence (SE) • 100%: 22.6% (1.2) • > 0% to 99%: 22.6% (2.0) • 0%: 28.0% (2.3)	PR (95% CI) • 100%: 0.84 (0.67 to 1.07) • > 0% to 99%: 0.81 (0.62 to 1.06) 0% exposure as ref	No significant decrease in caries prevalence associated with water fluoridation. (*Partial*)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
				(Adjustment for household income, parental education, dietary fluoride supplement use, age, and gender)	
Do et al. (2015) Australia Ecological Acceptable	Children aged 9 to 14 years N = 3,186	• CWF (F level NR) • Non-CWF (F level NR)	Caries prevalence (95% CI) • CWF: 29.4% (26.1 to 32.9) • Non-CWF: 39.3% (36.4 to 42.3)	PR = 1.49; 95% CI,1.01 to 2.21 CWF as ref (Adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age first use fluoride toothpaste, age of first dental visit, sugar drink consumption, and school type)	Children living in non-CWF areas had significantly higher caries prevalence compared with CWF areas. (*Partial*)
Da Silva et al. (2015) Brazil Ecological Low	Children aged 12 years N = NR	Fluoridated water supply (F level NR)	NR	Beta coefficient = 6.750; 95% CI, –1.131 to 14.63; *P* = 0.09 (Adjustment for economic deprivation and sociosanitary [a composite measure incorporating rates of urbanization, proper sanitation, and illiteracy])	Exposure to water fluoridation was associated with a non-significant increase in proportion of caries-free in permanent teeth. (*Limited*)
Evidence From the Updated Literature Search: Two Ecological Studies					
Aguiar et al. (2017)[82] Brazil Ecological Low	Children aged 12 years and 15 to 19 years N = 10,124	• CWF (F level NR) • Non-CWF (F level NR)	Prevalence of decay (DT ≥ 1) teeth • CWF: 43.9%; *P* < 0.01 • Non-CWF: 66.5% Prevalence of missing (MT ≥ 1) teeth • CWF: 13.3%; *P* < 0.01 • Non-CWF: 25.8%	OR (95% CI) for non-CWF DT ≥ 1: 1.42 (1.08 to 1.86) MT ≥ 1: 1.57 (1.16 to 2.14) FT ≥ 1: 0.85 (0.64 to 1.13) CWF as ref	The odds of decayed and missing teeth were significantly higher in non-CWF than CWF. (*Limited*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(*Applicability*[a])</th></tr>
<tr><td></td><td></td><td></td><td>Prevalence of filled (FT ≥ 1) teeth
• CWF: 48.7%; *P* < 0.01
• Non-CWF: 40.1%</td><td>(Adjustment for age, gender, equivalent household income, time since last dental visit [years], interviewee’s education [years of schooling], per capita gross domestic product, and population size)</td><td></td></tr>
<tr><td>Crouchley and Trevithick (2016)[75]
Australia
Ecological
Low</td><td>Children aged 6 to 12 years
N = 8,962</td><td>• CWF (F level NR)
• Non-CWF (F level NR)</td><td>Caries prevalence
<table>
<tr><th>Age</th><th>CWF</th><th>Non-CWF</th></tr>
<tr><td>6</td><td>2.9%</td><td>7.3%</td></tr>
<tr><td>7</td><td>8.1%</td><td>10.0%</td></tr>
<tr><td>8</td><td>12.6%</td><td>17.6%</td></tr>
<tr><td>9</td><td>14.9%</td><td>22.1%</td></tr>
<tr><td>10 to 11</td><td>22.9%</td><td>32.6%</td></tr>
<tr><td>11 to 12</td><td>28.6%</td><td>39.3%</td></tr>
</table></td><td>OR = 1.62; 95% CI, 1.33 to 1.98; *P* < 0.001

CWF as ref

(Adjustment for age, sex, Aboriginal status, and having a record of an initial examination at a dental treatment centre)</td><td>Children living in non-CWF areas had 1.6 times the odds of having one or more DMFT compared with those living in CWF areas. (*Partial*)</td></tr>
</table>

CDC = Centers for Disease Control and Prevention; CI = confidence interval; CWF = community water fluoridation; DMFT = decayed, missing, and filled permanent teeth; DT = decayed teeth; F = fluoride; MD = mean difference; MT = missing teeth; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; PHE = Public Health England; ppm = parts per million; PR = prevalence ratio; ref = reference; SE = standard error; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Incidence of Dental Caries in Permanent Teeth

Results for caries incidence of permanent teeth are presented in Table 8.

Evidence From the 2016 NHMRC Review

One cohort study assessed to be of acceptable quality was identified.

The cohort study by Broffitt (2013) assessed the first molar occlusal caries incidence in children aged 9 to 13 years who participated in the Iowa Fluoride Study in the US. Children were exposed to home tap water fluoride levels ranging from 0.03 ppm to 5.41 ppm, with a median level of 0.97 ppm and mean level of 0.82 ppm. After adjustment for confounding variables, the study found no association between the incidence of first molar occlusion caries and exposure to fluoride in drinking water.

Evidence From the Updated Literature Search

No additional studies were identified.

Summary

The NHMRC 2016 review identified one cohort study assessed to be of acceptable quality, which showed a non-association between the incidence of first molar occlusion caries and exposure to fluoride in drinking water. Confounding variables were adjusted for within the study. The findings were assessed to be partially applicable to the Canadian context. The updated literature search did not identify any additional studies; thus, there was insufficient evidence to draw a conclusion about an association between water fluoridation and the decrease in caries incidence of permanent teeth in children.

Table 8: Incidence of Dental Caries in Permanent Teeth

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Cohort Study					
Broffitt (2013) USA Cohort Acceptable	Children aged 9 to 13 years N = 523	Tap water fluoride level Mean: 0.82 ppm Median: 0.97 ppm Range: 0.03 ppm to 5.41 ppm	NR	OR = 0.32; 95% CI, 0.10 to 1.02; *P* = 0.056 (Adjustment for D2+FS > 0 at 9 years [vs. none], D1 score at 9 years [vs. none], brushing frequency (AUC, age 9 to 13), D1 x brushing frequency interaction, low income and low income x fluoride level interaction)	No association was found between the incidence of first molar occlusion caries[b] and exposure to fluoride in drinking water. (*Partial*)
Evidence From the Updated Literature Search: No Studies Identified					

AUC = area under curve; CI = confidence interval; ppm = parts per million; NHMRC = National Health and Medical Research Council; OR = odds ratio; vs. = versus.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] Defined as progression to cavitated lesion (D2 + S) or filled (D2 + FS).

Combined Measures of Caries in Mixed Dentition (Mean dmft/DMFT)

Results for combined measures of caries in mixed dentition are presented in Table 9.

Evidence From the 2016 NHMRC Review

One previous SR and three primary studies (two ecological studies and one prospective cohort study) assessed to be of acceptable quality reported combined caries measures.

The previous SR by McDonagh et al. (2000) included nine studies (no QA reported) assessing the combined dmft and DMFT among children aged 5 to 14 years in fluoridated areas versus low fluoride areas. The review found that the MD in the proportion (%) of caries-free children ranged from 5.0% to 64% with a median of 14.6% (interquartile ranges from 5.05% to 22.1%). Nineteen of 30 analyses reached statistical significance in favour of water fluoridation. Ten analyses found no association between caries prevalence and water fluoridation, and one analysis found a statistical significance in favour of non-fluoridated water.

The ecological study of acceptable quality in Australia by Zander et al. (2013) studied caries prevalence of combined deciduous and permanent teeth among children aged 3 to 12 years living in fluoridated and non-fluoridated areas. The study found that fluoridation was not associated with a reduction in caries prevalence, measured using composite dmft and DMFT (OR = 0.81; 95% CI, 0.46 to 1.43), after adjustment for Aboriginal status, age, gender, concession card status, parent education level, and toothbrushing frequency.

The ecological study of acceptable quality in Canada by McLaren and Emery (2012) examined the association between exposure to water fluoridation and the number of dmft/DMFT in children aged 6 to 11 years. After adjustment for socio-economic, sugary drink consumption, toothbrushing or flossing frequency, place of birth, and dental visits, no association was found between water fluoridation and mean dmft/DMFT counts (beta coefficient = –0.49; 95% CI, –1.0 to 0.03; $P < 0.10$).

The prospective cohort study of acceptable quality in the US by Chankanka et al. (2011) examined the association between water fluoridation and the incidence of non-cavitated and cavitated caries of mixed dentition in children aged 5, 9, and 15 years. A composite water fluoride level was determined as the weighted average of the water source (i.e., home or school; bottle, filtered, or tap water). No association was found between composite water fluoride level and the incidence of non-cavitated (beta coefficient = –0.28; $P = 0.34$) and cavitated caries (beta coefficient = –0.18; $P = 0.57$), after adjustment for gender, SES, and toothbrushing frequency.

Evidence From the Updated Literature Search

No additional studies were identified.

Summary

The NHMRC 2016 review reported the findings of the McDonagh 2000 review, which found mixed results for the effect of water fluoridation on the proportion of caries-free children when measured using composite dmft and DMFT. Three primary studies (two ecological and one cohort) assessed to be of acceptable quality identified by the 2016 NHMRC review showed no association between water fluoridation and caries prevalence of mixed dentition in children. Confounding variables were adjusted in the analyses of all three studies. The findings of one primary study conducted in Canada were assessed to be highly applicable to the Canadian context, while the other two were assessed to be of partial applicability. The updated literature search did not identify additional studies. There are major limitations of using the composite measure dmft and DMFT as the scores are dependent on the number of deciduous teeth remaining and the number of permanent teeth erupted; newly erupted permanent teeth have no caries, thereby lowering the combined score. Overall, there was insufficient evidence to draw a conclusion about the association between water fluoridation and the reduction in dental caries in mixed dentition.

Table 9: Combined Caries Measures (dmft/DMFT)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
Evidence From the 2016 NHMRC Review: One Previous SR and Three Studies (Two Ecological Studies and One Prospective Cohort Study)					
McDonagh et al. (2000) UK Previous SR	Children aged 5 to 14 years 9 studies (no QA) N = NR	Fluoridated areas Control (low fluoride areas)	NR	Proportion of caries-free MD = –5.0% to 64% Median = 14.6% IQR = 5.05% to 22.1% 19 of 30 analyses reached statistical significance in favour of water fluoridation. Ten analyses found no association between caries prevalence and water fluoridation, and one analysis found a statistical significance in favour of non-fluoridated water	Mixed evidence for the effect of water fluoridation on the proportion of caries-free children when measured using composite dmft and DMFT.
Zander et al. (2013) Australia Ecological Acceptable	Children 3 to 12 years N = 434	• CWF (F level NR) • Non-CWF (F level NR)	NR	Caries prevalence OR = 0.81; 95% CI, 0.46 to 1.43 (Adjusted for Aboriginal status, age, gender, concession card status, parent education level, and toothbrushing frequency)	Fluoridation was not associated with a reduction in caries prevalence when measured using composite dmft and DMFT. (*Partial*)
McLaren and Emery (2012) Canada Ecological Acceptable	Children 6 to 11 years N = 1,081	• CWF (F level NR) • Non-CWF (F level NR)	NR	Mean dmft/DMFT Beta coefficient = –0.49; 95% CI, –1.0 to 0.03; $P < 0.10$ (Adjusted for socio-economic, sugary drink consumption, toothbrushing or flossing frequency, place of birth, and dental visits)	Fluoridation was not associated with change in mean dmft/DMFT counts. (*High*)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
Chankanka et al. (2011) USA Prospective cohort Acceptable	Children 5, 9, and 15 years N = 156	Composite water fluoride level determined as weighted average of water source (i.e., home or school; bottle, filtered, or tap water)	NR	New non-cavitated caries Beta coefficient = –0.28; *P* = 0.34 New cavitated caries Beta coefficient = –0.18; *P* = 0.57 (Adjusted for gender, SES, and toothbrushing frequency)	Composite water fluoride level was not related to the incidence of non-cavitated caries and cavitated caries. (*Partial*)
Evidence From the Updated Literature Search: No Studies Identified					

CI = confidence interval; CWF = community water fluoridation; dmft = decayed, missing, and filled deciduous teeth; DMFT = decayed, missing, and filled permanent teeth; F = fluoride; IQR = interquartile range; MD = mean difference; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; QA = quality assessment; SES = socio-economic status; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Disparities

In this report, disparities in dental outcomes were examined from studies that reported the differences in dental caries between levels of socio-economic status, levels of deprivation, and Indigenous status. Results for disparities are presented in Table 10.

Evidence From the 2016 NHMRC Review

One previous SR, three ecological studies (two assessed to be of low quality and one of acceptable quality), and one retrospective cohort study, assessed to be of acceptable quality, were identified.

The previous SR by McDonagh et al. (2000) included 15 studies (three before-and-after studies and 12 cross-sectional studies, no QA reported) that assessed the disparities of the effect of water fluoridation on dental caries in children aged 5 to 16 years across social classes. The review found that the proportion of caries-free individuals across social classes was higher in fluoridated areas compared with non-fluoridated areas. However, the absolute difference in the proportion of caries-free individuals between the highest social class and lowest social class in the fluoridated areas was similar to that in the non-fluoridated areas. For dmft or DMFT, caries experience across social classes was higher in non-fluoridated areas compared with fluoridated areas. However, the absolute difference in mean dmft/DMFT between the highest social class and the lowest social class in the fluoridated areas was lower compared with that in the non-fluoridated areas. Thus, it appeared that water fluoridation did not reduce the disparity in the proportion of caries-free individuals, but reduced the disparity in dmft/DMFT between social classes.

The ecological study of low quality by Lalloo et al. (2015) examined the effect of CWF on the disparity of dental caries experience among non-Indigenous and Indigenous children aged 5 to 10 years (for deciduous teeth) and 6 to 15 years (for permanent teeth) in Australia. The study found that both non-Indigenous and Indigenous children in the CWF areas had a higher proportion of caries-free for deciduous and permanent teeth compared with those in the non-CWF areas. However, the absolute difference in the proportion of caries-free for deciduous teeth between non-Indigenous and Indigenous children 5 to 10 years old was 25.2% in the fluoridated areas (≥ 0.5 ppm) and 13.4% in the non-fluoridated areas (< 0.3 ppm). The absolute difference in the proportion of caries-free for permanent teeth between non-Indigenous and Indigenous children 6 to 15 years old was 20.4% in the fluoridated areas (≥ 0.5 ppm) and 9.5% in the non-fluoridated areas (< 0.3 ppm). Thus, it was concluded that water fluoridation did not reduce the gap in dental caries experience (measured using proportion of caries-free) between Indigenous and non-Indigenous children.

The ecological study of low quality by McGrady et al. (2012) included children aged 11 to 13 years from two areas in the UK, one with a fluoridated water supply and one without a fluoridated water supply. The study found that the absolute difference in the mean D_{4-6}MFT between the most and least deprived groups was 0.54 in the fluoridated water supply area and 0.97 in the non-fluoridated water supply area. It was, therefore, concluded that water fluoridation reduced the disparity in caries experience (measured using DMFT) between social classes.

The ecological study of acceptable quality conducted by the PHE (2014) investigated the effect of CWF on the disparities of dental caries in children aged 1 to 4, 5, and 12 years. The study found that water fluoridation had a stronger effect on reducing dental caries experiences in deciduous teeth (measured as mean d3mft [–0.51 versus –0.16], dental caries prevalence [–32% versus –17%], or hospital admissions for caries [–76% versus –27%]) in 1- to 4- and 5-year-old children, and dental caries experience in permanent teeth (measured as mean D3MFT [–0.25 versus –0.07] or dental caries prevalence [–26% versus –9%]) in 12 years old children in the most deprived quintile compared with the combined four least deprived quintiles.

The retrospective cohort study of acceptable quality by Neidell et al. (2010) studied the effect of exposure to CWF at birth on tooth loss among adults in the US of different SES. The study suggested that the impact of CWF exposure on reducing tooth loss was larger for adults of lower SES compared with those of higher SES characterized by race and education. The beta coefficients for tooth loss among black individuals, high school dropouts, and high school graduates exposed to CWF at birth were –0.37, –0.61, and –0.39, respectively, compared with –0.19 and –0.006 among white individuals and college graduates, respectively.

Evidence From the Updated Literature Search

The updated literature search identified four additional studies (one cross-sectional study assessed to be of acceptable quality and three ecological studies assessed to be of low quality).

The ecological study conducted by the PHE (2018) and assessed to be of acceptable quality determined the association between concentration of fluoride in public water supply in England and the change in disparity in dental caries among children aged five years for prevalence of d3mft > 0, and individuals aged 0 to 19 years for hospital admissions for caries-related dental extractions across levels of deprivation. When stratified by fluoride levels, the study found that the odds of caries prevalence were lower in children living in areas with highest fluoride levels (≥ 0.7 ppm) compared with areas of lowest fluoride levels (< 0.1 ppm) at all levels of deprivation. However, the magnitude of decrease in the odds of caries prevalence between highest and lowest fluoride levels was larger in the most deprived children (quintile 5) compared with the least deprived children (quintile 1), suggesting that fluoride exposure had the largest impact on the most deprived children. When stratified by fluoridation status (i.e., yes = fluoride level ≥ 0.7 ppm, median = 0.84 ppm in 2005 to 2015; no = fluoride level < 0.2 ppm, median = 0.11 ppm), the odds of caries prevalence in the most deprived children was 39% lower (OR = 0.61; 95% CI, 0.56 to 0.66) in areas with fluoridation compared with non-fluoridation areas. In the least deprived children, the difference was 19% lower in areas with fluoridation compared with non-fluoridation areas. Similar findings were obtained for hospital admissions for caries-related dental extractions. Age and gender were adjusted for in the analyses. Thus, there was a stronger association between water fluoridation and a decrease in caries prevalence, as well as hospital admissions for caries-related dental extractions in the most deprived children than in the least deprived children.

The cross-sectional study of low quality by Heima et al. (2017)[83] investigated the effect of sociogeographic factors, including CWF, on dental caries (measured as mean decayed teeth [dt]) among children aged 5 months to 5 years from low-income families in the US, in order to understand the mechanism of disparities. Compared with non-fluoridated areas, children from low-income families living in the fluoridated areas had significantly lower mean decayed teeth. However, after adjustment for children demographics (age, gender, Medicaid, and total number of primary teeth) and social demographic factors (total number of Medicaid dentists and population per 1,000), there was no significant association between water fluoridation and dental caries from children of low-income families (beta coefficient [SE] = 0.177 [0.304]; $P = 0.561$). In contrast, there was a negative association between dt and density of Medicaid dentists (beta coefficient [SE] = –0.003 [0.002]; $P = 0.030$). Thus, the study showed that dentist availability, but not CWF, may be an important factor to reduce early dental caries in children of low-income families.

The ecological study assessed to be of low quality by Ha et al. (2016)[84] investigated the trends in dental caries among Indigenous children in South Australia, and the contribution of area-level SES, remoteness, and water fluoridation status. The study included children aged 5 to 10 years for the measurement of dmft and children aged 6 to 15 years for the measurement of DMFT. The study found no statistically significant difference in dental caries of both dentitions (deciduous and permanent) among Indigenous children living in fluoridated areas and those living in non-fluoridated areas. The study also found that children living in areas of lowest SES (beta coefficient [SE] = 0.83 [0.28]; $P < 0.05$) and remoteness (beta coefficient [SE] = 1.25 [0.45]; $P < 0.05$) had significantly higher caries experience for deciduous teeth than those living in areas of highest SES and major cities. However, the multivariable mixed regression models adjusted for time trend, SES (highest to lowest), and remoteness showed no association between water fluoridation and dmft (beta coefficient [SE] = –0.10 [0.36]; not significant [NS]) or between water fluoridation and DMFT (beta coefficient [SE] = –0.02 [0.21]; NS).

The ecological study of low quality by Schluter and Lee (2016)[85] investigated the effect of CWF on dental caries in New Zealand children aged 5 years and 12 to13 years of different ethnicity (i.e., non-Māori and Māori). Mean dmft and mean DMFT for both non-Māori and Māori children aged 5 years and children aged 12 to 13 years, respectively, was significantly lower in fluoridated areas compared with non-fluoridated areas ($P < 0.001$). In both areas, mean dmft and mean DMFT for Māori children was significantly higher compared with that for non-Māori children ($P < 0.001$). Over the time course from 2004 to 2013 (as reported in graphs), there was no sign that water fluoridation reduced disparity in oral health between Māori and non-Māori children. Confounding variables adjusted for included age, ethnicity, fluoridation status, and year of data collection. Similar, but inverse, results were obtained for proportion of caries-free of deciduous teeth and proportion of caries-free of permanent teeth between fluoridated and non-fluoridated areas and between Māori and non-Māori ethnic groups. It was concluded that Māori children continue to experience disparity in oral health, despite living in areas with CWF.

Summary

The 2016 NHMRC review presented the results of an SR by McDonagh et al. (2000) and identified four primary studies (two assessed to be of acceptable quality and two of low quality). Adjustment for confounding variables was reported for two studies. The updated literature search identified four additional primary studies (one assessed to be of acceptable quality and three assessed to be of low quality), all of which reported adjustment for confounding variables in their analyses. The findings of all primary studies were assessed to be partially applicable to the Canadian context.

The findings of the SR and of one ecological study (McGrady et al. 2012) showed that water fluoridation reduced the disparity in caries experience (measured using dmft or DMFT) between social classes. However, water fluoridation did not appear to reduce the gap in caries experience (measured using the proportion of caries-free of both deciduous and permanent teeth) between social classes.

Two additional studies identified by the updated literature search (Heima et al. [2017][83] and Ha et al. [2016][84]) showed that there was no relationship between water fluoridation and decayed teeth, dmft, or DMFT in children from families of low SES (i.e., low-income families, Indigenous). A retrospective cohort study identified by the 2016 NHMRC review suggested a larger impact of CWF exposure on tooth loss for adults of lower SES compared with those of higher SES. Water fluoridation did not result in a reduction of disparity in caries experience by Indigenous status in two studies, one identified from the 2016 NHMRC review (Lalloo et al. 2015) and one from the updated literature search (Schluter and Lee 2016).[85] The PHE reports (2014 and 2018) showed that water fluoridation had stronger impact in reducing dental caries experience in children of lowest deprivation than those of other levels of deprivation. Overall, there was insufficient evidence for an association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth by SES; there was limited evidence for no association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth by Indigenous status; there was limited evidence for an association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth and hospital admissions for caries-related dental extractions by levels of deprivation.

Table 10: Disparities

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Previous SR and Four Studies (Three Ecological Studies and One Retrospective Cohort Study)					
McDonagh et al. (2000) UK Previous SR	Children aged 5 to 16 years 15 studies (no QA): 3 before-and-after studies and 12 cross-sectional studies N = NR	• CWF (F level NR) • Non-CWF (F level NR)	• Children 5 to 10 years old: Proportion of caries-free was higher across social class in the fluoridated areas compared with non-fluoridated areas. • Children 5 years old: In both areas, the proportion of caries-free was higher in the high social class (class I and II) compared with the low social class (class IV and V). The absolute difference in the proportion of caries-free between class I and II and class IV and V was 20% in the fluoridated areas and 18% in the non-fluoridated areas. • Children 5 years old: In both areas, there are more dental caries (measured using dmft) in the low social class (class IV and V) compared with the high social class (I and II). The absolute difference in mean dmft between class I and II and class IV and V was 0.7 in the fluoridated areas and 2.0 in the non-fluoridated areas. • Children 5 to 16 years old: Mean dmft/DMFT was lowered across age and social class in the fluoridated areas compared with non-fluoridated areas. • Other studies using different classification of social class reported mixed results.		Water fluoridation did not reduce the disparity in the proportion of caries-free, but reduced the disparity in dmft/DMFT between social classes.
Lalloo et al. (2015) Australia Ecological Low	Children aged 5 to 10 years (Indigenous and non-Indigenous) N = NR	• CWF (≥ 0.5 ppm) • Non-CWF (< 0.3 ppm)	Proportion of caries-free of deciduous teeth (95% CI) CWF (≥ 0.5 ppm) • Non-Ind: 52.5% (51.0 to 54.0) • Ind: 27.3% (23.7 to 31.2)	OR (95% CI) CWF (≥ 0.5 ppm) • Non-Ind: 3.78 (3.17 to 4.50) • Ind: 1.27 (0.98 to 1.63) Non-CWF (< 0.3 ppm) • Non-Ind: 1.93 (1.63 to 2.29)	Water fluoridation did not reduce the gap in dental caries experience (measured using the proportion of caries-free) between Indigenous and non-Indigenous children. (*Partial*)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings** **(*Applicability*[a])**
			Non-CWF (< 0.3 ppm) • Non-Ind: 36.3% (35.3 to 37.3) • Ind: 22.9% (20.2 to 25.5)	• Ind: Ref (Adjustment for age and gender)	
	Children aged 6 to 15 years N = NR	• CWF (≥ 0.5 ppm) • Non-CWF (< 0.3 ppm)	Proportion of caries-free of permanent teeth (95% CI) CWF (≥ 0.5 ppm) • Non-Ind: 70.7% (69.3 to 72.0) • Ind: 50.3% (45.1 to 55.4) Non-CWF (< 0.3 ppm) • Non-Ind: 53.8% (52.6 to 55.1) • Ind: 44.3% (40.2 to 48.6)	OR (95% CI) CWF (≥ 0.5 ppm) • Non-Ind: 3.72 (3.04 to 4.56) • Ind: 1.30 (1.01 to 1.68) Non-CWF (< 0.3 ppm) • Non-Ind: 1.60 (1.32 to 1.95) • Ind: ref (Adjustment for age and gender)	
McGrady et al. (2012) UK Ecological Low	Children aged 11 to 13 years N = 1,783	• CWF (1 ppm) • Non-CWF (F level NR)	The absolute difference in the mean $D_{4\text{-}6}$MFT between the most and least deprived groups was 0.54 in the fluoridated water supply area and 0.97 in the non-fluoridated water supply area.	NR	Water fluoridation reduced the disparity in caries experience (measured using DMFT) between social classes. (*Partial*)
PHE (2014) England Ecological Acceptable	Children aged 1 to 4, 5, and 12 years N = NR	• CWF (0.8 ppm to 1.0 ppm) • Non-CWF (F level NR)	• Difference in mean d3mft b between fluoridated and non-fluoridated areas was 0.16 lower (95% CI, –0.32 to –0.01) in children (5 years old) of the lowest deprived quintiles and was 0.51 lower (95% CI, –0.75 to –0.27) in children (5 years old) of the highest deprived quintile. • Compared with the non-fluoridated areas, the prevalence of any d3mft b in fluoridated areas was 17% lower (95% CI, –28% to –3.9%) in children (5 years old) of the lowest deprived quintiles and was 32% lower (95% CI, –42% to –19%) in children (5 years old) of the highest deprived quintile.		Compared with the least deprived quintiles, there was a strong association between fluoridation and mean dmft/DMFT in the most deprived quintile. Similar results were observed for caries prevalence and hospital admissions for caries. *(Partial)*

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
			• Difference in mean D3MFTb between fluoridated and non-fluoridated areas was 0.07 lower (95% CI, –0.17 to 0.04) in children (12 years old) of the lowest deprived quintiles and was 0.25 lower (95% CI, –0.44 to -0.07) in children (12 years old) of the highest deprived quintile. • Compared with the non-fluoridated areas, the prevalence of any D3MFTb in fluoridated areas was 9% lower (95% CI, –21% to 5%) in children (12 years old) of the lowest deprived quintiles and was 26% lower (95% CI, –40% to –8%) in children (12 years old) of the highest deprived quintile. • Compared with non-fluoridated areas, the rate of hospital admissions for caries in fluoridated areas was 27% lower (95% CI, –62% to –39%) in children 1 to 4 years old of the lowest deprived quintiles and was 76% lower (95% CI, –89% to –45%) in the highest deprived quintile.		
Neidell et al. (2010) USA Retrospective cohort Acceptable	Participants born between 1950 and 1969 living in the communities described in the 1992 Water Fluoridation Census N = NR	Water fluoridation status was assigned to participants using county-level water fluoride values based on the Water Fluoridation Census	NR	Tooth loss Beta coefficients (SE) • Black: –0.37 (0.18) • White: –0.19 (0.08) • < high school degree: –0.61 (0.40) • High school degree: –0.39 (0.09) • College degree: –0.06 (0.06)	The impact of CWF exposure on tooth loss at birth was larger for adults of lower SES compared with those of higher SES (race and education). (*Partial*)
Evidence From Updated Literature Search: One Cross-Sectional Study and Three Ecological Studies					
PHE 2018[86] England Ecological Acceptable	Children aged 5 years for d3mft[b], prevalence of d3mft[b] > 0 N = 111,455 Participants aged 0 to 19 years for hospital	Fluoride level in water supply (regardless of source): < 0.1 ppm, 0.1 ppm to < 0.2 ppm, 0.2 ppm to < 0.4 ppm, 0.4 ppm to < 0.7 ppm, ≥ 0.7 ppm	Disparity in caries prevalence in children aged 5 years (2014 to 2015) by fluoride level and stratified by index of multiple deprivation (IMD) • At all levels of deprivation, dental caries prevalence decreased with increasing fluoride level. • The magnitude of decreasing in odds of caries prevalence		There was a stronger association between water fluoridation and decrease in caries prevalence, as well as hospital admissions for caries-related dental extractions in the most deprived children

<table>
<thead>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>[a])</th></tr>
</thead>
<tbody>
<tr>
<td></td>
<td>admissions for dental extractions due to dental caries
N = 114,530,000 person-years</td>
<td></td>
<td colspan="2">
between highest (≥ 0.7 ppm) and lowest (< 0.1 ppm) fluoride levels was larger in the most deprived children (quintile 5) compared with the least deprived children (quintile 1).

Disparity in caries prevalence in children aged 5 years (2014 to2015) by fluoridation status and stratified by IMD
<table>
<thead>
<tr><th>Quintile of IMD</th><th>Fluoridation Status[a]</th><th>Adjusted OR (95% CI)[b]</th><th><i>P</i> Value</th></tr>
</thead>
<tbody>
<tr><td>1 (least deprived)</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.81 (0.70 to 0.94)</td><td>0.007</td></tr>
<tr><td>2</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.73 (0.63 to 0.84)</td><td>< 0.001</td></tr>
<tr><td>3</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.73 (0.64 to 0.83)</td><td>< 0.001</td></tr>
<tr><td>4</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.76 (0.68 to 0.85)</td><td>< 0.001</td></tr>
<tr><td>5 (most deprived)</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.61 (0.56 to 0.66)</td><td>< 0.001</td></tr>
</tbody>
</table>
[a] Yes = fluoride level ≥ 0.7 ppm; No = fluoride level < 0.2 ppm.
[b] Adjusted for ethnicity.

Disparity in incidence of hospital admissions for caries-related dental extractions in children aged 0 to 19 years (2007 to 2015) by fluoridation status and stratified by IMD
<table>
<thead>
<tr><th>Quintile of IMD</th><th>Fluoridation Status[a]</th><th>Adjusted IRR (95% CI)[b]</th><th><i>P</i> Value</th></tr>
</thead>
<tbody>
<tr><td>1 (least deprived)</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.52 (0.32 to 0.83)</td><td>0.007</td></tr>
<tr><td>2</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.53 (0.35 to 0.81)</td><td>0.003</td></tr>
<tr><td>3</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.55 (0.33 to 0.90)</td><td>0.016</td></tr>
</tbody>
</table>
</td>
<td>than the least deprived children. (<i>Partial</i>)</td>
</tr>
</tbody>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>^{a})</th></tr>
<tr><td></td><td></td><td></td><td colspan="2">
<table>
<tr><th>Quintile of IMD</th><th>Fluoridation Status^{a}</th><th>Adjusted IRR (95% CI)^{b}</th><th><i>P</i> Value</th></tr>
<tr><td>4</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.46 (0.26 to 0.80)</td><td>0.005</td></tr>
<tr><td>5 (most deprived)</td><td>No</td><td>Ref (1)</td><td></td></tr>
<tr><td></td><td>Yes</td><td>0.32 (0.17 to 0.60)</td><td>0.000</td></tr>
</table>
[a] Yes = fluoride level ≥ 0.7 ppm; No = fluoride level < 0.2 ppm.
[b] Adjusted for age and gender.
</td><td></td></tr>
<tr><td>Heima et al. (2017)[83]
USA
Cross-sectional
Low</td><td>Children aged 5 months to 5 years from low-income families
N = 388</td><td>• CWF (F level NR)
• Non-CWF (F level NR)</td><td>Mean dt (SD)

• CWF: 0.76 (2.09)
• Non-CWF: 2.39 (11.24); <i>P</i> = 0.015</td><td>Fluoridated water:
Beta coefficient (SE) = 0.177 (0.304); <i>P</i> = 0.561

(Adjustment for children demographics [age, gender, Medicaid, total number of primary teeth] and social demographic factors [total number of Medicaid dentists, Medicaid density, population/1000])

Medicaid dentist density:
Beta coefficient (SE) = –0.003 (0.002); <i>P</i> = 0.030

(Adjustment for children demographics [age, gender, Medicaid, total number of primary teeth] and social demographic factors [total number of Medicaid dentists, fluoridated water, population/1000])</td><td>Children from low-income families living in the fluoridated areas had significantly lower mean dt. After adjustment for covariates, the difference was no longer significant. The density of Medicaid dentists showed a negative significant association with dt. (<i>Partial</i>)</td></tr>
<tr><td>Ha et al. (2016)[84]</td><td>Indigenous children aged 5 to 10 years (dmft)</td><td>• With water fluoridation (> 0.5 ppm)</td><td>NR</td><td>dmft
Beta coefficient (SE) = –0.10</td><td>There was no association between dmft or DMFT and</td></tr>
</table>

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Australia Ecological Low	N = NR Indigenous children aged 6 to 15 years (DMFT) N = NR	- Without water fluoridation (F level NR)		(0.36); NS DMFT Beta coefficient (SE) = –0.02 (0.21); NS (Adjustment for time trend, SES and remoteness) Indigenous children living in areas of lowest SES (beta coefficient [SE] = 0.83 [0.28]; *P* < 0.05) and remoteness (beta coefficient [SE] = 1.25 [0.45]; *P* < 0.05) had significantly higher caries experience for deciduous teeth than those living in areas of highest SES and major cities	water fluoridation. (*Partial*)
Schluter and Lee (2016)[85] New Zealand Ecological Low	All children aged 5 years N = 417,318	- CWF (F level NR) - Non-CWF (F level NR)	Mean dmft CWF - Non-Māori: 1.50 (95% CI, 1.36 to 1.64) - Māori: 3.01 (95% CI, 2.86 to 3.15) Non-CWF - Non-Māori: 2.01 (95% CI, 1.87 to 2.15) - Māori: 4.60 (95% CI, 4.46 to 4.74)	Regression analysis on mean dmft Significant differences between Māori and non-Māori ethic groups (*P* < 0.001), fluoridated and non-fluoridated areas (*P* < 0.001) (Adjustment for age, ethnicity, fluoridation status, and year of data collection)	Mean dmft for both non-Māori and Māori children aged 5 years was significantly lower in fluoridated areas compared with non-fluoridated areas. (*Partial*) In both areas, mean dmft for Māori children was significantly higher compared with that for non-Māori children. (*Partial*)
	All children in school year 8 (~ 12 to 13 years of age) N = 417,333	- CWF (F level NR) - Non-CWF (F level NR)	Mean DMFT CWF - Non-Māori: 1.26 (95% CI, 1.17 to 1.36)	Regression analysis on mean DMFT Significant differences between	Mean DMFT for both non-Māori and Māori children aged 12 to 13 years was significantly lower in

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings** **(*Applicability*[a])**
			- Māori: 2.01 (95% CI, 1.91 to 2.10) Non-CWF - Non-Māori: 1.69 (95% CI, 1.58 to 1.77) - Māori: 2.95 (95% CI, 2.86 to 3.05)	Māori and non-Māori ethic groups (*P* < 0.001), fluoridated and non-fluoridated areas (*P* < 0.001) (Adjustment for age, ethnicity, fluoridation status, and year of data collection)	fluoridated areas compared with non-fluoridated areas. (*Partial*) In both areas, mean DMFT for Māori children was significantly higher compared with that for non-Māori children. (*Partial*)
	All children aged 5 years N = 417,318	- CWF (F level NR) - Non-CWF (F level NR)	Proportion of caries-free of deciduous teeth CWF - Non-Māori: 60.7% (95% CI, 58.4 to 62.9) - Māori: 37.8% (95% CI, 35.6 to 40.1) Non-CWF - Non-Māori: 53.3% (95% CI, 51.1 to 55.6) - Māori: 23.0% (95% CI, 20.7 to 25.2)	NR	Proportion of carries-free of deciduous teeth (dmft = 0) for both non-Māori and Māori children aged 5 years was significantly higher in fluoridated areas compared with non-fluoridated areas. (*Partial*) In both areas, proportion of carries-free of deciduous teeth (dmft = 0) for Māori children was significantly lower compared with that for non-Māori children. (*Partial*)
	All children in school year 8 (~ 12 to 13 years of age) N = 417,333	- CWF (F level NR) - Non-CWF (F level NR)	Proportion of caries-free of permanent teeth (95% CI) CWF - Non-Māori: 51.4% (49.4 to 53.4) - Māori: 38.0% (35.9 to 40.0)	NR	Proportion of caries-free of permanent teeth (DMFT = 0) for both non-Māori and Māori children aged 12 to 13 years was significantly higher in fluoridated areas compared with non-fluoridated areas. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
			Non-CWF • Non-Māori: 42.4% (40.4 to 44.4) • Māori: 25.3% (23.3 to 27.3)		In both areas, the proportion of caries-free of permanent teeth (DMFT = 0) for Māori children was significantly lower compared with that for non-Māori children. (*Partial*)

CI = confidence interval; CWF = community water fluoridation; dmft = decayed, missing, and filled deciduous teeth; DMFT = decayed, missing, and filled permanent teeth; dt = decayed teeth; F = fluoride; Ind. = Indigenous; IMD = index of multiple deprivation; NHMRC = National Health and Medical Research Council; NR = not reported; NS = not significant; OR = odds ratio; PHE = Public Health England; ppm = parts per million; QA = quality assessment; ref = reference; SD = standard deviation; SE = standard error; SES = socio-economic status; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] The “3” in d3mft denotes obvious decay into dentine.

2. Other Dental Outcomes

a) Tooth Loss

The results for tooth loss are presented in Table 11.

Evidence From the 2016 NHMRC Review

Four ecological studies (one assessed to be of low quality and three of acceptable quality) and one retrospective cohort study (assessed to be of acceptable quality) were identified.

The ecological study of low quality by Da Silva et al. (2015) investigated the relationship between water fluoridation and missing permanent teeth in children aged 12 years in Brazil. After adjustment for economic deprivation and sociosanitary conditions (a composite measure incorporating rates of urbanization, proper sanitation, and illiteracy), exposure to fluoridated water was inversely associated with the number of missing permanent teeth (beta coefficient = –0.33; 95% CI, –0.60 to –0.06; $P = 0.019$).

The ecological study of acceptable quality by Crocombe et al. (2013) examined a cohort of participants aged 15 to 45 years living outside capital cites of Australia. When comparing between two different lifetime exposures to fluoridated water (i.e., ≥ 50% versus < 50%), the study found that higher lifetime water fluoridation exposure was not significantly associated with a reduction in tooth loss in younger rural adults (beta coefficient = –0.03; $P = 0.92$), after adjustment for age, annual income, education, diabetes, and access to dental care.

The ecological study of acceptable quality by Barbato and Peres (2009) examined the effect of CWF (optimum at 0.8 ppm) and non-CWF on the tooth loss of permanent teeth among adolescents aged 15 to 19 years in Brazil. The study found that the prevalence of missing teeth was significantly greater in the non-CWF areas compared with the CWF areas (prevalence ratio = 1.40; 95% CI, 1.34 to 1.46), after adjustment for type of dental service, education gap, income, age, skin colour, gender, and locality.

The ecological study of acceptable quality by Kolterman et al. (2011) examined the relationship between exposure to CWF and functional dentition (defined as the presence of 20 or more teeth in the mouth) among adults aged 35 to 44 years in Brazil. Exposure to water fluoridation was classified as time exposure; i.e., ≥ 10 years, 5 to 9 years, and ≤ 5 years. After adjustment for contextual variables, individual demographic variables and individual health-system variables, the study found that adults with higher exposure (i.e., ≥ 10 years, 5 to 9 years) to water fluoridation had significantly higher functional dentition compared with those who had the lowest exposure (≤ 5 years).

The retrospective cohort study of acceptable quality by Neidell et al. (2010) studied the effect of CWF exposure on tooth loss among adults in the US. Exposure to CWF (0.7 ppm to 1.2 ppm) was classified as current, 20 years ago, and at birth. The study found that exposure at birth (duration of exposure not reported) to fluoridated water was inversely related with the number of missing permanent teeth (beta coefficient [SE] = –0.26 [0.07]; $P < 0.01$), after adjustment for indicator variables, individual-level variables, and 2000 county-level variables.

Evidence From the Updated Literature Search

The updated literature search identified two additional cross-sectional studies both assessed to be of low quality.

The cross-sectional study assessed to be of low quality by Chalub et al. (2016)[87] investigated the effect of CWF on the prevalence of functional dentition among Brazilian adults aged 35 to 44 years using four different definitions (see footnotes of Table 11 for definitions). After adjustment for gender, self-declared skin colour, schooling, monthly household income, age group, self-rated treatment need, dental appointment in the previous 12 months, dental services, and 2010 Municipal Human Development Index, it was found that adults living in the CWF areas had significantly higher prevalence of functional dentition (in all four oral health outcomes) compared with those in the non-CWF areas.

The cross-sectional study assessed to be of low quality by Babarto et al. (2015)[88] examined the effect of CWF availability (i.e., 27 years versus 13 years) on the prevalence of tooth loss among adults aged 20 to 59 years in Brazil. After adjustment for SES, gender, age, years of education, household income per capita, and length of residence in the same location, the study found that a shorter period of exposure to water fluoridation was associated with a higher risk of tooth loss (OR = 1.02; 95% CI,1.01 to 1.02).

Summary

Of five studies identified by the 2016 NHMRC review, four studies (three assessed to be of acceptable quality and one of low quality) found a significant association between water fluoridation exposure and decrease in tooth loss. The fifth study (assessed to be of acceptable quality) reported no association. Two additional studies identified in the updated literature search (both assessed to be of low quality) also found a relationship between water fluoridation and increased functional dentition. Of the seven primary studies, the findings of two were assessed to be partially applicable to the Canadian context, while those of five were of limited applicability. Overall, there was limited evidence for an association between water fluoridation at the current Canadian level and less tooth loss.

Table 11: Tooth Loss

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Four Ecological Studies and One Cohort Study					
Da Silva (2015) Brazil Ecological Low	Children aged 12 years N = NR	Fluoridated water supply (F level NR)	NR	Beta coefficient = –0.33; 95% CI, –0.60 to –0.06; *P* = 0.019 (Adjustment for economic deprivation and sociosanitary [a composite measure incorporating rates of urbanization, proper sanitation and illiteracy])	Exposure to water fluoridation was inversely associated with the number of missing permanent teeth. (*Limited*)
Crocombe et al. (2013) Australia Ecological Acceptable	Participants aged 15 to 45 years N = 466	Lifetime exposure to fluoridated water • ≥ 50% • < 50%	NR	Beta coefficient = –0.03; *P* = 0.92 (Adjustment for age, annual income, education, diabetes, and access to dental care)	No significant relationship was observed between higher lifetime water fluoridation exposure and a reduction in tooth loss. (*Partial*)
Neidell et al. (2010) USA Retrospective cohort Acceptable	Adults (age NR) N = 92,701 tooth loss category observations	CWF (0.7 ppm to 1.2 ppm) F was measured 3 times: • Current • 20 years ago • At birth	NR	Beta coefficient (SE) = –0.26 (0.07); *P* < 0.01 (Adjustment for indicator variables, individual-level variables, and 2000 county-level variables)	CWF exposure at birth was inversely related to the number of missing permanent teeth. (*Partial*)
Barbato and Peres (2009) Brazil Ecological Acceptable	Participants aged 15 to 19 years N = 16,833	• CWF (0.8 ppm) • Non-CWF (F level NR)	Prevalence of tooth loss • CWF: 30% • Non-CWF: 46%	PR = 1.40; 95% CI, 1.34 to 1.46 CWF as ref (Adjustment for type of dental service, education gap, income, age, skin colour, gender, and locality)	Prevalence of missing teeth was significantly greater in non-CWF areas compared with CWF areas. (*Limited*)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
Kolterman et al. (2011) Brazil Ecological Acceptable	Adults aged 35 to 44 years N = 10,625	Time since exposure to CWF (F level NR) - ≥ 10 years - 5 to 9 years - ≤ 5 years	NR	Functional dentition OR (95% CI) - ≥ 10 years: 1.78 (1.32 to 2.40); *P* < 0.01 - 5 to 9 years: 1.88 (1.20 to 2.95); *P* < 0.01 - ≤ 5 years as ref (Adjustment for contextual level [lifespan, income, education, location, fluoridation, population/dentist], individual demographic [age, gender, family income, schooling], and individual health-system variables [dentist visits, treatment facility, information on prevention])	Adults with higher exposure to water fluoridation had significantly higher functional dentition. (*Limited*)
Evidence From the Updated Literature Search: Two Cross-Sectional Studies					
Chalub et al. (2016)[87] Brazil Cross-sectional Low	Adults aged 35 to 44 years N = 9,564	- CWF (F level NR) - Non-CWF (F level NR)	Prevalence of four oral health outcomes FDWHO[b] - CWF: 78.9% - Non-CWF: 70.7% WDT[c] - CWF: 74.0% - Non-CWF: 64.6% FD_{class5}[d] - CWF: 43.5% - Non-CWF: 36.1%	PR (95% CI) FDWHO: 1.18 (1.10 to 1.27) WDT: 1.21 (1.12 to 1.31) FD_{class5}: 1.20 (1.04 to 1.38) FD_{class6}: 1.22 (1.05 to 1.41) Non-CWF as ref (Adjustment for gender, self-declared skin colour, schooling,	Adults living in the CWF areas had a significantly higher prevalence of functional dentition compared with those in the non-CWF areas. (*Limited*)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
			$\text{FD}_{\text{class6}}$[e] - CWF: 41.8% - Non-CWF: 33.5%	monthly household income, age group, self-rated treatment need, dental appointment in the previous 12 months, dental services, and 2010 Municipal Human Development Index)	
Babarto et al. (2015)[88] Brazil Cross-sectional Low	Adults aged 20 to 59 years N = 1,720	CWF availability - 27 years - 13 years	Prevalence of tooth loss (95% CI) - 27 years: 18.4% (16.3 to 20.7) - 13 years: 19.8% (16.5 to 23.5)	OR (95% CI) - 27 years: ref - 13 years: 1.02 (1.01 to 1.02) (Adjusted for SES, gender, age, years of education, household income per capita, and length of residence in the same location)	Shorter period of exposure to water fluoridation was associated with higher risk of tooth loss. (*Limited*)

CI = confidence interval; CWF = community water fluoridation; F = fluoride; $\text{FD}_{\text{class5}}$ = functional dentition classified by aesthetics and occlusion; $\text{FD}_{\text{class6}}$ = functional dentition classified by aesthetics, occlusion, and periodontal status; FDWHO = WHO functional dentition; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; ppm = parts per million; PR = prevalence ratio; ref = reference; SE = standard error; SES = socio-economic status; WDT = well-distributed teeth.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] FDWHO: ≥ 20% teeth presence.

[c] WDT: ≥ 10 teeth in each arch.

[d] $\text{FD}_{\text{class5}}$: ≥ 1 tooth in each arch, ≥ 10 teeth in each arch, all maxillary and mandibular anterior teeth, 3 or 4 premolar POPs, and ≥ 1 molar POP (pair of antagonist posterior) bilaterally.

[e] $\text{FD}_{\text{class6}}$: $\text{FD}_{\text{class5}}$ plus shallow pockets and/or clinical attachment level (CAL) of 5 mm (community periodontal index ≤ 3 or CAL ≤ 1).

b) Delayed Tooth Eruption

Exposure to water fluoridation may delay the eruption of permanent teeth.[89,90] Suggested mechanisms included prolonged retention of deciduous teeth or thickening of the bone around the emerging teeth. The results for tooth eruption are presented in Table 12.

Evidence From the 2016 NHMRC Review

Two ecological studies (one assessed to be of acceptable quality and one of low quality) were identified.

The ecological study of acceptable quality by Jolaoso et al. (2014) measured the number of erupted permanent teeth among children 5 to 17 years who had continuously been exposed to water fluoridation of different fluoride levels (i.e., < 0.3 ppm, 0.3 ppm to < 0.7 ppm, and 0.7 ppm to 1.2 ppm) in the US. After adjustment for age, gender, ethnicity, metropolitan status, and school region, the study found no significant difference in mean number of erupted permanent teeth between groups ($P = 0.12$).

The ecological study assessed to be of low quality by Singh et al. (2014) in India calculated the proportion of children aged 8 to 15 years with delayed tooth eruption (definition not reported in the NHMRC review) from areas with mean water fluoride levels of 2.7 ppm and 1.0 ppm. The study found 53.3% children in 2.7 ppm areas had delayed tooth eruption compared with 0% in 1.0 ppm. No statistical analysis was performed.

Evidence From the Updated Literature Search

No additional studies were identified.

Summary

The NHMRC 2016 review identified two ecological studies (one assessed to be of acceptable quality and one as low quality). The ecological study conducted in the US found no association between water fluoridation and delayed tooth eruption. The findings in the second ecological study conducted in India were inconclusive. Confounding variables were adjusted in the analysis of the US study, but not in the Indian study. The findings of the US study were assessed to be partially applicable to the Canadian context, while those of the Indian study were of limited applicability. The updated literature search identified no additional studies. Overall, there was insufficient evidence to assess an association between water fluoridation and delayed tooth eruption at current Canadian fluoride levels.

Table 12: Delayed Tooth Eruption

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Two Ecological Studies					
Jolaoso et al. (2014) US Ecological Acceptable	Children 5 to 17 years N = 13,348	Water fluoride level: • 0.7 ppm to 1.2 ppm • 0.3 ppm to < 0.7 ppm • < 0.3 ppm	Mean number of erupted permanent teeth (SE) • 0.7 ppm to 1.2 ppm: 28.52 (0.87) • 0.3 ppm to < 0.7 ppm: 31.03 (1.21) • < 0.3 ppm: 34.21 (0.89) (Adjustment for age, gender, ethnicity, metropolitan status, and school region)	NR	No significant difference in mean number of erupted permanent teeth between groups (P = 0.12). (*Partial*)
Singh et al. (2014) India Ecological Low	Children aged 8 to 15 years N = 70	Water fluoride level • 2.7 ppm (range 1.6 ppm to 5.5 ppm); n = 60 • 1.0 ppm (range 0.98 ppm to 1 ppm); n = 10	Delayed tooth eruption • 2.7 ppm: 53.3% • 1.0 ppm: 0%	NR	The association between high water fluoride level and delayed tooth eruption was inconclusive. (*Limited*)
Evidence From the Updated Literature Search: No Studies Identified					

NHMRC = National Health and Medical Research Council; ppm = parts per million; SE = standard error.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

c) Tooth Wear

The results for tooth wear are presented in Table 13.

Evidence From the 2016 NHMRC Review

One cross-sectional study assessed to be of acceptable quality from Ireland was identified.

Burke et al. (2010) conducted a cross-sectional study to investigate the severity of tooth wear among participants aged 16 to 24 years, 35 to 44 years, and ≥ 65 years who had different degrees of exposure to CWF (i.e., lifetime exposure, some exposure, or no exposure). The results of this study demonstrated no relationship between exposure to water fluoridation and tooth wear.

Evidence From the Updated Literature Search

No additional studies were identified.

Summary

The NHMRC identified one cross-sectional study (assessed to be of acceptable quality) that showed no relationship between water fluoridation and tooth wear in adolescents and adults. The findings of this study were assessed to be partially applicable to the Canadian context. The updated literature search identified no additional studies. Overall, there was insufficient evidence to assess an association between water fluoridation and tooth wear.

Table 13: Tooth Wear

Study Country Design Quality	Population	Exposures	Results		Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Cross-Sectional Study					
Burke et al. (2010) Ireland Cross-sectional Acceptable	Participants aged 16 to 24, 35 to 44, and ≥ 65 years N = 2,556	Exposure to CWF (0.8 ppm to 1.0 ppm since 1964 then reduced to 0.6 ppm to 0.8 ppm in 1970) • Full (lifetime or ≥ 35 years) • Part (some exposure) • No (no exposure)	Age 16 to 24 years • Full: 33.9% (mild), 3.3% (moderate), 0.4% (severe) • Part: 40.8% (mild), 0.7% (moderate), 0.0% (severe) • No: 33.4% (mild), 2.5% (moderate), 0.0% (severe) Age 35 to 44 years • Full: 71.3% (mild), 10.5% (moderate), 0.7% (severe) • Part: 60.1% (mild), 9.2% (moderate), 1.0% (severe) • No: 60.4% (mild), 16.3% (moderate), 3.5% (severe)	Age ≥ 65 years • Full: 51.2% (mild), 31.5% (moderate), 10.3% (severe) • Part: 54.2% (mild), 36.3% (moderate), 2.5% (severe) • No: 62.4% (mild), 19.3% (moderate), 11.6% (severe)	There was no association between exposure to water fluoridation and tooth wear. (*Partial*)
Evidence From the Updated Literature Search: No Studies Identified					

CWF = community water fluoridation; NHMRC = National Health and Medical Research Council; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

d) Hospital Admissions for Caries-Related Dental Extractions Under General Anesthesia

The results for hospital admissions are presented in Table 14.

Evidence From the 2016 NHMRC Review

One ecological study assessed to be of acceptable quality from England was identified.

PHE (2014) compared the rate of hospital admissions for extraction of decayed teeth under a general anesthetic among children aged 1 to 4 years between CWF areas and non-CWF areas. The study found that the rate of hospital admissions for caries in children aged 1 to 4 years was significantly lower in fluoridated areas (Difference in rate = –55%; 95% CI, –73% to –27%), after adjustment for deprivation.

Evidence From the Updated Literature Search

One ecological study assessed to be of acceptable quality from England was identified through the updated literature search.

PHE (2018)[86] determined the incidence rate of hospital admissions for dental extractions due to caries in children and adolescents aged 0 to 19 years in England from 2007 to 2015. A total of 114,530,000 person-years were included. Fluoride level was stratified from low (< 0.1 ppm) to high (≥ 0.7 ppm), regardless of source. The study found that fluoride levels above 0.1 ppm were significantly associated with a decrease in hospital admissions for caries-related dental extractions. The highest effect was seen at fluoride levels of ≥ 0.7 ppm.

Summary

Two ecological studies of acceptable quality (one identified by the NHMRC 2016 review and one identified by the updated literature search) provided evidence for an association between water fluoridation and the reduction of the incidence rate of hospital admissions for dental caries under general anesthesia. Confounding variables were adjusted in the analyses of both studies. The findings of the studies were assessed to be partially applicable to the Canadian context. Overall, there was limited evidence for an association between water fluoridation and hospital admissions for extraction of decayed teeth under a general anesthetic in children.

Table 14: Hospital Admissions

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td colspan="6">Evidence From the 2016 NHMRC Review: One Ecological Study</td></tr>
<tr><td>PHE (2014)
England
Ecological
Acceptable</td><td>Children aged 1 to 4 years
N = NR</td><td>• CWF (0.8 ppm to 1.0 ppm)
• Non-CWF (F level NR)</td><td>NR</td><td>Difference in rate of hospital admission for caries = –55%; 95% CI, –73 to –27

(Adjustment for deprivation)</td><td>Rate of hospital admissions for caries in children aged 1 to 4 years was significantly lower in fluoridated areas. (Partial)</td></tr>
<tr><td colspan="6">Evidence From the Updated Literature Search: One Ecological Study</td></tr>
<tr><td>PHE 2018[86]
England
Ecological
Acceptable</td><td>Participants aged 0 to 19 years for hospital admissions for dental extractions due to dental caries, England 2007 to 2015
N = 114,530,000 person-years</td><td>Fluoride level in water supply (regardless of source):
< 0.1 ppm, 0.1 ppm to < 0.2 ppm, 0.2 ppm to < 0.4 ppm, 0.4 ppm to < 0.7 ppm, ≥ 0.7 ppm</td><td colspan="2">Adjusted incidence rate ratios of hospital admissions for dental extractions due to dental caries in children aged 0 to 19 years (2007 to 2015), by fluoride level
<table>
<tr><th>Fluoride Level (ppm)</th><th>Adjusted IRR (95% CI)*</th><th>P Value</th></tr>
<tr><td>< 0.1</td><td>Ref (1)</td><td>–</td></tr>
<tr><td>0.1 to < 0.2</td><td>0.74 (0.62 to 0.88)</td><td>0.001</td></tr>
<tr><td>0.2 to < 0.4</td><td>0.55 (0.44 to 0.68)</td><td>0.000</td></tr>
<tr><td>0.4 to < 0.7</td><td>0.61 (0.46 to 0.80)</td><td>0.000</td></tr>
<tr><td>≥ 0.7</td><td>0.41 (0.24 to 0.67)</td><td>0.000</td></tr>
</table>
*Adjusted for age, gender, ethnicity, and deprivation.</td><td>Fluoride levels above 0.1 ppm were associated with a significant decrease in hospital admissions for caries-related dental extractions. (Partial)</td></tr>
</table>

CI = confidence interval; CWF = community water fluoridation; F = fluoride; IRR = incidence rate ratio; NHMRC = National Health and Medical Research Council; NR = not reported; PHE = Public Health England; ppm = parts per million ref = reference.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

e) Dental Care Visits

The results for dental care visits are presented in Table 15.

Evidence From the 2016 NHMRC Review

No studies were identified.

Evidence From the Updated Literature Search

Two ecological studies, one assessed to be of acceptable quality and one to be of low quality, were identified.

The ecological study of acceptable quality by Aggeborn and Öhman (2017)[76] from Sweden studied the effect of fluoride exposure through the drinking water throughout life on dental health in individuals aged 16 years and older who were born between 1985 and 1992. Sweden has naturally occurring fluoridated water with fluoride levels in community water of ≤ 1.5 ppm. Regression analysis showed no association between number of dental clinic visits and drinking water fluoride, after adjusting for covariates.

The ecological study of low quality by Cho et al. (2016)[91] from South Korea compared the prevalence of outpatient dental care visits among participants aged 19 to < 70 years living in the CWF and non-CWF areas. It was found that prevalence of outpatient dental care visits (proportion of the population who made a dental visit) was significantly lower in areas with water fluoridation compared with non-fluoridated areas, after adjusting for regional variables and patient variables. Hazard ratio was 0.95 (95% CI, 0.93 to 0.97); $P < 0.0001$.

Summary

The NHMRC 2016 review identified no studies for this outcome. Two studies identified by the updated literature search (one assessed to be of acceptable quality and one of low quality) found mixed evidence on the relationship between water fluoridation and dental care visits; one showed a no association, while the other found a significant association. Confounding variables were adjusted in the studies. The findings of both studies were assessed to be partially applicable to the Canadian context. Overall, there was insufficient evidence for an association between water fluoridation and number of dental care visits.

Table 15: Dental Care Visits

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: No Studies Identified					
Evidence From the Updated Literature Search: Two Ecological Studies					
Aggeborn and Öhma (2017)[76] Sweden Ecological Acceptable	Participants aged ≥ 16 years N = national population	NOF ≤ 1.5 ppm	NR	Visit to dental clinic Beta coefficient (SE) = –0.0044 (0.0212); *NS* Expressed in 0.1 ppm fluoride (Adjustment for sex, marital status, parent's education, parent's income, father's cognitive and non-cognitive ability, parent immigrant, and cohort mean education [at birth, at school start, at 16 years age])	Visit to dental clinic was not associated with drinking water fluoride, after adjustment for covariates. (*Partial*)
Cho et al. (2016)[91] South Korea Ecological Low	Participants aged 19 to < 70 years N = 472,250	• CWF (F level NR) • Non-CWF (F level NR)	Prevalence of outpatient dental care visit • CWF: 46.98% • Non-CWF: 48.66%; *P* < 0.0001	Outpatient dental care visits in areas with water fluoridation HR = 0.95; 95 % CI, 0.93 to 0.97; *P* < 0.0001 Beta coefficient = –0.029; *P* = 0.043 Non-CWF as ref (Adjustment for regional variables [number of dentist per 1,000 people and the financial independent rate of the local government] and patient variables [age, sex, income, type of insurance coverage, study year, dental care expenditures in the previous year, dental facial anomalies, and disorders of tooth development and eruption])	There was a significant inverse relationship between dental care visits and water fluoridation. (*Partial*)

CI = confidence interval; CWF = community water fluoridation; F = fluoride; HR – hazard ratio; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; NS = not significant; ref = reference; SE = standard error.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Research Question 2: Impact of Community Water Fluoridation Cessation on Dental Caries in Children and Adults

1. Dental Caries

a) Deciduous Teeth

Mean Number of Decayed, Missing or Extracted, and Filled Deciduous Teeth

Results for mean dmft and decayed, extracted and filled deciduous teeth (deft) are presented in Table 16.

Evidence From the McLaren and Singhal 2016 Review

The McLaren and Singhal 2016 review included 15 studies, 12 of which had results on the effects of post-CWF on dental caries. The results were synthesized qualitatively and quantitatively. In the qualitative synthesis, the results of both dmft and DMFT were combined. In the quantitative synthesis, only studies that provided usable data were included.

Qualitative synthesis for dental caries of both deciduous and permanent teeth

The 12 studies were classified according to the overall conclusion as to whether CWF cessation increased dental caries or not.

Eight studies showed an increase in dental caries after CWF cessation. The studies were from Europe (former Czechoslovakia, Scotland, and the Netherlands), Asia (China), and North America (US). The years of cessation indicated in the studies ranged from 1956 to 1991. The period between CWF cessation and last data collection ranged from four years to 15 years. It is important to have a reasonable time gap between cessation and data collection to allow the washout period and observe the impact; a minimum of a four-year follow-up period seems appropriate. Five studies were assessed to be of moderate methodological quality and three of low quality. Concerns among those five studies were insufficient control for confounding variables, no blinding on outcome assessment, and absence of a comparison community (in two studies).

Three studies did not show an increase in dental caries after CWF cessation. The studies were from former East Germany, Cuba, and Finland. The time frame of cessation ranged from 1990 to 1992. The period between CWF cessation and last data collection was three years in two studies and seven years in one study. All three studies were assessed to have moderate methodological quality. Important confounders that might have contributed to the findings included fluoride tablets provided to children post-CWF in Finland, post-cessation fissure sealants in East Germany, and post-cessation fluoride mouth rinse and varnish application in Cuba.

One study conducted in Canada was assessed to be of moderate methodological quality. Its findings were rather complex and could not be classified in either of the previously mentioned groups. Two study components showed different results. The prevalence of dental caries (measured using D1D2MFS score) was observed from a repeated cross-sectional survey and the incidence of dental caries was observed from a prospective longitudinal investigation. Year of fluoride cessation was 1993/1994 and the year of collected data was 1996/1997. The study found that the prevalence of dental caries decreased in the cessation community and remained unchanged in the still fluoridated community. The incidence of caries expressed in terms of D1D2MFS score did not differ between cessation and continued fluoridation. However, the incidence of caries progression on smooth surfaces was higher in the cessation community compared with the community with continued water fluoridation.

Quantitative Synthesis for deft

Pooled analyses from two included studies without a comparison community (N = 3,947 children aged 2.5 to 5 years). The studies were conducted in China and Scotland, and were assessed as high and low risk of bias, respectively. The period between CWF cessation and last data collection were five and seven years, respectively.

Pooled estimates across time points within age groups showed a significant increase in mean deft post-cessation compared with pre-cessation (MD = 0.49; 95% CI, 0.11 to 0.87; I^2 = NR).

Pooled estimates across age groups and time points for each study showed a significant increase in mean deft post-cessation compared with pre-cessation (MD = 0.99; 95% CI, 0.70 to 1.28; I^2 = 99.2%).

With a small number of studies and substantial heterogeneity in the pooled analysis, results should be interpreted with caution.

Evidence From the Updated Literature Search

The updated literature search identified two additional pre-post cross-sectional studies.

The pre-post cross-sectional study of acceptable quality by McLaren et al. (2017)[92] examined the short-term impact of fluoridation cessation on dental caries experience (measured in deft) in children aged seven years living in two Canadian cities: Calgary (CWF cessation in 2011) and Edmonton (CWF continued). Mean deft was measured as overall counts of all children or only in those with dmft > 0 in 2004 to 2005 and 2013 to 2014. Differences between post and pre periods showed an increase in mean dmft in both cities. However, the magnitude of change was significantly larger with CWF cessation compared with continued CWF (1.38 versus 0.26; $P < 0.05$).

The pre-post cross-sectional study low quality conducted by PHE (2015) compared the change in mean dmft of five-year-old children between water fluoridation in 2008 and without water fluoridation in 2015. The mean fluoride level in CWF pre-cessation was 0.69 ppm and the mean fluoride level in CWF post-cessation was 0.27 ppm. The study found no significant change in mean dmft between post- and pre-cessation (difference = +0.31; $P = 0.21$). Confounding variables were not adjusted for in the analysis.

Summary

The McLaren and Singhal 2016 review identified 15 studies; four were assessed as of low risk of bias, eight of moderate risk of bias, and three of high risk of bias. From the qualitative synthesis of twelve studies that had results on the effects of post-CWF on dental caries of both deciduous and permanent teeth (both deft and decayed, extracted, and filled permanent teeth [DEFT]), eight showed an increase in dental caries after CWF cessation, three did not, and the findings of one were deemed too complex to classify.

In the assessment of deft, pooled analysis of two studies without a comparison community that provided usable data for quantitative synthesis showed a significant increase in mean deft post-cessation compared with pre-cessation when analyzed across time points within age groups. The updated literature search identified two additional pre-post cross-sectional studies, one from Canada and one from England, with mixed results. The Canadian study adjusted for confounding variables in the analyses, and was assessed to be highly applicable to the Canadian context, while the English study did not adjust for confounding and was assessed to be partially applicable to the Canadian context. The findings in most studies included in the McLaren and Singhal 2016 review were assessed to be of limited applicability to the Canadian context. Overall, due to mixed evidence and high heterogeneity across studies, there was insufficient evidence for an association between CWF cessation and an increase in dental caries in children measured as dmft and deft.

Table 16: Mean dmft/deft

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From McLaren and Singhal 2016 Review					
McLaren and Singhal (2016)[52] Canada SR Pre-post cross-sectional	**Qualitative synthesis for both dmft and DMFT** Children 3 to 15 years Twelve studies N = 42,939	Reasons for CWF cessation varied: technical issues, political or economic, lack of pertinent laws, observed increase in dental fluorosis, opposition to fluoridation, public vote	Dental caries after CWF cessation: - Increase (8 studies) - No increase (3 studies) - Could not be classified (1 study)	NR	Mixed evidence.
	Quantitative synthesis for dmft Children aged 2.5 to 5 years Two studies (high and low risk of bias) N = 3,947	CWF cessation (without a comparison community) Post-cessation vs. Pre-cessation	NR	Pooled estimates across time points within age groups: MD = 0.49, 95% CI, 0.11 to 0.87; I^2 = NR Pooled estimates across age groups and time points for each study: MD = 0.99; 95% CI, 0.70 to 1.28; I^2 = 99.2%	Significant increase in mean deft post-cessation.
Evidence From the Updated Literature Search: Two Pre-Post Cross-Sectional Studies					
McLaren et al. (2017)[92] Canada Pre-post cross-sectional Acceptable	Children aged 7 years N = 11,689	- CWF cessation - CWF continued	Difference in mean deft (overall) between post- and pre-cessation - CWF cessation: 1.05; $P < 0.05$ - CWF continued: 0.34; $P < 0.05$ Difference in mean deft (those with deft > 0) between post- and pre-cessation - CWF cessation: 1.38;	Year x city interaction: Mean deft (overall) RR = 1.37; 95% CI, 1.25 to 1.51; $P < 0.001$ Mean deft (those with deft > 0) RR = 1.34; 95% CI, 1.23 to 1.46; $P < 0.001$ (Adjustment for general health of child's mouth, brushing, visit dentist only for emergencies or	There was significant increase (post minus pre) in mean deft (overall) and mean deft (those with deft > 0) in CWF cessation and continued. Magnitude of change was larger in CWF cessation compared with CWF continued. (*High*)

Study Country Design Quality	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
			P < 0.05 - CWF continued: 0.26; *NS*	never, last dentist visit within the last year, fruit or vegetable at least once a day, sugary drinks at least once a day, fluoride treatment at dentist office, household education of bachelor's degree or higher, home ownership, ethno-cultural background, and age)	
PHE (2015)[93] England Pre-post cross-sectional Low	Children aged 5 years N = 1,873	- CWF pre-cessation (0.61 ppm to 0.73 ppm, mean 0.69 ppm) in 2008 - CWF post-cessation (0.26 ppm to 0.27 ppm, mean 0.27 ppm) in 2015	Mean dmft (overall) - Pre: 0.85 - Post: 0.97 Difference = +0.12; *P* = 0.18 Mean dmft>0 - Pre: 3.26 - Post: 3.57 Difference = +0.31; *P* = 0.21	NR	There was no significant change in mean dmft between pre- and post-cessation. *(Partial)*

CI = confidence interval; CWF = community water fluoridation; deft = decayed, extracted, and filled deciduous teeth; dmft = decayed, missing, and filled deciduous teeth; DMFT = decayed, missing, and filled permanent teeth; MD = mean difference; NR = not reported; NS = not significant; PHE = Public Health England; ppm = parts per million; RR = rate ratio; SR = systematic review; vs. = versus.

[a] For primary studies that were judged to be (high, partial or low) applicable to the Canadian context, i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Mean Number of Decayed, Missing or Extracted, and Filled Deciduous Tooth Surfaces

Results for mean dmft/deft are presented in Table 17.

Evidence From the McLaren and Singhal 2016 Review

No study was identified.

Evidence From the Updated Literature Search

One pre-post study was identified.

A pre-post study of acceptable quality by McLaren et al. (2016a)[94] compared dental caries experience, measured by decayed, extracted, and filled deciduous tooth surfaces (defs), in children aged seven years living in two Canadian cities: Calgary (CWF cessation in 2011) and Edmonton (CWF continued). The study found that differences in mean defs (measured as all tooth surfaces or as smooth surfaces only) between post- (2013 to 2014) and pre-cessation (2004 to 2005) periods were significantly higher in Calgary (CWF cessation) compared with Edmonton (CWF continued).

Summary

The McLaren and Singhal 2016 review identified no study for this outcome. One study identified by the updated literature search and assessed to be of acceptable quality and highly applicable to the Canadian context showed insufficient evidence to assess an association between CWF cessation and a change in dental caries in children measured as defs. This study had several limitations, including short duration of follow-up since cessation.

Table 17: Mean dmfs/defs

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From McLaren and Singhal 2016 Review: No Study Identified					
Evidence From the Updated Literature Search: One Pre-Post Cross-Sectional Study					
McLaren et al. (2016a)[94] Canada Pre-post cross-sectional Acceptable	Children aged 7 years N = 12,581	• CWF cessation • CWF continued	a) All tooth surfaces: Difference (post – pre) in mean defs (overall) • CWF cessation: 3.8[b] • CWF continued: 2.1[b] Difference (post – pre) in mean defs (those with defs > 0) • CWF cessation: 5.9[b] • CWF continued: 2.9[b]	Year x city interaction term: Mean defs (overall) RR = 1.6; 95% CI, 1.4 to 1.8; *P* < 0.01 Mean defs (those with defs > 0) RR = 1.6; 95% CI, 1.4 to 1.8; *P* < 0.01	Significant difference (post minus pre) in mean defs (overall) or mean deft (those with defs > 0) was noted in CWF cessation and in CWF continued. The magnitude was higher in CWF cessation compared with CWF continued. *(High)*
			b) Smooth surfaces: Difference (post – pre) in mean defs between • CWF cessation: 2.9[b] • CWF continued: 1.6[b] Difference (post – pre) in mean defs (those with defs > 0) • CWF cessation: 5.3[b] • CWF continued: 3.0[b]	Year x city interaction term: Mean defs RR = 1.8; 95% CI, 1.6 to 2.2; *P* < 0.01 Mean defs (those with defs > 0) RR = 1.7; 95% CI, 1.5 to 2.0; *P* < 0.01	

CI = confidence interval; CWF = community water fluoridation; defs = decayed, extracted, and filled deciduous tooth surfaces; deft = decayed, extracted, and missing teeth.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] Statistically significant.

Dental Caries Prevalence or Proportion of Caries-Free of Deciduous Teeth

Results for dental caries prevalence or proportion of caries-free of deciduous teeth are presented in Table 18.

Evidence From the McLaren and Singhal 2016 Review

No study was identified.

Evidence From the Updated Literature Search

The updated literature search identified two additional pre-post studies.

The pre-post cross-sectional study assessed to be of acceptable quality by McLaren et al. (2017)[92] compared caries prevalence of deciduous teeth (defined as dmft ≥ 1) in children aged seven years living in two Canadian cities: Calgary (CWF cessation in 2011) and Edmonton (CWF continued). Differences between post and pre periods showed a statistically significant increase in caries prevalence of deciduous teeth in CWF cessation, but not when CWF was continued. However, the difference in change over time between CWF cessation and continued CWF was not statistically significant, based a year x city interaction term (OR = 1.18; 95% CI, 0.92 to 1.51; $P = 0.19$).

The pre-post cross-sectional study assessed to be of low quality conducted by PHE (2015) compared the caries prevalence of deciduous teeth of five-year-old children between water fluoridation in 2008 and without water fluoridation in 2015. The study found no significant difference in caries prevalence between post- and pre-cessation (difference = +0.9%; $P = 0.51$). No confounding variables were adjusted for in the analysis.

Summary

The McLaren and Singhal 2016 review did not identify any study for this outcome. The updated literature search identified two pre-post cross-sectional studies, one assessed to be of acceptable quality and one of low quality; both showed no change in the caries prevalence of deciduous teeth between the CWF cessation community and the CWF continued community, or between post- and pre-cessation. One study was assessed to be highly applicable and the other to be partially applicable to the Canadian context. Overall, there was limited evidence for no association between CWF cessation and caries prevalence of deciduous teeth in children.

Table 18: Dental Caries Prevalence or Proportion of Caries-Free Of Deciduous Teeth

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From McLaren and Singhal 2016 Review: No Study Identified					
Evidence From the Updated Literature Search: Two Pre-Post Cross-Sectional Studies					
McLaren et al. (2017)[92] Canada Pre-post cross-sectional Acceptable	Children aged 7 years N = 11,689	• CWF cessation • CWF continued	Difference (post – pre) in caries prevalence of deciduous teeth (dmft ≥ 1) • CWF cessation: 8%; $P < 0.05$ • CWF continued: 4%; *NS*	Year x city interaction term: OR = 1.18; 95% CI, 0.92 to 1.51; $P = 0.19$ (Adjustment for general health of child's mouth, brushing, visit dentist only for emergencies or never, last dentist visit within the last year, fruit or vegetable at least once a day, sugary drinks at least once a day, fluoride treatment at dentist office, household education of bachelor's degree or higher, home ownership, ethno-cultural background, and age)	Statistically significant increase (post minus pre) noted in caries prevalence of deciduous teeth in CWF cessation community but not in CWF continued. There was no significant difference in caries prevalence between cities. *(High)*
PHE (2015)[93] England Pre-post cross-sectional Low	Children aged 5 years N = 1,873	• CWF pre-cessation (0.61 ppm to 0.73 ppm, mean 0.69 ppm) in 2008 • CWF post-cessation (0.26 ppm to 0.27 ppm, mean 0.27 ppm) in 2015	Caries prevalence • Pre: 26.2% • Post: 27.1% Difference = +0.9%; $P = 0.51$	NR	There was no significant difference in caries prevalence between pre- and post-cessation. *(Partial)*

CI = confidence interval; CWF = community water fluoridation; dmft = decayed, missing, and filled deciduous teeth; NS = not significant; OR = odds ratio; PHE = Public Health England; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

b) Permanent Teeth

Mean Number of Decayed, Missing, and Filled Permanent Teeth

Results for mean DMFT are presented in Table 19.

Evidence From the McLaren and Singhal 2016 Review

Qualitative synthesis for dental caries of both deciduous and permanent teeth was reported in the deft section above.

Quantitative synthesis for DMFT:

Three studies without a comparison community that provided usable data (N = 9,503 children aged 6 to 16 years) were included in the quantitative synthesis for DMFT. A comparison was made between post-cessation and pre-cessation. The period between CWF cessation and last data collection was seven years in two studies and three years in one study. The studies were conducted in East Germany, Cuba, and Czech Republic, and were assessed as having a high risk of bias.

- Pooled estimates across time points within age groups showed a significant decrease in mean DMFT post-cessation compared with pre-cessation (MD = –1.02; 95% CI, –1.42 to –0.62; I^2 = NR).
- Pooled estimates across age groups and time points for each study showed no difference in mean DMFT post-cessation compared with pre-cessation (MD = –0.36; 95% CI, –1.04 to 0.32; I^2 = 99.8%).
- With a small number of studies and substantial heterogeneity in the pooled analysis, results should be interpreted with caution.

Three studies with a comparison community (N = 111,436 children aged 6 to 15 years) that provided usable data were included in the quantitative synthesis for DMFT. A comparison was made between cessation community and comparison community using differences (post minus pre) of DMFT. The period between CWF cessation and last data collection was 3 years, 5 years and 15 years. The studies were conducted in East Germany, Scotland, and the Netherlands, and were assessed as high risk of bias in one study and low risk of bias in the other two studies.

- Pooled estimates across time points within age groups showed a significant increase in mean DMFT in CWF cessation communities compared with comparison communities (MD= 0.54; 95% CI, 0.24 to 0.84; I^2 = NR).
- Pooled estimates across age groups and time points for each study showed no difference in mean DMFT between CWF cessation communities and comparison communities MD = 2.29; 95% CI, –1.04 to 5.61; I^2 = 99.1%).
- With a small number of studies and substantial heterogeneity in the pooled analysis, results should be interpreted with caution.

Evidence From the Updated Literature Search

The updated literature search identified one additional pre-post cross-sectional study assessed to be of acceptable quality by McLaren et al. (2017).[92]

McLaren et al. (2017)[92] compared the change in mean DMFT (post- and pre-cessation) among children aged seven years living in two Canadian cities: Calgary (CWF cessation in

2011) and Edmonton (CWF continued). Mean DMFT was measured as overall counts of all children (i.e., DMFT ≥ 0) or only in those with DMFT > 0 in 2004 to 2005 and 2013 to 2014. Differences between post and pre periods showed a significant decrease in mean DMFT in CWF cessation, but not with continued CWF. Estimates showed a significant decrease in mean DMFT (overall) in CWF cessation compared with continued CWF. However, adjusted estimates for mean DMFT (those with DMFT > 0) showed no difference.

Summary

The McLaren and Singhal 2016 review provided mixed evidence on the impact of CWF cessation on the change in mean DMFT in children and adolescents. The review included three studies without a comparison community and three studies with a comparison community. Two were assessed to be of low risk of bias and four were assessed to be of high risk of bias. Of the six studies, four were assessed to be of limited applicability and two of high applicability to the Canadian context. The additional pre-post study identified from the updated literature search and assessed to be of acceptable quality found a significant decrease in mean DMFT (overall, those with DMFT ≥ 0), but not in mean DMFT (those with DMFT > 0), in CWF cessation compared with CWF continued. The study was assessed to be of high applicability to the Canadian context. Overall, there was insufficient evidence for an association between CWF cessation and mean DMFT in children.

Table 19: Mean Decayed, Missing, and Filled Permanent Teeth

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From McLaren and Singhal 2016 Review					
McLaren and Singhal (2016)[52] Canada SR	Children aged 6 to 16 years Three studies (high risk of bias) N = 9,503	CWF cessation (without a comparison community) Post-cessation vs. Pre-cessation	NR	Pooled estimates across time points within age groups: MD = –1.02; 95% CI, –1.42 to –0.62); I^2 = NR Pooled estimates across age groups and time points for each study: MD = –0.36; 95% CI, –1.04 to 0.32; I^2 = 99.8%	Significant decrease in mean DMFT post-cessation across time points within age groups. No significant difference between post-cessation and pre-cessation across age and time points.
	Children aged 6 to 15 years Three studies (two of low risk of bias; one of high risk of bias) N = 111,436 participants	CWF cessation (with a comparison community) Post – pre (cessation community) vs. post – pre (comparison community)	NR	Pooled estimates across time points within age groups: MD = 0.54; 95% CI, 0.24 to 0.84 Pooled estimates across age groups and time points for each study: MD = 2.29; 95% CI, –1.04 to 5.61; I^2 = 99.1%	Significant increase in mean DMFT in CWF cessation across time points within age groups compared with a CWF. No significant difference between groups across age and time points.
Evidence From the Updated Literature Search: One Pre-Post Cross-Sectional Study					
McLaren et al. (2017)[92] Canada Pre-post cross-sectional Acceptable	Children aged 7 years N = 11,689	• CWF cessation • CWF continued	Difference (post – pre) in mean DMFT (overall) • CWF cessation: -0.24; *P* < 0.05 • CWF continued: -0.01; *NS* Difference (post – pre) in mean DMFT (those with DMFT > 0) • CWF cessation: –0.21; *NS*	Year x city interaction term: DMFT (overall) RR = 0.70; 95% CI, 0.51 to 0.95; *P* = 0.024 DMFT (those with DMFT > 0) RR = 0.88; 95% CI, 0.77 to 1.01; *P* = 0.062	Statistically significant decrease (post minus pre) in mean DMFT (overall) in CWF cessation community but not in CWF continued. *(High)*

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
			- CWF continued: –0.04; *NS*	Several covariates (i.e., general health of child's mouth, brushing, visit dentist only for emergencies or never, last dentist visit within the last year, fruit or vegetable at least once a day, sugary drinks at least once a day, fluoride treatment at dentist office, household education of bachelor's degree or higher, home ownership, ethno-cultural background, and age) were considered but could not be included in the models because they were only available at post-cessation	

CI = confidence interval; CWF = community water fluoridation; DMFT = decayed, missing, and filled permanent teeth; MD = mean difference; NR = not reported; NS = not significant; RR = rate ratio; SR = systematic review; vs. = versus.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Mean Number of Decayed, Missing, and Filled Permanent Tooth Surfaces

Results for mean DMFS are presented in Table 20.

Evidence From the McLaren and Singhal 2016 Review

No study was identified.

Evidence From the Updated Literature Search

The updated literature search identified one pre-post study.

The pre-post cross-sectional study assessed to be of acceptable quality by McLaren et al. (2016a)[94] reported the mean DMFS for all tooth surfaces and for smooth surfaces among children aged seven years living in two Canadian cities: Calgary (CWF cessation in 2011) and Edmonton (CWF continued). The study found no significant differences in mean DMFS (measured from all tooth surfaces or smooth surfaces only) between CWF cessation and CWF continued.

Summary

The McLaren and Singhal 2016 review identified no study for this outcome. One study identified by the updated literature search, and assessed to be of acceptable quality and highly applicable to the Canadian context, showed insufficient evidence to assess an association between CWF cessation and change in mean DMFS in children.

Table 20: Mean Decayed, Missing, and Filled Permanent Tooth Surfaces

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the McLaren and Singhal 2016 Review: No Studies Identified					
Evidence From the Updated Literature Search: One Pre-Post Cross-Sectional Study					
McLaren et al. (2016a)[94] Canada Pre-post cross-sectional Acceptable	Children aged 7 years N = 12,581	• CWF cessation • CWF continued	a) All tooth surfaces: Difference (post – pre) in mean DMFS (overall) • CWF cessation: –0.3[b] • CWF continued: –0.04 Difference (post – pre) in mean DMFS (those with DMFS > 0) • CWF cessation: –0.2 • CWF continued: –0.2	Year x city interaction term: Mean DMFS RR = 0.8; 95% CI, 0.6 to 1.1; *P* = 0.3 Mean DMFS (those with DMFS > 0) RR = 0.96; 95% CI, 0.8 to 1.2; *P* = 0.6	There were no significant differences in mean DMFS (measured from all tooth surfaces or smooth surfaces only) between CWF cessation and CWF continued. *(High)*
			b) Smooth surfaces: Difference in mean DMFS between post and pre-cessation CWF cessation: –0.02 CWF continued: 0.0 Difference in mean DMFS (those with DMFS > 0) between post and pre-cessation CWF cessation: 0.3 CWF continued: 0.0	Year x city interaction term: Mean DMFS RR = 2.7; 95% CI, 1.0 to 7.4; *P* = 0.06 Mean DMFS (those with DMFS > 0) RR = 1.2; 95% CI, 0.8 to 1.8; *P* = 0.3	

CI = confidence interval; CWF = community water fluoridation; DMFS = decayed, missing, and filled permanent tooth surfaces; RR = rate ratio.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] Significant difference.

Dental Caries Prevalence or Proportion of Caries-Free Permanent Teeth

Results for caries prevalence are presented in Table 21.

Evidence From the McLaren and Singhal 2016 Review

No study was identified.

Evidence From the Updated Literature Search

The updated literature search identified one pre-post study.

The pre-post cross-sectional study assessed to be of acceptable quality by McLaren et al. (2017)[92] compared caries prevalence of permanent teeth (defined as DMFT ≥ 1) in children aged seven years living in two Canadian cities: Calgary (CWF cessation in 2011) and Edmonton (CWF continued). Differences between the post and pre periods showed a statistically significant decrease in caries prevalence of permanent teeth in CWF cessation, but not with continued CWF (OR = 0.37; 95% CI, 0.28 to 0.49; *P* < 0.001).

Summary

The McLaren and Singhal 2016 review identified no study for this outcome. One study identified by the updated literature search and assessed to be of acceptable quality and highly applicable to the Canadian context, included insufficient evidence to assess an association between CWF cessation and dental caries prevalence of permanent teeth in children.

Table 21: Dental Caries Prevalence or Proportion of Caries-Free Permanent Teeth

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the McLaren and Singhal 2016 Review: No Study Identified					
Evidence From the Updated Literature Search: One Pre-Post Cross-Sectional Study					
McLaren et al. (2017)[92] Canada Pre-post cross-sectional Acceptable	Children aged 7 years N = 11,689	• CWF cessation • Continued CWF	Difference (post – pre) in caries prevalence (DMFT ≥ 1) • CWF cessation: –12%; *P* < 0.05 • Continued CWF: –1%; *NS*	Year x city interaction term OR = 0.37; 95% CI,0.28 to 0.49; *P* < 0.001 Several covariates (i.e., general health of child's mouth, brushing, visit dentist only for emergencies or never, last dentist visit within the last year, fruit or vegetable at least once a day, sugary drinks at least once a day, fluoride treatment at dentist office, household education of bachelor's degree or higher, home ownership, ethno-cultural background, and age) were considered but could not be included in the models because they were only available at post-cessation	Statistically significant decrease (post – pre) noted in caries prevalence of permanent teeth in the CWF cessation community but not in the CWF continued group. *(High)*

CI = confidence interval; CWF = community water fluoridation; DMFT = decayed, missing, and filled permanent teeth; NS = not significant; OR = odds ratio.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Treatment of Caries

Results for treatment of caries are presented in Table 22.

Evidence From the McLaren and Singhal 2016 Review

No study was identified.

Evidence From the Updated Literature Search

The updated literature search identified one pre-post study.

The pre-post cross-sectional study, assessed to be of acceptable quality by McLaren et al. (2017),[92] compared complete treatment of caries among children aged seven years living in two Canadian cities: Calgary (CWF cessation in 2011) and Edmonton (CWF continued). The complete caries care was defined as no untreated decay, but one or more fillings and/or extractions. Differences between post and pre periods showed a statistically significant increase in complete treatment of caries in CWF cessation, and a significant decrease in CWF continued (OR = 2.53; 95% CI, 2.04 to 3.13; $P < 0.001$). The result was reversed for no treatment of caries (defined as one or more instances of untreated decay, but no fillings or extractions). The findings suggested that dental treatment increased in CWF cessation but not with continued CWF.

Summary

The McLaren and Singhal 2016 review identified no study for this outcome. One study identified by the updated literature search and assessed to be of acceptable quality and highly applicable to the Canadian context included insufficient evidence to assess an association between CWF cessation and complete treatment of caries in children.

Table 22: Treatment of Caries

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the McLaren and Singhal 2016 Review: No Study Identified					
Evidence From the Updated Literature Search: One Pre-Post Cross-Sectional Study					
McLaren et al. (2017)[92] Canada Pre-post cross-sectional Acceptable	Children aged 7 years N = 11,689	• CWF cessation • CWF continued	Difference (post – pre) in complete caries care • CWF cessation: 13% [b] • CWF continued: –6% [b] Difference (post – pre) in no caries care • CWF cessation: –5% [b] • CWF continued: 4%[b]	Complete treatment of caries: OR = 2.53; 95% CI,2.04 to 3.13; *P* < 0.001 No treatment of caries care: OR = 0.38; 95% CI,0.28 to 0.52; *P* < 0.001 Several covariates (i.e., general health of child's mouth, brushing, visit dentist only for emergencies or never, last dentist visit within the last year, fruit or vegetable at least once a day, sugary drinks at least once a day, fluoride treatment at dentist office, household education of bachelor's degree or higher, home ownership, ethno-cultural background, and age) were considered but could not be included in the models because they were only available at post-cessation	Significant increase in the proportion of treatment of caries in CWF cessation compared with CWF continued. No treatment of caries significantly decreased in CWF cessation compared with CWF continued. *(High)*

CI = confidence interval; CWF = community water fluoridation; OR = odds ratio.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] $P < 0.05$.

Disparities

Results for disparities are presented in Table 23.

Evidence From the McLaren and Singhal 2016 Review

No study was identified.

Evidence From the Updated Literature Search

The updated literature search identified two pre-post studies reporting the disparities in dental caries among children in families of different socio-economic groups.

The pre-post cross-sectional study of acceptable quality by McLaren et al. (2016b)[95] compared the socio-economic patterns of children's dental caries in Calgary, Canada, between pre-cessation (2009 to 2010) and post-cessation (2013/ to 2014) periods of CWF. The study measured three dental caries indices; i.e., deft, DMFT and two or more teeth (primary or permanent) with untreated decay in children aged seven years. Two socio-economic indicators were dental insurance and material deprivation assessed by the Pampalon index. The results are presented in Table 23 and showed the following:

- Compared with presence of insurance, absence of dental insurance showed no significant difference in mean deft at both pre-cessation and post-cessation. Absence of dental insurance showed a significant increase in mean DMFT at post-cessation, but not in the pre-cessation. Absence of dental insurance showed a significant increase in two or more teeth (primary or permanent) with untreated decay at both pre- and post-cessation. Analyses using year x no dental insurance interaction term showed a significant increase in mean DMFT between post- and pre-cessation (RR = 1.80; 95% CI, 1.10 to 2.39; *P* = 0.02). There was no statistically significant year x no dental insurance interaction term for deft and two or more teeth (primary or permanent) with untreated decay.
- Compared with lowest deprivation, highest or middle deprivation had significantly higher deft and two or more teeth (primary or permanent) with untreated decay at post-cessation, but not in the pre-cessation. Highest or middle deprivation showed no significant difference in mean DEFT at both pre-cessation and post-cessation compared with lowest deprivation. Analyses using year x highest or middle deprivation interaction terms showed no significant difference in all three dental caries indices between post- and pre-cessation.

The cross-sectional study assessed to be of low quality conducted by PHE (2015)[93] investigated the disparities in dental caries among five-year-old children from families of different deprivation status living in CWF pre-cessation and CWF post-cessation. Children were classified by IMD quintiles: 1 (most deprived), 2, 3, 4, 5 (most affluent). The children were also subgrouped based on fluoride levels at the CWF pre-cessation (i.e., ≥ 0.7 ppm or < 0.7 ppm). Mean fluoride level in CWF post-cessation was 0.27 ppm. The results are presented in Table 23 and showed the following:

- For CWF pre-cessation (fluoride level ≥ 0.7 ppm), mean dmft and dental caries prevalence increased from most affluent group to most deprived group in both pre- and post-cessation. However, there was no statistically significant difference in mean dmft and caries prevalence within groups between pre- and post-cessation.
- For CWF pre-cessation (fluoride level < 0.7 ppm), mean dmft and caries prevalence were lowest in the most affluent groups compared with others. In the most affluent group,

mean dmft and caries prevalence significantly increased in post-cessation compared with pre-cessation.

Summary

The McLaren and Singhal 2016 review identified no study for this outcome. The updated literature search identified two studies, which were assessed to be of acceptable and low quality, and be highly and partially applicable to the Canadian context.The pre-post cross-sectional study by McLaren et al. (2016b)[95] showed that children from families of lower SES had significantly higher dental caries experience, which usually occurred post-CWF cessation compared with higher socio-economic counterparts. Significant differences were observed in the post-cessation groups for mean DMFT among non-dental insurers, and for mean deft and two or more teeth (primary or permanent) with untreated decay among the highest deprivation and middle deprivation groups. In PHE (2015),[93] mean dmft and caries prevalence were lowest in the most affluent group and highest in the most deprived group, which were observed in both pre- and post-cessation. From both studies, when compared between pre-cessation and post-cessation, there was no significant difference in dental caries experience within each socio-economic group. The findings suggest that children of low socio-economic group experience higher dental caries than those of high socio-economic group regardless of the presence or absence of CWF. Discontinuation of CWF was associated with a greater likelihood of dental caries (measured as DMFT) in children of family without dental insurance. Overall, there was limited evidence for no association between CWF cessation and a change in disparities in dental caries in children by levels of deprivation.

Table 23: Disparities

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td colspan="6">Evidence From the McLaren and Singhal 2016 Review: No Study Identified</td></tr>
<tr><td colspan="6">Evidence From the Updated Literature Search: Two Pre-Post Cross-Sectional Studies</td></tr>
<tr><td>McLaren et al. (2016b)[95]
Canada
Pre-post cross-sectional
Acceptable</td><td>Children aged 7 years
N = 3,787</td><td>• Pre-CWF cessation
• Post-CWF cessation</td><td colspan="2">By dental insurance status (presence of dental insurance as ref)
<table>
<tr><th rowspan="2">Dental Caries Index</th><th colspan="2">Effect Estimates of Absence (vs. Presence) of Dental Insurance on Dental Caries Outcomes</th><th rowspan="2">Year X no Dental Insurance Interaction Term</th></tr>
<tr><th>2009/10 (pre)</th><th>2013/14 (post)</th></tr>
<tr><td>deft
RR (95% CI)</td><td>1.05 (0.94 to 1.17);
P = 0.40</td><td>0.94 (0.86 to 1.03); P = 0.18</td><td>0.90 (0.78 to 1.04);
P = 0.14</td></tr>
<tr><td>DMFT
RR (95% CI)</td><td>0.87 (0.65 to 1.16);
P = 0.33</td><td>1.56 (1.05 to 2.33); P = 0.03</td><td>1.80 (1.10 to 2.39);
P = 0.02</td></tr>
<tr><td>2 or more teeth (primary or permanent) with untreated decay
OR (95% CI)</td><td>1.76 (1.34 to 2.32);
P < 0.001</td><td>2.0 (1.57 to 2.53); P < 0.001</td><td>1.13 (0.81 to 1.58);
P = 0.46</td></tr>
</table>
</td><td>Absence of dental insurance showed a significant increase in mean DMFT between post- and pre-cessation. (High)
No statistically significant year x highest or middle deprivation terms were observed for all three dental caries indices. (High)</td></tr>
</table>

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
			By deprivation categories (low deprivation as ref)		

Dental Caries Index	Effect Estimates of Highest or Middle Deprivation (vs. Lowest Deprivation) on Dental Caries Outcomes		Year X Highest or Middle Deprivation Interaction Terms
	2009/10 (pre)	2013/14 (post)	
deft			
Highest deprivation RR (95% CI)	1.07 (0.93 to 1.23); *P* = 0.34	1.19 (1.08 to 1.30); *P* < 0.001	1.11 (0.95 to 1.30); *P* = 0.20
Middle deprivation RR (95% CI)	1.03 (0.88 to 1.19); *P* = 0.73	1.15 (1.02 to 1.30); *P* = 0.02	1.12 (0.91 to 1.37); *P* = 0.27
DMFT			
Highest deprivation RR (95% CI)	1.42 (0.74 to 2.69); *P* = 0.27	1.04 (0.68 to 1.59); *P* = 0.85	0.74 (0.36 to 1.50); *P* = 0.40
Middle deprivation RR (95% CI)	1.08 (0.61 to 1.91); *P* = 0.77	0.80 (0.49 to 1.30); *P* = 0.37	0.74 (0.36 to 1.51); *P* = 0.41
2 or more teeth (primary or permanent) with untreated decay			
Highest deprivation OR (95% CI)	2.95 (0.89 to 9.82); *P* = 0.07	2.23 (1.66 to 2.98); *P* < 0.001	0.75 (0.24 to 2.36); *P* = 0.63
Middle deprivation OR (95% CI)	0.90 (0.31 to 2.62); *P* = 0.83	1.43 (1.05 to 1.94); *P* = 0.02	1.59 (0.57 to 4.43); *P* = 0.37

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
PHE (2015)[93] England Pre-post cross-sectional Low	Children aged 5 years N = 1,010	Subgroup 1: • CWF pre-cessation (≥ 0.7 ppm) in 2008 • CWF post-cessation (no fluoridation; 0.27 ppm) in 2015	Mean dmft (95% CI) Most deprived (group 1) • Pre: 1.40 (0.91 to 1.90) • Post: 1.51 (1.06 to 1.95); $P = 0.75$ Most affluent group (group 5) • Pre: 0.22 (0.10 to 0.34) • Post: 0.58 (0.23 to 0.93); $P = 0.06$ Caries prevalence Most deprived group • Pre: 34.2% (25.5 to 42.9) • Post: 40.6% (31.2 to 49.9); $P = 0.33$ Most affluent group • Pre: 14.4% (7.4 to 21.4) • Post: 21.8% (10.9 to 32.7); $P = 0.25$	NR	Mean dmft and dental caries prevalence increased from most affluent group to most deprived group in both pre- and post-cessation. However, there was no statistically significant difference in mean dmft and caries prevalence within groups between pre- and post-cessation. *(Partial)*
	Children aged 5 years N = 727	Subgroup 2: • CWF pre-cessation (<0.7 ppm) in 2008 • CWF post-cessation (no fluoridation; 0.27 ppm) in 2015	Mean dmft (95% CI) Group 3[b] • Pre: 0.86 (0.55 to 1.17) • Post: 0.72 (0.30 to 1.11); $P = 0.57$ Most affluent group (group 5) • Pre: 0.23 (0.10 to 0.35) • Post: 0.55 (0.26 to 0.84); $P = 0.05$ Caries prevalence Group 3[b] • Pre: 23.7% (16.9 to 30.4) • Post: 23.2% (14.0 to 32.3);	NR	Mean dmft and caries prevalence were lowest in the most affluent groups compared with others. In the most affluent group, mean dmft and caries prevalence significantly increased in post-cessation compared with pre-cessation. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
			P = 0.93 Most affluent group • Pre: 9.0% (4.3 to 13.6) • Post: 20.2% (12.1 to 28.3); *P* = 0.01		

CI = confidence interval; CWF = community water fluoridation; dmft = decayed, missing, and filled deciduous teeth; DMFT = decayed, missing, and filled permanent teeth; OR = odds ratio; PHE = Public Health England; ref = reference; RR = rate ratio; vs. = versus.

[a] For primary studies that were judged to be (high, partial or low) applicable to the Canadian context, i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

[b] No data for group 1 (most deprived) and group 2 (number of children below 20).

Research Question 3: Effects of Community Water Fluoridation on Human Health Outcomes Including Dental Fluorosis

1. Dental Fluorosis

Dental fluorosis is characterized by the internal discoloration of the teeth, a side-effect associated with prolonged exposure to higher than recommended levels of fluoride.96-99 Depending on the severity of the condition, dental fluorosis varies from mild (e.g., barely noticeable white flecks) to severe (e.g., brown stains).[97]

Results for dental fluorosis are presented in Table 24.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review did not conduct a de novo SR on primary studies for dental fluorosis. Instead, it included two previous SRs (McDonagh et al. [2000] and NHMRC 2007) and one recent Cochrane review by Iheozor-Ejiofor et al. (2015).

The previous SR by McDonagh et al. (2000) included 88 studies, each of which were assessed as low quality. The analysis showed that dental fluorosis prevalence increased with water fluoride levels in a dose-dependent manner. From a dose-dependent analysis of fluoride levels ranging from 0 ppm to 5 ppm, it was found that the prevalence of dental fluorosis of any level of severity at 1 ppm was 48% (95% CI, 40 to 75), of which 12.5% (95% CI, 7.0 to 21.5) had fluorosis of aesthetic concern.

The previous 2007 NHMRC review included 10 studies of low quality published after McDonagh et al. on the prevalence of dental fluorosis of any severity (any fluorosis) and the prevalence of “fluorosis of aesthetic concern” in children aged 5 to 15 years living in CWF areas (0.8 to 1.2 ppm) and in non-CWF areas (≤ 0.4 ppm). The SR found that although there was approximately a four- to five-fold risk in developing “any fluorosis” and “fluorosis of aesthetic concern” (OR = 4.61; 95% CI, 3.48 to 6.11), the prevalence of “any fluorosis” with optimal water fluoridation increased by 26% compared with non-CWF (rate difference = 0.26; 95% CI, 0.19 to 0.32), while the absolute increase in prevalence of “fluorosis of aesthetic concern” was 5% (rate difference = 0.05; 95% CI, 0.03 to 0.07).

The SR by Iheozor-Ejiofor et al. (2015), which was rated to be of high quality, included 90 studies on dental fluorosis of “any degree” and 40 studies on fluorosis of “aesthetic concern.” All the included studies were assessed as high risk of bias. Participants included children, adolescents, and adults up to 65 years old. The results are presented in Table 24 and showed the following:

Any Dental Fluorosis

- For fluoride levels of 5 ppm or less (ranged from 0 ppm to 5 ppm; mean 1.22 ppm) (90 studies, 180,530 participants), the odds of dental fluorosis of “any level” increased by a factor of 3.60 (95% CI, 2.86 to 4.53) for each one unit (1 ppm fluoride) increase in fluoride exposure.
- For all fluoride levels (ranged from 0 ppm to 14 ppm; mean 1.28 ppm) (90 studies, 182,233 participants), the odds of dental fluorosis of “any level” increased by a factor of 3.13 (95% CI, 2.55 to 3.85) for each one unit increase in fluoride exposure.
- At 0.7 ppm, the percentage of dental fluorosis of “any level” was 40% (95% CI, 35% to 44%).

Aesthetic Concern

- For fluoride levels of 5 ppm or less (ranged from 0 ppm to 4.9 ppm; mean 0.8 ppm) (40 studies, 59,630 participants), the odds of dental fluorosis of “aesthetic concern” increased by a factor of 2.90 (95% CI, 2.05 to 4.10) for each one unit increase in fluoride exposure.
- For all fluoride levels (ranged from 0 ppm to 7.6 ppm; mean 0.85 ppm) (40 studies, 60,030 participants), the odds of dental fluorosis of “aesthetic concern” increased by a factor of 2.84 (95% CI, 2.00 to 4.03) for each one unit increase in fluoride exposure.
- At 0.7 ppm, the percentage of dental fluorosis of “aesthetic concern” was 12% (95% CI, 8% to 17%).

Evidence From the Updated Literature Search

The updated literature search identified one ecological study assessed to be of acceptable quality and 20 cross-sectional studies all assessed to be of low quality. The findings of one ecological study (Arora et al. [2017][100] from the US) and three ecological studies (Bal et al. [2015][101] from Australia; Pretty et al. [2016],[102] and Balmer et al. [2015][103] from the UK) were assessed to be partially applicable to the Canadian context. The rest of the studies were conducted in countries with different socio-economic characteristics and water fluoride levels compared with Canada, such as India,[104-111] Mexico,[112-114] Brazil,[115] Ethiopia,[116,117] Nigeria,[118] and Sudan.[119] These studies had significant methodological limitations and many did not adjust for confounding variables in their analyses. Their findings were assessed to be of limited applicability to the Canadian context. Most studies measured dental fluorosis using either Dean’s index or the Thylstrup-Fejerskov index.

The ecological study of acceptable quality by Arora et al. (2017)[100] examined the prevalence of dental fluorosis in children and adolescents aged 7 to 17 years who were exposed to three different levels of water fluoridation in the US (i.e., < 0.3 ppm, 0.3 ppm to < 0.7 ppm, and 0.7 ppm to 1.2 ppm.). The weighted prevalences of dental fluorosis (i.e., any fluorosis including mild, moderate and severe) in participants exposed to those three levels of water fluoridation were 12.5%, 19.6%, and 27.9%. After adjustment for age, gender, race and ethnicity, other sources of fluoride and region, it was found that exposure to water fluoridation at 0.7 ppm to 1.2 ppm, but not 0.3 ppm to < 0.7 ppm, had significantly higher odds of developing enamel fluorosis compared with < 0.3 ppm (maximum likelihood estimate = 0.79; $P = 0.00$).

The cross-sectional study of low quality by Pretty et al. (2016)[102] compared the prevalence of dental fluorosis among children aged 11 to 14 years in fluoridated (1.0 ppm) and non-fluoridated (naturally occurring fluoride [NOF]) English cities. It was found that the prevalence of overall dental fluorosis was higher in fluoridated cities compared with non-fluoridated cities (61.5% versus 37.2%; $P < 0.0001$). However, there was no significant difference in the mean of self-perceived aesthetic score between respondents from fluoridated and non-fluoridated cities ($P = 0.572$) from an aesthetic survey.

The cross-sectional study of low quality by Bal et al. (2015)[101] investigated whether the adjustment of the fluoride concentration to 1 ppm in the drinking water in 1992 was associated with the incidence of fluorosis in Blue Mountains, Australia. The study included children aged 7 to 11 years from Blue Mountains (fluoridated in 1992) and Hawkesbury (fluoridated in 1969). Lifetime fluoride exposure was stratified as 0%, 1 to 99%, and 100%. The study found that the prevalence of dental fluorosis was the same in both regions (39% for overall dental fluorosis and 1.5% for moderate-to-severe fluorosis). Compared with no exposure (0%), 100% lifetime exposure to fluoridated water had increased odds of developing dental fluorosis (OR = 1.55; 95% CI, 1.21 to 2.13), after adjusting for frequency of toothbrushing, rinsing habit after toothbrushing, and licked or ate toothpaste).

The cross-sectional study be of low quality by Balmer et al. (2015)[103] found no significant difference for the occurrence of molar incisor hypomineralization among children aged 12 years living in fluoridated and non-fluoridated areas in five regions in Northern England, after adjustment for gender and IMD. Further analysis found that children living in the fluoridated areas had a significantly higher risk for incisor or first molar tooth having a demarcated, diffuse, or hypoplastic defect.

The cross-sectional study of low quality by Wong et al. (2014)[120] from Hong Kong, China, compared the prevalence and severity of diffuse opacities, a measure of dental fluorosis, among 12-year-old children whose maxillary incisors developed during periods with different concentrations of fluoride in Hong Kong's public water system. Data were from four previous epidemiological surveys in Hong Kong (1983, 1991, 2002, and 2010), in which the community water fluoride level was 1.0 ppm, 0.7 ppm, 0.5 ppm, and 0.5 ppm, respectively. The study found that the prevalence of diffuse opacities decreased with decreasing water fluoride concentrations from 1983 to 2002, and then increased in 2010. The authors suggested that the increase in the prevalence of opacities in 2010 could be linked to the exposure of other fluoride sources. The analysis in this study did not adjust for any confounding variables.

The rest of the cross-sectional studies[104-119] determined the prevalence and severity of dental fluorosis in children and adolescents being exposed to a wide range of NOF levels, ranging from 0.07 ppm to 18 ppm. The findings of these studies were presented together because they were conducted in countries with different socio-economic characteristics and water fluoride levels compared with Canada. These studies found that the prevalence of dental fluorosis and its severity increased with increased water fluoride levels. Collectively, the prevalence of overall dental fluorosis in participants exposed to naturally occurring water fluoride levels between 0.7 ppm and 1.36 ppm ranged from 20.0% to 70%.[104,108,109,111,113,115,119] The prevalence of moderate-to-severe fluorosis in areas of 0.7 ppm to 1.2 ppm ranged from 2.1% to 9.1%.[114,115]

Summary

Evidence the SRs identified in the 2016 NHMRC review showed that the prevalence of dental fluorosis of "any level" at 0.7 ppm and 1.0 ppm was 40% and 48%, respectively, while the prevalence of dental fluorosis of "aesthetic concern" was 12.0% and 12.5%, respectively. There was a significantly higher risk of developing dental fluorosis in high fluoridated areas compared with in low fluoridated areas. The additional studies identified from the updated literature search also found that the prevalence of dental fluorosis and its severity increased with increased water fluoride levels. However, the majority of evidence derived from countries where water fluoride levels were many folds higher than the current Canadian levels had limited applicability to the Canadian context. Overall, there was consistent evidence for an association between an increase in the level of fluoride in drinking water and an increase in the prevalence of dental fluorosis.

Table 24: Dental Fluorosis

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Two Previous SRs and One Identified SR					
McDonagh et al. (2000) UK Previous SR	Participants aged NR 88 studies (low quality) N = NR	Fluoridated areas Control (low fluoride areas)	NR	Regression analysis: Prevalence of any fluorosis at 1 ppm CWF 48% (95% CI, 40 to 57) Percent of fluorosis of aesthetic concern at 1 ppm CWF (95% CI) = 12.5% (7.0 to 21.5)	The prevalence of dental fluorosis of any level at 1 ppm was 48%, of which 12.5% had fluorosis of aesthetic concern.
NHMRC 2007 Australia Previous SR	Children aged 5 to 15 years 10 additional studies (quality not reported) after McDonagh et al. (2000)	CWF (0.8 ppm to 1.2 ppm) Non-CWF (≤ 0.4 ppm)	NR	Prevalence of “any fluorosis”: OR (95% CI) = 4.61 (3.48 to 6.11) RD (95% CI) = 0.26 (0.19 to 0.32) Prevalence of “fluorosis of aesthetic concern”: OR (95% CI) = 4.58 (3.54 to 5.93) RD (95% CI) = 0.05 (0.03 to 0.07)	Although there was a fourfold risk in the development of fluorosis of aesthetic concern in optimal water fluoridation, the absolute increase in prevalence was about 5%.
Iheozor-Ejiofor et al. (2015) UK; Canada SR High	Children, adolescents, and adults aged up to 65 years 90 studies for dental fluorosis (high risk of bias) N = 180,530 40 studies for dental fluorosis of aesthetic concern (high risk of bias) N = 59,630	All F levels F ≤ 5 ppm F = 0.7 ppm		Any fluorosis • All F levels (0 ppm to 14 ppm; mean 1.28 ppm): OR (95% CI) = 3.13 (2.55 to 3.18) • F ≤ 5 ppm (0 ppm to 5 ppm; mean 1.22 ppm): OR (95% CI) = 3.60 (2.86 to 4.53) • F = 0.7 ppm: Prevalence (95% CI) = 40% (35% to 44%) Aesthetic concern • All F levels (0 ppm to 7.6 ppm; mean 0.85 ppm): OR (95% CI) = 2.84 (2.00 to 4.03)	The prevalence of dental fluorosis of any level at 0.7 ppm was 40%, of which 12% had fluorosis of aesthetic concern.

Study Country Design Quality	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
				- F ≤ 5 ppm (0 ppm to 4.9 ppm; mean 0.8 ppm): OR (95% CI) = 2.90 (2.05 to 4.10) - F = 0.7 ppm: Prevalence (95% CI) = 12% (8 to 17)	
Evidence From Updated Literature Search: One Ecological Study and 20 Cross-Sectional Studies					
Khandare et al. (2018)[121] India Cross-sectional Low	Children aged 8 to 14 years living in areas having different fluoride levels N = 1,934	Mean NOF (SD) - 0.877 (0.108) ppm - 2.53 (0.606) ppm - 3.77 (0.197) ppm Intervention with safe drinking water for 5 years - < 1.0 ppm (initial 4.515 (0.077) ppm)	Prevalence of any fluorosis - 0.877 ppm: 21.2% - 2.53 ppm: 81.9% - 3.77 ppm: 61.8% - < 1.0 ppm: 81.3%	NR	The prevalence of dental fluorosis was higher in high fluoride levels (i.e., 3.77 ppm, 2.53 ppm, < 1 ppm [previous 4.515 ppm five years ago]) compared with low fluoride levels (0.877 ppm). (*Limited*)
Arora et al. (2017)[100] USA Ecological Acceptable	Children aged 7 to 17 years N = 16,060	Water fluoridation - 0.7 ppm to 1.2 ppm - 0.3 ppm to < 0.7 ppm - < 0.3 ppm	Weighted prevalence of dental fluorosis (95% CI) - 0.7 ppm to 1.2 ppm: 27.9% (21.4 to 34.3) - 0.3 ppm to < 0.7 ppm: 19.6% (7.3 to 31.9) - < 0.3 ppm: 12.5% (8.9 to 16.1) (Adjustment for age, gender, race and ethnicity, other sources of fluoride, and region)	Maximum likelihood estimates - 0.7 ppm to 1.2 ppm: 0.79; *P* = 0.00 - 0.3 ppm to < 0.7 ppm: –0.12; *P* = 0.73 - < 0.3 ppm: ref (Adjustment for age, gender, race and ethnicity, other sources of fluoride, and region)	Exposure to water fluoridation at 0.7 ppm to 1.2 ppm had significantly higher odds of developing enamel fluorosis. (*Partial*)
Bonola-Galardo et al. (2017)[112] Mexico Cross-sectional Low	Schoolchildren aged 9 to 12 years N = 141	NOF - 1.8 ppm - 0.4 ppm	Prevalence of dental fluorosis (mild) - 1.8 ppm: 81.4% - 0.4 ppm: 1.4%; *P* < 0.001	NR	The prevalence of dental fluorosis was significantly higher in high fluoridated areas compared with low fluoridated areas. (*Limited*)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings (*Applicability*[a])**
			Prevalence of dental fluorosis (moderate to severe) - 1.8 ppm: 12.9% - 0.4 ppm: 1.4%; *P* < 0.001		
Garcia-Perez et al. (2017)[113] Mexico Cross-sectional Low	Schoolchildren aged 8 to 12 years N = 524	NOF - 1.61 ppm - 0.70 ppm	Prevalence of dental fluorosis (overall) - 1.61 ppm: 53.4% - 0.70 ppm: 29.2% Prevalence of dental fluorosis (moderate to severe) - 1.61 ppm: 28.1% - 0.70 ppm: 9.5%	NR	The prevalence of dental fluorosis was higher in high fluoridated areas compared with low fluoridated areas. (*Limited*)
Ibiyemi (2017)[118] Nigeria Cross-sectional Low	Children aged 8 years N = 322	NOF - Urban, higher F: 0.85 (0.19) ppm; Rural, higher F: 2.13 (0.64) ppm - Urban, lower F: 0.07 (0.02) ppm; Rural, lower F: 0.09 (0.02) ppm	Prevalence of dental fluorosis (TFI > 0) - Urban, higher F: 20/81 (24.7%) - Rural, higher F: 65/79 (82.3%) - Urban, lower F: 4/79 (5.1%) - Rural, lower F: 7/83 (8.4%) - All areas: 96/322 (29.8%)	Association between dental fluorosis and fluoride concentration in drinking water: OR (95% CI) = 1.57 (0.87 to 2.81), NS (Adjustment for age, gender, exclusive breastfeeding, age breastfeeding ceased, infant or childhood disease, age of toothbrushing, frequency of toothbrushing, amount of toothpaste used per brushing, fluoride toothpaste ingestion, normal birth, and family history of tooth discoloration)	Prevalence of dental fluorosis was highest in rural higher F areas and lowest in urban lower F areas. After adjusting for independent variables, the association between dental fluorosis and fluoride concentration in drinking water was not statistically significant. (*Limited*)
Khandare et al. (2017)[105] India Cross-sectional Low	8 to 15 years old schoolchildren living in high fluoride rural areas (intervention)	NOF - High (1.43 ppm to 3.84 ppm) - Low (0.32 ppm to 1.18 ppm)	Prevalence of dental fluorosis (Dean's score > 0) - High F: 44% in males and 50% in females - Low F: 27% in males and	NR	The prevalence of dental fluorosis in the low fluoride areas was lower than that in the high fluoride areas. (*Limited*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
	Older schoolchildren (age not reported) from higher secondary school living in lower fluoride urban areas (comparator) N = 824		31% in females		
Rango et al. (2017)[116] Ethiopia Cross-sectional Low	Participants aged 10 to 50 years N = 386	NOF (range: 0.6 ppm to 15 ppm)	• As F in drinking water increased from 0.6 ppm to 15 ppm, prevalence of severe enamel fluorosis increased and the prevalence of mild-to-moderate enamel fluorosis decreased • At 0.6 ppm, the prevalence of fluorosis was 0 • Between 1.4ppm and 2.0 ppm the prevalence of fluorosis was 4.3%. As the concentration of F in the drinking water increased to 4 ppm and 15 ppm, the prevalence of severe fluorosis was 16% and 64%, respectively	Enamel fluorosis severity Correlation coefficient, *r* = 0.42; *P* < 0.001 Mean TFI score Beta coefficient (SE) = 0.37 (0.008); *P* < 0.01 (Adjustment for age, sex, BMI, and community fixed effects)	There was significant positive association between drinking water fluoride and enamel fluorosis. (*Limited*)
Razdan et al. (2017)[106] India Cross-sectional Low	Children aged 12 to 14 years N = 219	NOF • 4.99 ppm • 1.70 ppm • 0.6 ppm	• All children living in 0.6 ppm fluoride area had normal teeth • All children living in 1.7 ppm and 4.99 ppm areas had dental fluorosis • The proportions of children with mild (18.7% vs. 10.7%), moderate (53.3% vs. 60.0%), and severe	NR	All children living in 1.7 ppm and 4.99 ppm areas had dental fluorosis. (*Limited*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
			(28.0% vs. 29.3%) dental fluorosis in 1.7 ppm compared with 4.99 ppm were similar		
Irigoyen-Camacho et al. (2016)[114] Mexico Cross-sectional Low	Children aged between 8 and 12 years N = 734	NOF • 1.60 ppm • 0.70 ppm • 0.56 ppm	Prevalence of dental fluorosis (moderate to severe [TFI ≥ 4]) • 1.60 ppm: 31.9% • 0.70 ppm: 9.1% • 0.56 ppm: 6.3%	OR (95% CI) • 1.60 ppm: 6.27 (5.93 to 6.63); *P* = 0.003 • 0.70 ppm: 1.19 (1.06 to 1.34); *P* < 0.001 • 0.56 ppm: ref (Adjustment for sex, number of teeth, source of drinking water, use of fluoridated toothpaste, and weight-for-age) OR (95% CI) • 1.60 ppm: 5.85 (5.45 to 6.29); *P* = 0.003 • 0.70 ppm: 1.20 (1.06 to 1.35); *P* < 0.001 • 0.56 ppm: ref (Adjustment for sex, number of teeth, source of drinking water, use of fluoridated toothpaste, and height-for-age)	There were significant associations between dental fluorosis (TFI ≥ 4) and tap water fluoride concentration of 0.70 ppm and 1.60 ppm in both adjusted models, using 0.56 ppm as reference. (*Limited*)
Mahantesha et al. (2016)[107] India Cross-sectional Low	Children aged 9 to 15 years N = 289	NOF • 1.36 ppm • 0.381 ppm • 0.136 ppm	Prevalence of dental fluorosis (moderate to severe) • 1.36 ppm: 100% • 0.381 ppm: 8.1% • 0.136 ppm: 0.0% Dental fluorosis severity Mean Dean's index (SE)	Relationship between prevalence of dental fluorosis (Dean's index > 1) and water fluoride concentration Beta coefficient: 3.33; *P* = 0.00001 (Adjustment for tea consumption, nutritional status, and water consumption)	Drinking water fluoride was significantly positively associated with the prevalence of dental fluorosis. (*Limited*)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings** **(*Applicability*[a])**
			- 1.36 ppm: 4.71 (0.047) - 0.381 ppm: 1.42 (0.15); $P < 0.001$ - 0.136 ppm: 0.12 (0.047); $P < 0.001$	Relationship between dental fluorosis severity (Dean's index: 4, 5) and water fluoride concentration Beta coefficient: 22.90; $P = 0.81$) (Adjustment for diet and nutritional status)	
Pretty et al. (2016)[102] UK Cross-sectional Low	Children aged 11 to 14 years in four English cities N = 1,904	- CWF (1 ppm) - Non-CWF (NOF, level NR)	- Compared with non-fluoridated cities, fluoridated cities had a significantly higher prevalence of dental fluorosis at TFI > 0 (61.5% vs 37.2%; $P < 0.0001$) and at TFI > 2 (10.4% vs 2.2%; $P < 0.0001$) - There was no significant difference in the response rate among aesthetic score between fluoridated and non-fluoridated cities	NR	The prevalence of dental fluorosis was higher in fluoridated cities compared with non-fluoridated cities. However, the response rate to self-perceived aesthetic score was the same in both areas. (*Partial*)
Ramadan and Ghandour (2016)[119] Sudan Cross-sectional Low	Residents in two communities, mean age 17.43 years and 16.9 years N = 800	NOF - 1.36 ± 0.08 ppm (range: 1.29 ppm to 1.43 ppm) - 0.45 ± 0.39 ppm (range: 0.24 to 1.31 ppm)	Prevalence of dental fluorosis (overall) - 1.36 ppm: 70% - 0.45 ppm: 42.5%; $P < 0.001$	NR	The prevalence of dental fluorosis was significantly higher in the high fluoridated area compared with the low fluoridated area. (*Limited*)
Sebastian et al. (2016)[108] India Cross-sectional Low	Children aged 10 to 12 years N = 405	NOF - 2.0 ppm - 1.2 ppm - 0.4 ppm	Prevalence of dental fluorosis (overall) - 2.0 ppm: 87.4%; $P = 0.03$ - 1.2 ppm: 27.4%; $P = 0.03$ - 0.4 ppm: 10.3%	NR	The prevalence of dental fluorosis as a whole or at various degree of severity increased with increasing drinking water fluoride level. (*Limited*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td>Bal et al. (2015)[101]
Australia
Cross-sectional
Low</td><td>Children aged 7 to 11 years
N = 1,326</td><td>Lifetime fluoride exposure (1 ppm)
• 100%
• 1 to 99%
• 0%</td><td></td><td>OR (95% CI)
• 100%: 1.55 (1.21 to 2.13)
• 1% to 99%: 1.46 (0.98 to 2.18)
• 0%: ref
(Adjustment for frequency of toothbrushing, rinsing habit after toothbrushing, and licked or ate toothpaste)</td><td>Compared with no exposure (0%), lifelong exposure (100%) to fluoridated water had a significantly higher risk of overall dental fluorosis. (Partial)</td></tr>
<tr><td>Balmer et al. (2015)[103]
UK
Cross-sectional
Low</td><td>Children aged 12 years
N = 3,233</td><td>• CWF (F level NR)
• Non-CWF (F level NR)</td><td colspan="2">
<table>
<tr><th></th><th>Non-Fluoridated</th><th>Fluoridated</th></tr>
<tr><td></td><td colspan="2">OR (95% CI)</td></tr>
<tr><td>MIH children</td><td>Ref (1)</td><td>1.26 (0.89 to 1.79)[a]</td></tr>
<tr><td>Demarcated defects</td><td></td><td></td></tr>
<tr><td>Incisors</td><td>Ref (1)</td><td>1.73 (1.33 to 2.25)[b]</td></tr>
<tr><td>First permanent molars</td><td>Ref (1)</td><td>1.30 (1.07 to 1.57)[b]</td></tr>
<tr><td></td><td colspan="2">RR (95% CI)</td></tr>
<tr><td>Diffuse defects</td><td></td><td></td></tr>
<tr><td>Incisors</td><td>Ref (1)</td><td>2.8 (2.3 to 3.4)[c]</td></tr>
<tr><td>First permanent molars</td><td>Ref (1)</td><td>2.2 (1.8 to 2.8)[c]</td></tr>
<tr><td>Hypoplastic defects</td><td></td><td></td></tr>
<tr><td>Incisors</td><td>Ref (1)</td><td>1.8 (0.8 to 3.4)</td></tr>
<tr><td>First permanent molars</td><td>Ref (1)</td><td>1.4 (1.03 to 1.86)[d]</td></tr>
</table>
[a] Adjusted for gender and index of multiple deprivation.
[b] Adjusted for index of multiple deprivation.
[c] P < 0.001.
[d] P = 0.035.</td><td>Compared with non-fluoridated areas, children living in fluoridated areas had no significant difference for the occurrence of MIH, but had a significantly higher risk for incisor or first molar tooth having a demarcated, diffuse, or hypoplastic defect. (Partial)</td></tr>
<tr><td>Moimaz et al. (2015)[115]
Brazil
Cross-sectional</td><td>Children aged 12 years
N = 496</td><td>NOF
• 1.2 ppm
• 0.7 ppm</td><td>Prevalence of dental fluorosis (overall)
• 1.2 ppm: 68.4%
• 0.7 ppm: 52.1%</td><td>NR</td><td>There was no significant difference in the prevalence of dental fluorosis of various degrees between areas.</td></tr>
</table>

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Low			Prevalence of dental fluorosis (very mild to mild) - 1.2 ppm: 65.0% - 0.7 ppm: 50.0%; *P* = 0.0781 Prevalence of dental fluorosis (moderate to severe) - 1.2 ppm: 3.4% - 0.7 ppm: 2.1%; *P* = 0.4615 98.3% of children with dental fluorosis in both areas had no knowledge about fluorosis		(*Limited*)
Sebastien and Sunitha (2015)[109] India Cross-sectional Low	Children aged 10 to 12 years N = 405	NOF - 2.0 ppm - 1.2 ppm - 0.4 ppm	Prevalence of dental fluorosis (overall) - 2.0 ppm: 74.1% - 1.2 ppm: 20.0% - 0.4 ppm: 8.1% In the 2 ppm area, severe dental fluorosis prevalence was 28% compared with 0.7% in the other two areas	NR	The prevalence of dental fluorosis was higher in high fluoridated area compared with low fluoridated areas. (*Limited*)
Punitha et al. (2014)[110] India Cross-sectional Low	Children aged 7 to 15 years N = 348	NOF - 2.05 ppm - 0.47 ppm	Prevalence of dental fluorosis (overall) - 2.05 ppm: 44.0% - 0.47 ppm: 2.4%	Correlation coefficient, $r = 0.457$; $P < 0.0001$	The prevalence of dental fluorosis was higher in high fluoridated areas compared with low fluoridated areas. There was a positive correlation between occurrence of fluorosis and fluoride levels. (*Limited*)

<table>
<thead>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
</thead>
<tbody>
<tr>
<td>Rango et al. (2014)[117]
Ethiopia
Cross-sectional
Low</td>
<td>Children aged 10 to 15 years
N = 491</td>
<td>NOF: 1.06 ppm to 18.0 ppm</td>
<td colspan="2">Prevalence of dental fluorosis (multivariable analyses controlling for age, sex, BMI, and breast feeding duration)
• 100% dental fluorosis prevalence (TFI scores ≥ 1) for children drinking groundwater fluoride levels of 1.06 ppm to 18.0 ppm
• At fluoride levels ≥ 6 ppm, most of the TFI scores were of 5 and 6 (i.e., moderate to severe)
• At fluoride levels < 1.6 ppm, most children had normal teeth (TFI scores of 0)
• At 1.5 ppm, the prevalence of mild and moderate dental fluorosis was 53% and 5%, respectively
• At 2.0 ppm, the prevalence of moderate and severe dental fluorosis was 14.7% and 2.8%, respectively
• At 4.0 ppm, the prevalence of mild, moderate, and severe dental fluorosis was 28.5%, 28% and 26%, respectively
• The prevalence of moderate and severe dental fluorosis approached zero at fluoride levels below 1.2ppm and 1.8ppm, respectively</td>
<td>The prevalence of dental fluorosis and its severity increased with increased water fluoride levels. (Limited)</td>
</tr>
<tr>
<td>Sukhabogi et al. (2014)[111]
India
Cross-sectional
Low</td>
<td>Children aged 12 and 15 years
N = 1,875</td>
<td>NOF
• 4.0 to 6.28 ppm
• 1.2 to < 4.0 ppm
• 0.7 to < 1.2 ppm
• < 0.7 ppm</td>
<td colspan="2">Prevalence of dental fluorosis among 12 years old children
<table>
<tr><th rowspan="2">Fluoride Level</th><th>Total</th><th>Male</th><th>Female</th></tr>
<tr><th colspan="3">%</th></tr>
<tr><td>< 0.7 ppm
(N = 238)</td><td>31.1</td><td>38.2</td><td>26.7</td></tr>
<tr><td>0.7 ppm to < 1.2 ppm (N = 59)</td><td>47.5</td><td>53.1</td><td>40.7</td></tr>
<tr><td>1.2 ppm to < 4.0 ppm (N = 458)</td><td>95.9</td><td>96.7</td><td>95.1</td></tr>
<tr><td>4.0 ppm to 6.28 ppm (N = 169)</td><td>100.0</td><td>100.0</td><td>100.0</td></tr>
</table>
</td>
<td>The prevalence of dental fluorosis increased with increased water fluoride levels. (Limited)</td>
</tr>
</tbody>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td></td><td></td><td></td><td colspan="2">Prevalence of dental fluorosis among 15 years old children
<table>
<tr><th rowspan="2">Fluoride Level</th><th>Total</th><th>Male</th><th>Female</th></tr>
<tr><th colspan="3">%</th></tr>
<tr><td>< 0.7 ppm (N = 258)</td><td>28.7</td><td>28.6</td><td>28.8</td></tr>
<tr><td>0.7 ppm to < 1.2 ppm (N = 49)</td><td>46.9</td><td>46.1</td><td>47.8</td></tr>
<tr><td>1.2 ppm to < 4.0 ppm (N = 446)</td><td>97.3</td><td>96.7</td><td>97.9</td></tr>
<tr><td>4.0 ppm to 6.28 ppm (N = 198)</td><td>100.0</td><td>100.0</td><td>100.0</td></tr>
</table>
</td><td></td></tr>
<tr><td>Wong et al. (2014)[120]
China (Hong Kong)
Cross-sectional
Low</td><td>Children aged 12 years from the four previous epidemiological surveys in Hong Kong (1983, 1991, 2001, and 2010)
N = 2,658</td><td>CWF
• 1.0 ppm (1983)
• 0.7 ppm (1991)
• 0.5 ppm (2001)
• 0.5 ppm (2010)</td><td colspan="2">Prevalence of diffuse opacities at mouth level
<table>
<tr><th>1983,
N = 700</th><th>1991;
N = 670</th><th>2001;
N = 620</th><th>2010;
N = 668</th></tr>
<tr><td>1.0 ppm</td><td>0.7 ppm</td><td>0.5 ppm</td><td>0.5 ppm</td></tr>
<tr><td>89.3%[a]</td><td>48.5%[b]</td><td>32.4%</td><td>42.1%[c]</td></tr>
</table>
[a] $P < 0.0001$ for 1983 vs. 1991, 2001, and 2010.
[b] $P < 0.0001$ for 1991 vs. 2001.
[c] $P < 0.0001$ for 2010 vs. 2001.

Prevalence of diffuse opacities at tooth level
<table>
<tr><th>1983,
N = 2,667</th><th>1991;
N = 2,569</th><th>2001;
N = 2,398</th><th>2010;
N = 2,573</th></tr>
<tr><td>1.0 ppm</td><td>0.7 ppm</td><td>0.5 ppm</td><td>0.5 ppm</td></tr>
<tr><td>81.7%[a]</td><td>44.9%[b]</td><td>26.1%</td><td>37.3%[c]</td></tr>
</table>
[a] $P < 0.0001$ for 1983 vs. 1991, 2001, and 2010,
[b] $P < 0.0001$ for 1991 vs. 2001 and 2010,
[c] $P < 0.0001$ for 2010 vs. 2001,
</td><td>The prevalence of diffuse opacities among Hong Kong children decreased from 1983 to 2001 and then increased in 2010. (Limited)</td></tr>
</table>

BMI = body mass index; CI = confidence interval; CWF = community water fluoridation; F = fluoride; MIH = molar incisor hypomineralization; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; NS = not significant; OR = odds ratio; ppm = parts per million; RD = rate difference; ref = reference; RR = rate ratio; SD = standard deviation; SE = standard error; SR = systematic review; TFI = Thylstrup-Fejerskov Index; vs. = versus.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

2. All-Cause Mortality

Results for all-cause mortality are presented in Table 25.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified one ecological study.

The ecological study assessed to be of acceptable quality conducted by PHE (2014) compared the incidence rate of all-cause mortality among residents in CWF and non-CWF areas. The study found that the incidence rate of all-cause mortality between January 2009 and January 2012 was 1.3% lower in CWF areas than in non-CWF areas (difference in incidence rate = –1.3%; 95% CI,–2.5 to –0.1; *P* = 0.04). The authors suggested that the small effect estimate was likely due to chance or residual confounding.

Evidence From the Updated Literature Search

No additional study was identified.

Summary

One study identified by the 2016 NHMRC review was assessed to be of acceptable quality and partially applicable to the Canadian context. Confounding variables were adjusted for in the analysis. The updated literature search identified no additional study. There was insufficient evidence to assess an association between water fluoridation and all-cause mortality.

Table 25 : All-Cause Mortality

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Ecological Study					
PHE (2014) England Ecological Acceptable	Residents in CWF and non-CWF areas N = 208,570,962	• CWF (0.8 ppm to 1.0 ppm) • Non-CWF (F level NR)	NR	Difference in incidence rate of all-cause mortality in CWF areas (95% CI) = 1.3% (–2.5 to –0.1); *P* = 0.04 (Adjustment for age, gender, deprivation, and ethnicity)	The incidence rate of all-cause mortality was 1.3% lower in CWF areas than non-CWF areas (*P* = 0.04). (*Partial*)
Evidence From the Updated Literature Search: No Study Identified					

CI = confidence interval; CWF = community water fluoridation; F = fluoride; NHMRC = National Health and Medical Research Council; NR = not reported; PHE = Public Health England; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

3. Atherosclerosis

Results for any atherosclerosis are presented in Table 26.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified one cross-sectional study.

The cross-sectional study of low quality by Liu et al. (2014) determined the prevalence of carotid artery atherosclerosis by carotid ultrasound examinations among Chinese adults aged > 40 years who resided in areas of different NOF levels (≤ 1.20 ppm, 1.21 ppm to 2.00 ppm, 2.01 ppm to 3.00 ppm, ≥ 3.01 ppm). The prevalence of carotid artery atherosclerosis was lowest in the low fluoride group (16.1% at fluoride level ≤ 1.20 ppm) and highest in the high fluoride group (29.7% at fluoride level ≥ 3.01 ppm). After adjustment for sex, age, diastolic blood pressure, total cholesterol, and high density lipoprotein, the study found that the odds of having carotid artery atherosclerosis were significantly greater in the three areas with high fluoride levels compared with the odds in the lowest fluoride level areas (≤1.20 ppm). The findings of the study were assessed to be of limited applicability to the Canadian context.

Evidence From the Updated Literature Search

No additional study was identified.

Summary

One study identified by the 2016 NHMRC review was assessed to be of low quality and of limited applicability to the Canadian context. Confounding variables were adjusted for in the analysis. The updated literature search identified no additional study. There was insufficient evidence to assess an association between water fluoridation at the current Canadian levels and carotid artery atherosclerosis.

Table 26: Atherosclerosis

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Cross-Sectional Study					
Liu et al. (2014) China Cross-sectional Low	Adults (> 40 years) N = 500	NOF • ≥ 3.01 ppm • 2.01 ppm to 3.00 ppm • 1.21 ppm to 2.00 ppm • ≤ 1.20 ppm	Prevalence of carotid artery atherosclerosis by carotid ultrasound examinations • ≥ 3.01 ppm: 29.7% • 2.01 ppm to 3.00 ppm: 27.1% • 1.21 ppm to 2.00 ppm: 27.2% • ≤ 1.20 ppm: 16.1%	OR (95% CI) • ≥ 3.01 ppm: 2.33 (1.12 to 4.85); $P < 0.05$ • 2.01 ppm to 3.00 ppm: 2.02 (1.13 to 3.60) ; $P < 0.05$ • 1.21 ppm to 2.00 ppm: 1.93 (1.11 to 3.35) ; $P < 0.05$ ≤ 1.20 ppm as ref (Adjustment for sex, age, DBP, total cholesterol, and HDL)	There were significantly greater odds of carotid artery atherosclerosis in the three areas with highest fluoride levels compared with ≤ 1.20 ppm areas. (*Limited*)
Evidence From the Updated Literature Search: No Studies Identified					

CI = confidence interval; CWF = community water fluoridation; DBP = diastolic blood pressure; HDL = high density lipoprotein; NHMRC = National Health and Medical Research Council; OR = odds ratio; ppm = parts per million; ref = reference; SE = standard error; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

4. Hypertension

Results for hypertension are presented in Table 27.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified two ecological studies and one cross-sectional study.

The ecological study of low quality by Amini et al. (2011) investigated the relationship between ground water fluoride (range: 0.23 ppm to 1.86 ppm) and prevalence of hypertension in the Iranian population. The definition of hypertension was not reported. The unadjusted analysis found a weak positive correlation between fluoride exposure and prevalence of hypertension ($r = 0.496$; $P < 0.001$).

The ecological study of low quality by Ostovar et al. (2013) also investigated the relationship between ground water fluoride (range: 0.2 ppm to 2.2 ppm) and the prevalence of hypertension of residents of 91 villages in Southern Iran. The definition of hypertension was not reported. The unadjusted analysis found a weak negative correlation between fluoride exposure and prevalence of hypertension (Spearman's rho = –0.578; $P = 0.005$).

The cross-sectional study assessed to be of low quality by Sun et al. (2013) measured the blood pressure of adults aged 40 to 75 years living in eight Chinese villages with different naturally occurring water fluoride levels (i.e., ≥ 3.01 ppm, 2.01 ppm to 3.00 ppm, 1.21 ppm to 2.00 ppm, ≤ 1.20 ppm). Hypertension was defined when systolic blood pressure (SBP) was > 140 mm Hg and diastolic blood pressure (DBP) was > 90 mm Hg. It was found that the prevalence of hypertension increased with increasing water fluoride concentrations. After adjusting for sex, age, smoking, alcohol consumption, body mass index (BMI), and endothelin-1 level, the study found significantly greater odds of hypertension in the areas with the highest fluoride levels (≥ 3.01 ppm) compared with the areas of lowest fluoride levels (≤ 1.20 ppm). No significant difference in the risk of hypertension was observed between 2.01 ppm and 3.00 ppm and ≤ 1.20 ppm, or between 1.21 ppm and 2.00 ppm and ≤ 1.20 ppm.

Evidence From the Updated Literature Search

Two additional cross-sectional studies were identified.

The cross-sectional study of low quality by Yousefi et al. (2018)[122] investigated the association between drinking water fluoride and hypertension, BMI, and waist circumference. Residents aged 27 to 43 years living in two villages with high (10.15 ppm) and low (0.79 ppm) groundwater fluoride levels in Iran were included. The study found there were significant differences in both SBP and DBP of residents between the two villages. The mean SBPs (SE) were 111.6 (1.33) and 118.7 (1.06), and mean DBPs (SE) were 71.4 (0.622) and 74.3 (0.787) for low and high fluoride areas, respectively. Though the authors did not define prehypertension, the prevalence of prehypertension was found to be significantly higher in the high fluoride areas compared with low fluoride areas. Multivariate logistic regression showed a significant and increased risk of hypertension in the village with the higher fluoride level. The analysis adjusted for age, sex, BMI, and waist circumference.

The cross-sectional study assessed to be of low quality by Aghaei et al. (2015b)[123] evaluated the association between naturally occurring drinking water fluoride and hypertension among adults aged 20 to 65 years living in high (3.94 ppm) and low fluoride (0.25 ppm) areas. The study found that the prevalence of hypertension of unknown etiology was 37.0% in a 0.25 ppm area and 42.3% in a 3.94 ppm area. A logistic regression model revealed no significant difference in the prevalence of hypertension of unknown etiology between high and low fluoride areas (*P* = 0.556), after adjusting for age and sex. Other confounding variables related to hypertension were not adjusted for in the analysis.

Summary

Two ecological studies and one cross-sectional study, all assessed to be of low quality, identified from the 2016 NHMRC review showed mixed evidence for an association between fluoridated water exposure and the prevalence of hypertension. Two additional cross-sectional studies, also assessed to be of low quality, identified from the updated literature search found mixed evidence that fluoride exposure increased hypertension. None of studies had fluoride levels in the intervention groups that are comparable to the current optimum fluoride level in Canada. Confounding variables were adjusted for in three out of five studies. The findings in all primary studies were assessed to be of limited applicability to the Canadian context. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and hypertension.

Table 27: Hypertension

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings** **(*Applicability*[a])**
Evidence From the 2016 NHMRC Review: Two Ecological Studies and One Cross-Sectional Study					
Amini et al. (2011) Iran Ecological Low	Iranian population Age: NR N = NR	NOF: 0.23 to 1.86 ppm	–	$r = 0.496$; $P < 0.001$ (No adjustment for confounders)	There was a weak positive correlation between fluoride exposure and prevalence of hypertension. (*Limited*)
Ostovar et al. (2013) Iran Ecological Low	Residents of villages Age: NR N = 160,150	NOF: 0.2 to 2.2 ppm	–	Spearman's rho = – 0.578; $P = 0.005$ (No adjustment for confounders)	There was a weak negative correlation between fluoride exposure and prevalence of hypertension. (*Limited*)
Sun et al. (2013) China Cross-sectional Low	Adults aged 40 to 75 years N = 487	NOF • ≥ 3.01 ppm • 2.01 to 3.00 ppm • 1.21 to 2.00 ppm • ≤ 1.20 ppm	Prevalence of hypertension: • ≥ 3.01 ppm: 49.2% • 2.01 ppm to 3.00 ppm: 32.3% • 1.21 ppm to 2.00 ppm: 24.5% • ≤ 1.20 ppm: 20.2%	OR (95% CI) • ≥ 3.01 ppm: 2.84 (1.38 to 5.83); $P < 0.001$ • 2.01 ppm to 3.00 ppm: 1.73 (0.94 to 3.19) ; $P = 0.18$ • 1.21 ppm to 2.00 ppm: 1.02 (0.56 to 1.86) ; $P = 0.401$ ≤ 1.20 ppm as ref (Adjustment for sex, age, smoking, alcohol consumption, BMI, and endothelin-1)	There was a significantly higher risk of hypertension in the areas with highest fluoride levels (≥ 3.01 ppm) compared with ≤ 1.20 ppm areas. (*Limited*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td colspan="6">Evidence From the Updated Literature Search: Two Cross-Sectional Studies</td></tr>
<tr><td>Yousefi et al. 2018[122]
Iran
Cross-sectional
Low</td><td>Residents aged 27 to 43 years
N = 346</td><td>NOF
• 10.15 ppm (High)
• 0.75 ppm (Low)</td><td colspan="2">Blood Pressure (Mean ± SE) of Participants in Two Areas
<table>
<tr><th></th><th colspan="2">Fluoride Level</th><th>P Value</th></tr>
<tr><th></th><th>0.79 ppm</th><th>10.15 ppm</th><th></th></tr>
<tr><td>SBP (mm Hg)</td><td>111.6 ± 1.33</td><td>118.7 ± 1.06</td><td>< 0.001</td></tr>
<tr><td>DBP (mm Hg)</td><td>71.4 ± 0.622</td><td>74.3 ± 0.787</td><td>0.005</td></tr>
</table>
Prehypertension prevalence: [No definition for prehypertension given]
• High fluoride (10.15 ppm): 48.94% (93/190)
• Low fluoride (0.79 ppm): 6.41% (10/156)

Regression analysis on hypertension:
• High fluoride (10.15 ppm): OR (95% CI) = 2.3 (1.03 to 5.14); P = 0.041
• Low fluoride (0.79 ppm): ref

(Adjustment for age, sex, BMI, and waist circumference)</td><td>Higher prevalence of prehypertension was seen in areas with high water fluoride levels. (Limited)</td></tr>
<tr><td>Aghaei et al. (2015b)[123]
Iran
Cross-sectional
Low</td><td>Adults aged 20 to 65 years
N = 2,878</td><td>NOF
• 3.94 ppm
• 0.25 ppm</td><td>Prevalence of hypertension (known etiology)
• 3.94 ppm: 57.7%
• 0.25 ppm: 63.0%

Prevalence of hypertension (unknown etiology)
• 3.94 ppm: 42.3%
• 0.25 ppm: 37.0%</td><td>Logistic regression model revealed no significant difference in the prevalence of hypertension of unknown etiology between high and low fluoride areas (P = 0.556), after adjustment for age and sex</td><td>There was no evidence to support that fluoride exposure increases hypertension. (Limited)</td></tr>
</table>

BMI = body mass index; CI = confidence interval; CWF = community water fluoridation; DBP = diastolic blood pressure; NOF = naturally occurring fluoride; NR = not reported; OR = odds ratio; ppm = parts per million; ref = reference; SBP = systolic blood pressure; SE= standard error.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

5. Bone Cancer

Results for bone cancer are presented in Table 28.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review reported the findings of two previous SRs and identified six observational studies (five ecological studies and one case-control study).

The previous SR by McDonagh et al. (2000) included eight studies (no QA reported), seven of which reported incidence of osteosarcoma, and the other study reported unspecified bone-related cancer among participants living in the fluoridated and non-fluoridated areas. The review found mixed results among included studies. The authors concluded that there was no clear association between water fluoridation and the incidence of bone cancer.

The previous 2007 NHMRC review identified one additional case-control study (QA not reported) published after the SR by McDonagh et al. (2000). In an exploratory analysis limited to children aged 7 years, the study found that males with > 99% exposure to fluoridated water had a significantly higher risk of developing osteosarcoma, but females did not, compared with < 30% exposure. Due to limitations in the methodology and reporting of the study (the authors mentioned that they had been unable to replicate the findings in a broader study), the 2007 NHMRC review concluded that there was no clear association between water fluoridation and the incidence of osteosarcoma.

Five ecological studies (three assessed to be of acceptable quality and two of low quality) investigated the relationship between the incidence of osteosarcoma and CWF at fluoride levels similar to the current Canadian levels. The studies were from England (PHE, 2014), US (Levy and Leclerc, 2012), Ireland (Comber et al., 2010), UK (Blakey et al., 2014), and New Zealand (National Fluoridation Service, 2013). Participants were of all ages (0 to 65+ years). All studies found no significant differences in incidence rates of osteosarcoma between CWF and non-CWF areas. Confounding variables were adjusted for in two studies.

One case-control study assessed to be of low quality from India by Kharb et al. (2012) measured the water fluoride levels from the homes of 10 cases of osteosarcoma and 10 cases of healthy individuals (control). The study found that fluoride level in drinking water in 10 osteosarcoma patients' home was 1.3 ppm compared with the 0.48 ppm fluoride level in drinking water from 10 healthy volunteers' home.

Evidence From the Updated Literature Search

The updated literature search identified one additional case-control study and one ecological study.

The case-control study assessed to be of acceptable quality by Archer (2016)[124] examined the association between fluoride levels in public drinking water and childhood and adolescent osteosarcoma in Texas. The study included children and adolescents aged 0 to 19 years who were exposed to three public water system fluoride levels: 0 ppm to 0.6 ppm, 0.7 ppm to 1.2 ppm, and ≥ 1.3 ppm. After adjustment for age, sex, race and ethnicity, and per cent of census tract below poverty index, the study found no association between public water system fluoride levels and osteosarcoma in the overall population, or among either male or female participants.

The ecological study assessed to be of acceptable quality conducted by PHE (2018)[86] determined the incidence rate of osteosarcoma among individuals aged 0 to 49 years in England from 1995 to 2015. A total of 710,260,000 person-years were included. Fluoride level was stratified from low (< 0.1 ppm) to high (≥ 0.7 ppm), regardless of source. The study found no association between fluoride concentration and osteosarcoma incidence, after adjusting for age and gender. When stratified by fluoridation status (i.e., yes = fluoride level ≥ 0.2 ppm, median = 0.84 ppm in 2005 to 2015; no = fluoride level < 0.2 ppm, median = 0.11 ppm), the risk of osteosarcoma incidence was similar in both fluoridation and non-fluoridation areas.

Summary

The previous SRs included in the 2016 NHMRC did not find a clear association between water fluoridation and the incidence of bone cancer. Five of the six primary studies (whose fluoride levels were comparable with the current Canadian levels) identified by the 2016 NHMRC review found no significant differences in the incidence rates of osteosarcoma between CWF and non-CWF areas. Two additional studies identified from the updated literature search also found no association between public water system fluoride levels and the incidence of osteosarcoma. Confounding variables were adjusted for in four out of eight primary studies. The findings of all primary studies, except one, were assessed to be partially applicable to the Canadian context. Overall, there was consistent evidence for no association between water fluoridation at the current Canadian levels and the incidence of bone cancer.

Table 28: Bone Cancer

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Two Previous SRs and Six Observational Studies (Five Ecological Studies and One Case-Control Study)					
McDonagh et al. (2000) UK Previous SR	All ages 8 studies (No QA) N = NR	Fluoridated areas Control (low fluoride areas)	Osteosarcoma (7 studies) • Five studies: no significant association between water fluoridation and development of osteosarcoma • One study: a reduction of osteosarcoma risk with water fluoridation • One study: a significant increased risk of osteosarcoma with water fluoridation in men, but not in women Unspecified bone-related cancer (8 analyses from 4 studies) • Three analyses: negative association (fewer cancers) • Four analyses: positive association (more cancers) • One analysis: no clear association	NR	There was no clear association between incidence of bone cancer and water fluoridation.
NHMRC 2007 Australia Previous SR	1 additional case-control study (No QA) after McDonagh et al. (2000) Case (n = 103) Control (n = 215)	Exposure to drinking water target level of fluoride: • > 99% • 30% to 99% • < 30%	NR	Exploratory analysis limited to children aged 7 years OR (95% CI) • > 99% Males: 5.46 (1.50 to 19.90) Females: 1.75 (0.48 to 6.35)	Exploratory analysis suggested an association between fluoride exposure in drinking water and the incidence of osteosarcoma in males, but not in females.

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
				- 30% to 99% - Males: 3.36 (0.99 to 11.42) - Females: 1.39 (0.41 to 4.76) < 30% as ref (Adjustment for income of residence area, county population, ever use of bottle water, age, and any use of fluoride products)	
PHE (2014) England Ecological Acceptable	Residents in CWF and non-CWF areas Age: < 25 years or ≥ 50 years N = 248,234,551	- CWF (0.8 ppm to 1.0 ppm) - Non-CWF (F level NR)	NR	Per cent difference in incidence rate of osteosarcoma (95% CI) - < 25 years, all: 8.2% (–9.3 to 29); *P* = 0.38 - < 25 years, males: 17% (–7.1 to 46); *P* = 0.19 - < 25 years, females: –2.5% (–27 to 30); *P* = 0.86 - ≥ 50 years, all: –15% (–34 to 9.6); *P* = 0.21 (Adjustment for age, gender, deprivation, and ethnicity)	There were no significant differences in incidence rates between CWF and non-CWF. (*Partial*)
Levy and Leclerc (2012) USA Ecological Low	Children aged 5 to 19 years N = NR	- ≥ 85% population received CWF (0.7 ppm to 1.2 ppm) - ≤ 30% population received CWF	NR	IRR (95% CI) Males - 5 to 9 years: 0.99 (0.67 to 1.45); *P* = 0.95 - 10 to 14 years: 0.96 (0.76 to 1.21); *P* = 0.70 - 15 to 19 years:1.01 (0.83 to 1.23); *P* = 0.93 Females - 5 to 9 years: 1.05 (0.71 to	There were no significant differences in incidence rates of osteosarcoma between CWF and non-CWF. (*Partial*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
				1.65); *P* = 0.81 • 10 to 14 years: 0.85 (0.68 to 1.06); *P* = 0.15 • 15 to 19 years: 1.08 (0.82 to 1.43); *P* = 0.60	
Comber et al. (2010) Ireland Ecological Acceptable	Residents (all ages) of the Republic of Ireland and Northern Ireland N = 5,531,835	• CWF (0.8 ppm to 1.0 ppm) • Non-CWF (F level NR)	NR	IRR (95% CI) • All ages: 1.17 (0.87 to 1.58) • 0 to 24 years, all: 1.01 (0.88 to 1.15) • 0 to 24 years, males: 1.00 (0.85 to 1.17) • 0 to 24 years, females: 1.05 (0.83 to 1.33)	There were no significant differences in incidence rates of osteosarcoma between CWF and non-CWF. (*Partial*)
Blakey et al. (2014) UK Ecological Acceptable	Residents aged 0 to 49 years in England, Scotland, and Wales N = 2,566	Mean water fluoride levels: 0.0 ppm to 1.27 ppm	NR	Incidence of osteosarcoma RR (90% CI) = 1.001 (0.871 to 1.151) Incidence of Ewing Sarcoma RR (90% CI) = 0.929 (0.773 to 1.115) (Adjustment for different confounding variables [age, gender and deprivation for osteosarcoma; age, gender, population density, and non-car ownership for Ewing Sarcoma])	There was no association between water fluoridation and the incidence of osteosarcoma or Ewing sarcoma. (*Partial*)
National Fluoridation Service (2013) New Zealand Ecological Low	Residents aged 0 to 65+ years N = Total population of New Zealand	• CWF (0.8 ppm to 1.0 ppm) • Non-CWF (~0.1 ppm to 0.2 ppm)	No difference in incidence rates of osteosarcoma between CWF and non-CWF in all age groups of males or females	NR	There was no significant difference in the incidence rates of osteosarcoma between CWF and non-CWF for both males and females of all age groups. (*Partial*)

Study **Country** **Design** **Quality**	**Population**	**Exposures**	**Results**	**Effect Estimate**	**Study Findings** **(*Applicability*[a])**
Kharb et al. (2012) India Case-control Low	NR 10 cases (osteosarcoma) 10 controls (healthy)	Water F level: • 1.3 ppm (cases) • 0.48 ppm (controls)	NR	NR (The publication reported no patient characteristics, recruitment information, disease status, and potential confounding variables)	Fluoride level in drinking water was higher in 10 osteosarcoma patients' home (1.3 ppm) compared with fluoride level in drinking water from 10 healthy volunteers' homes (0.48 ppm). (*Limited*)
Evidence From Updated Literature Search: One Case-Control Study and One Ecological Study					
Archer (2016)[124] USA Case-control Acceptable	Children and adolescents aged 0 to 19 years N = 1,663	Public water system fluoride levels • ≥ 1.3 ppm • 0.7 ppm to 1.2 ppm • 0 ppm to 0.6 ppm	–	OR (95% CI) For all • ≥ 1.3 ppm: 0.96 (0.58 to 1.58) • 0.7 ppm to 1.2 ppm: 0.85 (0.62 to 1.16) • 0 ppm to 0.6 ppm: ref For males • ≥ 1.3 ppm: 1.31 (0.70 to 2.46) • 0.7 ppm to 1.2 ppm: 1.03 (0.68 to 1.55) • 0 ppm to 0.6 ppm: ref For females • ≥ 1.3 ppm: 0.58 (0.25 to 1.36) • 0.7 ppm to 1.2 ppm: 0.68 (0.42 to 1.09) • 0 ppm to 0.6 ppm: ref (Adjustment for age, sex, race and ethnicity, and per cent of census tract below poverty index)	There was no association between public water system fluoride levels and osteosarcoma among either males or females. (*Partial*)
PHE 2018[86] England	Participants aged 0 to 49 years, England (1995 to	Fluoride level in water supply (regardless of	Adjusted incidence rate ratios of osteosarcoma, by fluoride levels, England 1995 to 2015		There was no association between water fluoridation and

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>[a])</th></tr>
<tr>
<td>Ecological
Acceptable</td>
<td>2015)
Osteosarcoma
N = 710,260,000 person-years</td>
<td>source):
< 0.1 ppm, 0.1 ppm to < 0.2 ppm, 0.2 ppm to < 0.4 ppm, 0.4 ppm to < 0.7 ppm, ≥ 0.7 ppm</td>
<td colspan="2">
<table>
<tr><th>Fluoride Levels (ppm)</th><th>Adjusted IRR (95% CI)[a]</th><th><i>P</i> Value</th><th><i>P</i> Trend</th></tr>
<tr><td>< 0.1</td><td>Ref (1)</td><td>–</td><td>0.569</td></tr>
<tr><td>0.1 to < 0.2</td><td>1.04 (0.93 to 1.15)</td><td>0.511</td><td></td></tr>
<tr><td>0.2 to < 0.4</td><td>0.99 (0.86 to 1.13)</td><td>0.852</td><td></td></tr>
<tr><td>0.4 to < 0.7</td><td>1.14 (0.94 to 1.39)</td><td>0.191</td><td></td></tr>
<tr><td>≥ 0.7</td><td>0.90 (0.75 to 1.07)</td><td>0.228</td><td></td></tr>
</table>
[a] Adjusted for age and gender.

Adjusted incidence rate ratios of osteosarcoma, by fluoridation status, England (1995 to 2015)
<table>
<tr><th>Fluoridation Status[a]</th><th>Adjusted IRR (95% CI)[b]</th><th><i>P</i> Value</th></tr>
<tr><td>No</td><td>Ref (1)</td><td>–</td></tr>
<tr><td>Yes</td><td>0.96 (0.90 to 1.11)</td><td>0.550</td></tr>
</table>
[a] No = fluoride level < 0.2 ppm; yes = fluoride level ≥ 2 ppm.
[b] Adjusted for age and gender.
</td>
<td>incidence of osteosarcoma.
(<i>Partial</i>)</td>
</tr>
</table>

CI = confidence interval; CWF = community water fluoridation; F = fluoride; IRR = incidence rate ratio; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; PHE = Public Health England; ppm = parts per million; QA = quality assessment; ref = reference; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

6. Total Cancer Incidence and Cancer-Related Mortality

Results for total cancer incidence and cancer-related mortality are presented in Table 29.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review reported the findings of two previous SRs and identified two additional ecological studies.

The previous SR by McDonagh et al. (2000) investigated the association of water fluoridation and overall cancer incidence or mortality from 10 studies (QA not reported). Participants were of all ages living in fluoridated and non-fluoridated areas. Among the 22 analyses, 10 showed a positive association, nine showed a negative association, two showed no association, and one showed significant negative effect in two of eight subgroups. The authors concluded that there was no clear association between water fluoridation and overall cancer incidence or mortality for “all cause” cancer.

The previous 2007 NHMRC review included three additional ecological studies carried out after the SR by McDonagh et al. (2000). One study assessed as of low quality showed mixed results, another low quality study showed an inverse correlation, and one study assessed as of acceptable quality showed an association between cancer mortality and water fluoridation. The authors concluded that there was no clear association between water fluoridation and overall cancer incidence or mortality.

The ecological study assessed to be of acceptable quality conducted by PHE (2014) compared the incidence of all cancer and invasive bladder cancer among residents living in CWF and non-CWF areas in England. After adjustment for age, gender, deprivation and ethnicity, the study found no significant difference in the incidence of all cancer between CWF and non-CWF (Difference in incidence = -0.4; 95% CI,-1.2 to 0.4; *P* = 0.29). The incidence of invasive bladder cancer, on the other hand, was significantly lower in CWF than non-CWF (Difference in incidence = -8.0; 95% CI, -9.9 to -6.0; *P* < 0.001).

The ecological study assessed to be of acceptable quality by Schwartz (2014) investigated the relationship between age-adjusted incidence of eye and orbit cancer and proportion of non-Hispanic Whites exposed to CWF in the US. After adjustment for latitude, the study found an inverse correlation between percentage of the population receiving fluoridated water and incidence of eye and orbit cancer (*r* = -0.45; *P* = 0.002).

Evidence From the Updated Literature Search

One ecological study assessed to be of acceptable quality from England was identified.

PHE (2018)[86] determined the incidence rate of bladder cancer in England from 2007 to 2015. A total of 827,660,000 person-years were included. Fluoride level was stratified from low (< 0.1 ppm) to high (≥ 0.7 ppm), regardless of source. The study found that fluoride level at ≥ 0.7 ppm was associated with a 7% lower incidence rate of bladder cancer diagnosis compared with fluoride level of < 0.1 ppm, after adjusting for age, gender, ethnicity and deprivation status. Test of trend suggested a potential threshold effect above 0.7 ppm, rather than a linear relationship, since they further analyzed the effect by subcategorizing ≥ 0.7 ppm into two levels of 0.7 to < 0.9 ppm and ≥ 0.9 ppm. Results revealed similar risk of bladder cancer at both fluoride levels (IRR = 0.92; 95% CI, 0.86 to 0.98; *P* = 0.015 for 0.7 to < 0.9 ppm and IRR = 0.94; 95% CI, 0.89 to 0.99; *P* = 0.017 for ≥ 0.9 ppm). When stratified by fluoridation status (i.e., yes = fluoride level ≥ 0.2 ppm, median = 0.84 ppm in 2005 to

2015; no = fluoride level < 0.2 ppm, median = 0.11 ppm), the risk of bladder cancer incidence was 6% lower (95% CI, 2% to 10%) in fluoridated areas compared with non-fluoridated areas.

Summary

Two previous SRs included in the 2016 NHMRC review did not find a clear association between water fluoridation and overall cancer incidence or cancer-related mortality. In two PHE reports (2014, 2018), both assessed to be of acceptable quality, the risk of bladder cancer was significantly lower in fluoridation areas compared with no fluoridation areas. In the 2014 PHE report, however, no significant difference was observed in the incidence of all cancer between CWF and non-CWF areas. Similarly, one ecological study assessed to be of acceptable quality found an inverse association between water fluoridation and incidence of eye cancer. Due to small effect sizes, it was unclear if the results showed a true association or they were attributable to residual confounding or multiplicity. Confounding variables were adjusted for in all primary studies. The findings of all studies were assessed to be partially applicable to the Canadian context. Overall, there was consistent evidence for no association between water fluoridation at the current Canadian levels and the overall incidence of cancer or cancer-related mortality. The evidence surrounding eye and bladder cancer remains unclear.

Table 29: Total Cancer Incidence and Cancer-Related Mortality

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Two Previous SRs and Two Ecological Studies					
McDonagh et al. (2000) UK Previous SR	All ages 10 studies (No QA) N = NR	Fluoridated areas Control (Low fluoride areas)	22 analyses: • Positive association (n = 10) • Negative association (n = 9) • No association (n = 2) • Significant negative effect in 2 of 8 subgroups (n = 1)	NR	There was no clear association between water fluoridation and overall cancer incidence or mortality for "all cause" cancer
NHMRC 2007 Australia Previous SR	All ages Two ecological studies (low quality) One ecological study (acceptable quality)	CWF Non-CWF	• Mixed results (one poor quality study) • An inverse correlation (one poor quality study) • An association between cancer mortality and water fluoridation (one fair quality study)	NR	There was no clear association between water fluoridation and overall cancer incidence or mortality
PHE (2014) England Ecological Acceptable	Residents in CWF and non-CWF areas All cancer (N = 208,770,962) Bladder cancer (N = 555,127,448)	• CWF (0.8 to 1.0 ppm) • Non-CWF (F level NR)	NR	All cancer Difference in incidence (95% CI) = –0.4 (–1.2 to 0.4); *P* = 0.29 Bladder cancer Difference in incidence (95% CI) = –8.0 (–9.9 to –6.0); *P* < 0.001 (Adjustment for age, gender, deprivation and ethnicity)	There was no significant difference in the incidence of all cancer between CWF and non-CWF (*Partial*) The incidence of invasive bladder cancer was significantly lower in CWF than non-CWF (*Partial*)
Schwartz (2014) USA Ecological Acceptable	Non-Hispanic whites in US All ages N = NR	Proportion of population in each state exposed to CWF	NR	Age-adjusted incidence of eye and orbit cancer *r* = –0.45; *P* = 0.002 (Adjustment for latitude)	There was an inverse correlation between percentage of the population receiving fluoridated water and incidence of eye and orbit cancer (*Partial*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td colspan="6">Evidence From the Updated Literature Search: One Ecological Study</td></tr>
<tr>
<td>PHE 2018[86]
England
Ecological
Acceptable</td>
<td>Participants aged NR
Bladder cancer
N = 827,660,000 person-years</td>
<td>Fluoride level in water supply (regardless of source):
< 0.1 ppm, 0.1 to < 0.2 ppm, 0.2 to < 0.4 ppm, 0.4 to < 0.7 ppm, ≥ 0.7 ppm</td>
<td colspan="2">Adjusted incidence rate ratios of bladder cancer, by fluoride levels, England 2007 to 2015
<table>
<tr><th>Fluoride Levels</th><th>Adjusted IRR (95% CI)*</th><th>P Value</th><th>P Trend</th></tr>
<tr><td>< 0.1</td><td>Ref (1)</td><td>--</td><td>0.027</td></tr>
<tr><td>0.1 to < 0.2</td><td>0.99 (0.96 to 1.02)</td><td>0.434</td><td></td></tr>
<tr><td>0.2 to < 0.4</td><td>1.00 (0.97 to 1.03)</td><td>0.897</td><td></td></tr>
<tr><td>0.4 to < 0.7</td><td>1.00 (0.95 to 1.05)</td><td>0.902</td><td></td></tr>
<tr><td>≥ 0.7</td><td>0.93 (0.88 to 0.98)</td><td>0.004</td><td></td></tr>
</table>
* Adjusted for age, gender, ethnicity and deprivation status

Adjusted incidence rate ratios of bladder cancer, by fluoridation status, England (2007 to 2015)
<table>
<tr><th>Fluoridation Status[a]</th><th>Adjusted IRR (95% CI)[b]</th><th>P Value</th></tr>
<tr><td>No</td><td>Ref (1)</td><td>--</td></tr>
<tr><td>Yes</td><td>0.94 (0.90 to 0.98)</td><td>0.002</td></tr>
</table>
[a] No = fluoride level < 0.2 ppm; Yes = fluoride level ≥ 2 ppm
[b] Adjusted for age, gender, ethnicity and deprivation status</td>
<td>Incidence of bladder cancer was significantly lower in fluoridation areas compared with no fluoridation areas (Partial)</td>
</tr>
</table>

CI = confidence interval; CWF = community water fluoridation; IRR = incidence rate ratio; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; ppm = parts per million; QA = quality assessment; SR = systematic review.

[a] For primary studies that were judged to be (high, partial or low) applicable to the Canadian context, i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

7. Skeletal Fluorosis

Results for skeletal fluorosis are presented in Table 30. Long-term exposure to high levels of fluoride through ingestion or respiration may result in joint stiffness and pain due to fluoride-induced increase in bone density.[125] This pathological condition is termed skeletal fluorosis. The condition can be divided into a preclinical phase and three clinical phases.[125] The last clinical phase, also refers as "crippling skeletal fluorosis," is the most severe condition that results in limitation of joint movement due to major calcification of ligaments of the vertebral column, and crippling deformities of spine and major joints.[125]

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review included one previous SR and two ecological studies.

The previous SR by McDonagh et al. (2000) included one study (QA not reported) reporting that skeletal fluorosis was only present in areas of high fluoride levels (i.e., 3.8 ppm to 8.0 ppm).

The ecological study assessed to be of low quality by Hussain et al. (2010) determined the prevalence of skeletal fluorosis in households of villages in India having high groundwater fluoride levels: < 4 ppm, 4 ppm to 6 ppm, and > 6 ppm. With no statistical analysis or adjustment for confounding variables, the study found no clear relationship between water fluoride level and prevalence of skeletal fluorosis.

The ecological study assessed to be of low quality by Srikanth et al. (2008) also found no clear relationship between water fluoride level and prevalence of skeletal fluorosis when it examined the prevalence of skeletal fluorosis among adults in five villages in India. The mean groundwater fluoride levels ranged between 1.51 ppm and 3.71 ppm. This study did not conduct any statistical analysis or adjust for confounding variables.

Evidence From the Updated Literature Search

Two additional cross-sectional studies, both assessed to be of low quality, were identified from the updated literature search.

The cross-sectional study by Mohammadi et al. (2017)[126] evaluated the association between exposure to drinking water fluoride and skeletal fluorosis in five villages in Iran. The study included adults aged ≤ 40 years, 41 to 50 years, 51 to 60 years, 60 to 70 years, and ≥ 71 years who were exposed either to high groundwater fluoride levels (i.e., 4.02 ppm, 7.63 ppm, or 10.15 ppm) or low fluoride levels (i.e., 0.68 ppm or 0.79 ppm). The prevalence of skeletal fluorosis was significantly higher in high fluoride levels compared with low fluoride levels (21.1% versus 3.0%; $P < 0.001$). After adjustment for age, sex, and fast food and dairy consumption, it was found that adults living in areas with high fluoride levels had significantly higher odds of developing skeletal fluorosis compared with areas with low fluoride levels (OR = 9.09; 95% CI, 5.25 to 16.67; $P < 0.001$). The study did not determine the severity of skeletal fluorosis. Skeletal fluorosis was assessed by physical examination and not by radiographical methods.

The cross-sectional study by Shruthi et al. (2016)[127] assessed the prevalence of skeletal fluorosis among two groups of adults (20 to 90 years old) exposed to different groundwater fluoride levels (i.e., > 1.5 ppm and < 1.0 ppm) in three villages in India. With no statistical analysis or adjustment for confounding variables, the study found no difference in the prevalence of skeletal fluorosis between groups.

Summary

Three primary studies conducted in India, two identified from the NHMRC review and one from the updated literature search, found no clear relationship between water fluoride level and prevalence of skeletal fluorosis. The study conducted in Iran found that adults living in areas with high fluoride levels had a significantly higher risk of developing skeletal fluorosis. All these studies had significant methodological limitations and were conducted in areas where water fluoride levels were substantially higher than the current Canadian levels. Their findings of all primary studies were assessed to be of limited applicability to the Canadian context. No studies from Canada or from countries having socio-economic characteristics and health care systems comparable with Canada were identified. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and skeletal fluorosis.

Table 30: Skeletal Fluorosis

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Previous SR and Two Ecological Studies					
McDonagh et al. (2000) UK Previous SR	All ages 1 study (No QA) N = NR	NR	Skeletal fluorosis was only present in areas of high fluoride levels (3.8 ppm to 8.0 ppm)	NR	The prevalence of skeletal fluorosis was increased at higher fluoride concentrations.
Hussain et al. (2010) India Ecological Low	Households of villages N = 1,998	NOF • > 6 ppm • 4 ppm to 6 ppm • < 4 ppm	Prevalence of skeletal fluorosis Grade II • > 6 ppm: 17.4% • 4 ppm to 6 ppm: 20.1% • < 4 ppm: 16.8% Grade III • > 6 ppm: 0.6% • 4 ppm to 6 ppm: 0.9% • < 4 ppm: 0.0%	NR	No clear relationship between water fluoride level and prevalence of skeletal fluorosis. (*Limited*)
Srikanth et al. (2008) India Ecological Low	Adults in five villages N = 818	NOF: • 1.51 ppm • 2.54 ppm • 2.91 ppm • 2.97 ppm • 3.71 ppm	Prevalence of skeletal fluorosis in 5 villages Grade II: 7.6% (range 4.7% to 14.8%) Grade III: 1.3% (range 0.7% to 3.9%)	NR	No clear relationship between water fluoride level and prevalence of skeletal fluorosis. (*Limited*)
Evidence From the Updated Literature Search: Two Cross-Sectional Studies					
Mohammadi et al. (2017)[126] Iran Cross-sectional Low	Adults aged ≤ 40 years and 41 to ≥ 70 years N = 915	NOF: • High: 4.02 ppm, 7.63 ppm, 10.15 ppm • Low: 0.68 ppm, 0.79 ppm	Prevalence of skeletal fluorosis • High F: 21.1% • Low F: 3.0%; *P* < 0.001	OR (95% CI) • All: 9.09 (5.25 to 16.67); *P* < 0.001 • Males: 6.05 (3.59 to 10.19); *P* < 0.001 • Females: 8.73 (4.31 to 17.67); *P* < 0.001 Low F as ref (Adjustment for age, sex, fast food, and diary consumption)	Adults living in areas with high fluoride levels had significantly higher odds of developing skeletal fluorosis compared with areas with low fluoride levels. (*Limited*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Shruthi et al. (2016)[127] India Cross-sectional Low	Adults aged 20 to 90 years N = 680	NOF: • > 1.5 ppm • < 1.0 ppm	The prevalence of skeletal fluorosis • > 1.5 ppm: 5% • < 1.0 ppm: 5% Within each group and between groups, there was no difference in skeletal fluorosis prevalence in males or females	NR	There was no difference in the prevalence of skeletal fluorosis between groups. (*Limited*)

CI = confidence interval; F = fluoride; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; OR = odds ratio; ppm = parts per million; QA = quality assessment; Ref = reference; SR = systematic review.

[a] For primary studies that were judged to be (high, partial or low) applicable to the Canadian context, i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

8. Hip Fracture

Results for hip fracture are presented in Table 31.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review included two previous SRs and two observational studies (one ecological study and one retrospective cohort study).

The previous SR by McDonagh et al. (2000) included 18 studies (most of which were assessed to be of low quality) that had hip fracture among adults as an outcome. Of 30 analyses, 14 found that hip fracture decreased with increasing water fluoride level, 13 found that hip fracture increased with increasing water fluoride level, and three found no association between hip fracture and water fluoridation. The authors concluded that there was no clear association between hip fracture and water fluoridation.

The previous 2007 NHMRC review identified one additional study assessed to be of fair quality, published after McDonagh et al. (2000). The study found no increased risk of hip fracture in those exposed to the CWF compared with non-CWF.

The ecological study assessed to be of acceptable quality conducted by PHE compared the incidence rates of hip fracture between residents in the CWF (0.8 ppm to 1.0 ppm) and non-CWF areas. After adjustment for age, gender, deprivation, and ethnicity, the study found no significant difference in the incidence of hip fracture between CWF and non-CWF areas.

The retrospective cohort study assessed to be of acceptable quality by Nasman et al. (2013) from Sweden investigated the relationship between water fluoridation and the risk of hip fracture among residents (median age: 62.8 years) born between 1900 and 1919, alive and living in area of birth at start of follow-up. The study compared non-fluoridated water (< 0.3 ppm) with three naturally occurring water fluoride levels: 0.3 ppm to 0.69 ppm, 0.7 ppm to 1.49 ppm and ≥ 1.5 ppm. After adjustment for gender, age group, county of residence, and calendar group, the study found that there was no increased risk of hip fracture in individuals exposed to fluoride levels of 0.3 ppm to 0.69 ppm, 0.7 ppm to 1.49 ppm, or ≥ 1.5 ppm compared with fluoride level < 0.3 ppm.

Evidence From the Updated Literature Search

One ecological study assessed to be of acceptable quality from England was identified.

PHE (2018)[86] determined the incidence rate of hospital admissions for hip fracture among individuals aged 0 to 80 and older in England from 2007 to 2015. A total of 477,610,000 person-years were included. Fluoride level was stratified from low (< 0.1 ppm) to high (≥ 0.7 ppm), regardless of source. The study found that the association between fluoride levels and hip fracture varied by age group in both females and males. At age 0 to 49 years, water fluoride levels of ≥ 0.1 ppm were associated with 13% to 14% lower risk of hospital admission for hip fractures in both males and females. At age 50 to 64 years and 65 to 79 years, there was no clear relationship between water fluoride and risk of hospital admission in either gender. In older adults (80 years and older), the risk of admission was increased by 3% to 5% at all water fluoride levels above 0.1 ppm. When stratified by gender and fluoridation status (i.e., yes = fluoride level ≥ 0.2 ppm, median = 0.84 ppm in 2005 to 2015; no = fluoride level < 0.2 ppm, median = 0.11 ppm), the adjusted rate of hip fracture was 4% higher in females living in the fluoridation areas. The authors suggested that the results should be interpreted with caution due to small effect size and the multifactorial etiology of hip fracture, such as bone mineral density, age, smoking, alcohol consumption, systemic corticosteroid use, rheumatoid arthritis, and previous history of hip fracture.

Summary

The previous SR and two primary studies identified from the 2016 NHMRC review showed no association between water fluoridation and hip fracture. One large ecological study identified from the updated literature search found that the association between water fluoridation and hip fracture was age dependent and there was a weak association between water fluoridation and hip fractures observed in females, but not in males, that might be attributable to residual confounding. The fluoride levels in the CWF from PHE studies and the two NOF levels from the Swedish study were within the range of Canadian fluoride levels. The findings of those studies were assessed to be partially applicable to the Canadian context. Overall, there was consistent evidence for no association between water fluoridation and hip fracture.

Table 31: Hip Fracture

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Two Previous SRs, One Ecological Study, and One Retrospective Cohort Study					
McDonagh et al. (2000) UK Previous SR	Age: 35+ 18 studies (most low quality) N = NR	NR	30 analyses • Hip fracture decreased with increase water fluoride level (n = 14); 5 showed statistically significant associations • Hip fracture increased with increase water fluoride level (n = 13); 4 showed statistically significant associations • No association between hip fracture and water fluoridation (n = 3)	NR	There was no clear association of hip fracture with water fluoridation.
NHMRC 2007 Australia Previous SR	1 additional study (fair quality) after McDonagh et al. (2000)	CWF Non-CWF	NR	RR = 1.02; 95% CI, 0.96 to 1.09	There was no increased risk of hip fracture in those exposed to the CWF.
PHE (2014) England Ecological Acceptable	Residents in CWF and non-CWF areas N = 312,856,448	• CWF (0.8 ppm to 1.0 ppm) • Non-CWF (F level NR)	NR	Difference in incidence rate of hip fracture (95% CI) = 0.7% (–1.0 to 2.4); *P* = 0.42 (Adjustment for age, gender, deprivation, and ethnicity)	There was no significant difference in the incidence of hip fracture between CWF and non-CWF areas. (*Partial*)
Nasman et al. (2013) Sweden Retrospective cohort Acceptable	Residents born between 1900 and 1919, alive and living in area of birth at start of follow-up Median age: 62.8 years N = 473,277	NOF • ≥ 1.5 ppm • 0.7 ppm to 1.49 ppm • 0.3 ppm to 0.69 ppm • < 0.3 ppm	NR	Risk of hip fracture HR (95% CI) • ≥1.5 ppm: 0.98 (0.93 to 1.04) • 0.7 ppm to 1.49 ppm: 0.97 (0.94 to 1.00) • 0.3 ppm to 0.69 ppm: 0.97 (0.94 to 0.99) < 0.3 ppm as ref (Adjustment for gender, age group, county of residence, and calendar group)	Compared with < 0.3 ppm, there was no increased risk of hip fracture or first low-trauma hip fracture due to fluoride exposure. (*Partial*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings (<i>Applicability</i>[a])</th></tr>
<tr><td colspan="6">Evidence From the Updated Literature Search: One Ecological Study</td></tr>
<tr>
<td>PHE 2018[86]
England
Ecological
Acceptable</td>
<td>Participants aged 0 to 80+ years for hospital admissions for hip fracture
N = 477,610,000 person-years</td>
<td>Fluoride level in water supply (regardless of source):
< 0.1 ppm, 0.1 ppm to < 0.2 ppm, 0.2 ppm to < 0.4 ppm, 0.4 ppm to < 0.7 ppm, ≥ 0.7 ppm</td>
<td colspan="2">Adjusted incidence rate ratios of hip fracture admission, stratified by age group, fluoride levels, and gender, England (2007 to 2015):

At age 0 to 49 years, water fluoride levels of ≥ 0.1 ppm were associated with 13% to 14% lower risk of hip fracture admission in both males and females.
At age 50 to 64 years and 65 to 79 years, there was no clear relationship between water fluoride and fracture admission risk in both males and females.
At age ≥ 80 years, the risk of hip fracture admission was increased by 3 to 5% at all water fluoride levels greater than 0.1 ppm.

Adjusted incidence rate ratios of hip fracture admission, stratified by gender and fluoridation status, England (2007 to 2015)
<table>
<tr><th>Gender</th><th>Fluoridation Status[a]</th><th>Adjusted IRR (95% CI)[b]</th><th><i>P</i> Value</th></tr>
<tr><td>Male</td><td>No</td><td>Ref (1)</td><td>–</td></tr>
<tr><td></td><td>Yes</td><td>1.02 (1.00 to 1.05)</td><td>0.053</td></tr>
<tr><td>Female</td><td>No</td><td>Ref (1)</td><td>–</td></tr>
<tr><td></td><td>Yes</td><td>1.04 (1.01 to 1.06)</td><td>0.001</td></tr>
</table>
[a] No = fluoride level < 0.2 ppm; yes = fluoride level ≥ 2 ppm.
[b] Adjusted for age, gender, ethnicity, and deprivation status.</td>
<td>In fluoridation areas, there was a slight increase of hip fracture in female by 4% compared with no fluoridation areas. (<i>Partial</i>)</td>
</tr>
</table>

CI = confidence interval; CWF = community water fluoridation; F = fluoride; HR = hazard ratio; IRR = incidence rate ratio; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; PHE = Public Health England; ppm= parts per million; ref = reference; RR = relative risk; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

9. Osteoporosis

Results for osteoporosis are presented in Table 32.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review reported the findings of one previous SR and identified one ecological study.

The previous 2007 NHMRC included one SR, which included 27 human studies (most of which were assessed to be of low quality), 12 of which used fluoride to treat osteoporosis and were excluded from the 2016 NHRMC review, and the rest reporting bone mineral density and water fluoridation. The authors concluded that the addition of fluoride to drinking water at a level of 1 ppm was not associated with a decrease in bone mineral density compared with non-fluoridated water.

The ecological study assessed to be of low quality by Huang (2013) compared the prevalence of osteoporosis among residents aged 16 to 60 years from villages in China. The participants were divided into two groups based on groundwater fluoride levels from the villages: 1.5 ppm to 7.0 ppm and 0.5 ppm to 1.0 ppm. There was no significant difference in the prevalence of osteoporosis between groups. Confounding variables were not adjusted for in the analysis.

Evidence From the Updated Literature Search

No additional study was identified.

Summary

A previous SR and one ecological study assessed to be of low quality identified in the NHMRC 2016 review showed no evidence for association between water fluoridation and osteoporosis. No studies of acceptable quality or studies from Canada or from countries with comparable socio-economic characteristics and health care system with Canada were identified. Overall, there was insufficient evidence as none of the studies measured the direct association between water fluoridation at the current Canadian levels and osteoporosis.

Table 32: Osteoporosis

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Previous SR and One Ecological Study					
NHMRC 2007 Australia Previous SR	Included 1 SR (27 studies [12 of which on the use of fluoride to treat osteoporosis], mostly low quality)	NR	NR	NR	Addition of fluoride to drinking water at a level of 1 ppm did not associate with a decrease in bone mineral density compared with non-fluoridated water.
Huang (2013) China Ecological Low	Participants aged 16 to 60 years N = 675	NOF • 1.5 ppm to 7.0 ppm • 0.5 ppm to 1.0 ppm	Prevalence of osteoporosis • 1.5 ppm to 7.0 ppm: 6.2% • 0.5 ppm to 1.0 ppm: 6.8%, NS	NR	Prevalence of osteoporosis was not significantly different between groups. (*Limited*)
Evidence From the Updated Literature Search: No Study Identified					

NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NS = not significant; ppm = parts per million; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

10. Musculoskeletal Pain

Results for musculoskeletal pain are presented in Table 33.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified one ecological study and one cross-sectional study. Both studies were assessed to be of low quality.

The cross-sectional study by Namkaew and Wiwantanadate (2012) conducted in Thailand investigated the prevalence of lower back pain, knee pain, and leg pain among adults aged 50 to 80 years living in areas where the drinking water fluoride level was either ≥ 0.7 ppm or < 0.7 ppm. The prevalence of knee pain and leg pain were found to be similar between areas. The prevalence of lower back pain was higher in high fluoride areas compared with low fluoride areas (69.7% versus 60.4%). After adjusting for family history of pain and history of injury to lower body, the study found that higher water fluoride levels (≥ 0.7 ppm) were associated with increased odds of lower back pain (OR = 1.58; 95% CI, 1.10 to 2.28).

The ecological study by Ranjan and Yasmin (2012) included residents in 31 villages in India, where groundwater fluoride levels were grouped as < 0.4 ppm, 0.4 ppm to 1.5 ppm, and > 1.5 ppm. Crude prevalence of self-reported joint pain for the total population was 14.8%, 12.4%, and 54.3%, respectively. Tests of significance and adjustment for confounding variables were not conducted.

Evidence From the Updated Literature Search

No additional study was identified.

Summary

The two studies identified by the 2016 NHMRC review were assessed to be of low methodological quality and were conducted in countries having different socio-economic parameters, water fluoride levels, and health care systems than Canada. The findings of those studies were assessed to be of limited applicability to the Canadian context. The updated literature search identified no additional study. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and musculoskeletal pain.

Table 33: Musculoskeletal Pain

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Ecological Study and Cross-Sectional Study					
Namkaew and Wiwantanadate (2012) Thailand Cross-sectional Low	Adults aged 50 to 80 years N = 534	NOF • ≥ 0.7 ppm • < 0.7 ppm	Prevalence of lower back pain • ≥ 0.7 ppm: 69.7% • < 0.7 ppm: 60.4% Prevalence of knee pain • ≥ 0.7 ppm: 59.9% • < 0.7 ppm: 60.4% Prevalence of leg pain • ≥ 0.7 ppm: 36.9% • < 0.7 ppm: 37.3%	Lower back pain OR = 1.58; 95% CI, 1.10 to 2.28 (Adjustment for family history of pain and history of injury to lower body)	Higher water fluoride levels were associated with increased odds of lower back pain. (*Limited*)
Ranjan and Yasmin (2012) India Ecological Low	Residents in 31 villages Age: NR N = 2,732	NOF • > 1.5 ppm • 0.4 ppm to 1.5 ppm • < 0.4 ppm	Crude prevalence of self-reported joint pain Total • > 1.5 ppm: 54.3% • 0.4 ppm to 1.5 ppm: 12.4% • < 0.4 ppm: 14.8% Same observations for children, adult males, and adult females	NR	Residents in areas with water fluoride levels > 1.5 ppm had higher prevalence of self-reported joint pain. (*Limited*)
Evidence From the Updated Literature Search: No Study Identified					

CI = confidence interval; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; OR = odds ratio; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

11. Newborn Height and Weight

Results for newborns' height and weight are presented in Table 34.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified one case-control study assessed to be of low quality.

The case-control study by Diouf et al. (2012) conducted in Senegal investigated the relationship between mothers' exposure to different drinking water sources (i.e., drill water [4.7 ppm], well water [0.009 ppm], and mineral water [0.0 ppm]) and the low birth weight of newborns. After adjusting for Dean's index, parity, consanguinity, anemia and hypertension, the study found that mothers who had been exposed to drill water with fluoride level of 4.7 ppm had significantly higher odds of giving birth to low birth weight newborns (OR = 1.99; 95% CI, 1.3 to 3.67; $P = 0.04$).

Evidence From the Updated Literature Search

The current literature search identified one additional cross-sectional study assessed to be of low quality.

The cross-sectional study by Aghaei et al. (2015a)[128] investigated the correlation between newborns' height or weight and NOF levels in drinking water (i.e., > 1.5 ppm, 0.7 ppm to 1.5 ppm, < 0.7 ppm) in 35 villages in Iran. The study found a positive correlation between newborns' height and drinking water fluoride ($r = 0.69$; $P < 0.001$), and a positive correlation between newborns' weight and drinking water fluoride ($r = 0.44$; $P < 0.001$). The statistical analysis did not adjust for any confounding variables.

Summary

The findings of two low-quality studies revealed mixed evidence for the relationship between high fluoride levels and newborns' height or weight. The highest fluoride levels in both studies were much higher than the current Canadian levels. The findings of both studies were assessed to be of limited applicability to the Canadian context. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and newborns' weight or newborns' height.

Table 34: Neonatal Height and Weight

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(*Applicability*[a])</th></tr>
<tr><td colspan="6">**Evidence From the 2016 NHMRC Review: One Case-Control Study**</td></tr>
<tr><td>Diouf et al. (2012)
Senegal
Case-control
Low</td><td>Mothers giving birth at a hospital
Cases (N = 108)
Controls (N = 216)</td><td>• 4.7 ppm (Drill water)
• 0.009 ppm (Well water)
• 0.0 ppm (Mineral water)</td><td>NR</td><td>Low birth weight
OR (95% CI)
• 4.7 ppm (Drill water): 1.99 (1.3 to 3.67); *P* = 0.04
• 0.009 ppm (Well water): 0.88 (0.5 to 2.51); *P* = NR

0.0 ppm (Mineral water) as ref

(Adjustment for Dean’s index, parity, consanguinity, anemia, and hypertension)</td><td>Mothers who had been exposed to drill water with fluoride level of 4.7 ppm had significantly higher odds of giving birth to low birth weight newborns. (*Limited*)</td></tr>
<tr><td colspan="6">**Evidence From the Updated Literature Search: One Cross-Sectional Study**</td></tr>
<tr><td>Aghaei et al. (2015a)[128]
Iran
Cross-sectional
Low</td><td>Babies born during 2013 from 35 villages
N = 492</td><td>NOF
• > 1.5 ppm
• 0.7 ppm to 1.5 ppm
• < 0.7 ppm</td><td colspan="2">Mean height and weight, and correlation between height or weight and fluoride level in drinking water
<table>
<tr><th>Fluoride Level, ppm</th><th>Height, cm (SD)</th><th>Weight, g (SD)</th></tr>
<tr><td>< 0.7</td><td>47.7 (0.7)</td><td>2,728.8 (233.7)</td></tr>
<tr><td>0.7 to 1.5</td><td>49.1 (0.3)</td><td>2,808.3 (175.5)</td></tr>
<tr><td>> 1.5</td><td>51.2 (1.4)</td><td>3,201.4 (146.0)</td></tr>
<tr><td>Correlation coefficient</td><td></td><td></td></tr>
<tr><td>r</td><td>0.69</td><td>0.44</td></tr>
<tr><td>*P* value</td><td>< 0.001</td><td>< 0.001</td></tr>
</table></td><td>There was a positive correlation between newborns’ height and drinking water fluoride, and a positive correlation between babies’ weight and drinking water fluoride. (*Limited*)</td></tr>
</table>

CI = confidence interval; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; OR = odds ratio; ppm = parts per million; Ref = reference; SD = standard deviation.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

12. Down Syndrome

Results for Down syndrome are presented in Table 35.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review included two previous SRs and identified one ecological study.

The previous SR by McDonagh et al. (2000) included six studies, all assessed to be of low quality. Three studies found a negative association, one found a positive association, one reported conflicting results, and one found no association between water fluoridation and Down syndrome. The authors of all studies concluded that there was no clear association of Down syndrome with water fluoridation.

The previous 2007 NHMRC review identified an additional SR, which included six low-quality studies. Of the nine reported analyses, four showed a positive association and five showed no association between water fluoridation and Down syndrome.

The ecological study of acceptable quality conducted by PHE (2014) compared the incidence rate of Down syndrome among residents living in areas with CWF (0.8 ppm to 1.0 ppm) and without CWF in England. After adjusting for maternal age, difference in incidence was 0.9% (95% CI, –0.8 to 2.6). The study concluded that there was no significant difference in the incidence of Down syndrome between areas with CWF and non-CWF.

Evidence From the Updated Literature Search

One ecological study assessed to be of acceptable quality from England was identified.

PHE (2018)[86] determined the incidence rate of Down syndrome in England from 2012 to 2014. A total of 2,020,259 live births were included. Fluoride levels were stratified from low (< 0.1 ppm) to high (≥ 0.7 ppm), regardless of source. Compared with the lowest fluoride levels (< 0.1 ppm), there was a significant increase in incidence rate of Down syndrome at fluoride levels of 0.1 ppm to < 0.2 ppm (by 11%) and 0.4 ppm to < 0.7 ppm (by 21%), but not at fluoride levels of ≥ 0.7 ppm. A trend test showed no evidence of a relationship between fluoride level and incidence of Down syndrome (P = 0.941). When stratified by fluoridation status (i.e., yes = fluoride level ≥ 0.2 ppm, median = 0.84 ppm in 2005 to 2015; no = fluoride level < 0.2 ppm, median = 0.11 ppm), the study found no association between water fluoridation status and incidence of Down syndrome, after adjustment for maternal age.

Summary

Two previous SRs found no clear association of Down syndrome with water fluoridation. Two large ecological studies conducted in England, where the water fluoride levels and the socio-economic parameters are comparable to those in Canada, found no significant difference in the incidence of Down syndrome between CWF and non-CWF areas. Overall, there was limited evidence for no association between water fluoridation at the current Canadian levels and Down syndrome.

Table 35: Down Syndrome

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td colspan="6">Evidence From the 2016 NHMRC Review: Two Previous SRs and One Ecological Study</td></tr>
<tr><td>McDonagh et al. (2000)
UK
Previous SR</td><td>6 studies (low quality)
Age: NR
N = NR</td><td>NR</td><td>• Negative association (3 studies)
• Positive association (1 study)
• Conflict results (1 study)
• No association (1 study)</td><td>NR</td><td>There was no clear association between Down syndrome and water fluoridation.</td></tr>
<tr><td>NHMRC 2007
Australia
Previous SR</td><td>1 additional SR (6 studies, low quality) after McDonagh et al. (2000)</td><td>CWF
Non-CWF</td><td>9 analyses
• Positive association (n = 4)
• No association (n = 5)</td><td>NR</td><td>There was no clear association between Down syndrome and water fluoridation.</td></tr>
<tr><td>PHE (2014)
England
Ecological
Acceptable</td><td>Residents in CWF and non-CWF areas
(N = 2,727,300)</td><td>• CWF (0.8 ppm to 1.0 ppm)
• Non-CWF (F level NR)</td><td>NR</td><td>Difference in incidence rate of Down syndrome (95% CI) = 0.9% (–0.8 to 2.6); P = 0.68
(Adjustment for maternal age)</td><td>There was no significant difference in the incidence of Down syndrome between CWF and non-CWF. (Partial)</td></tr>
<tr><td colspan="6">Evidence From the Updated Literature Search: One Ecological Study</td></tr>
<tr><td>PHE 2018[86]
England
Ecological
Acceptable</td><td>Live births from 2012 to 2014 in England
N = 2,020,259</td><td>Fluoride level in water supply (regardless of source):
< 0.1 ppm, 0.1 ppm to < 0.2 ppm, 0.2 ppm to < 0.4 ppm, 0.4 ppm to < 0.7 ppm, ≥ 0.7 ppm</td><td colspan="2">Adjusted incidence rate ratios of Down syndrome, by fluoride levels, England 2012 to 2014
<table>
<tr><th>Fluoride Levels, ppm</th><th>Adjusted IRR (95% CI)[a]</th><th>P Value</th><th>P Trend</th></tr>
<tr><td>< 0.1</td><td>Ref (1)</td><td>–</td><td>0.941</td></tr>
<tr><td>0.1 to < 0.2</td><td>1.11 (1.03 to 1.19)</td><td>0.003</td><td></td></tr>
<tr><td>0.2 to < 0.4</td><td>0.96 (0.88 to 1.06)</td><td>0.446</td><td></td></tr>
<tr><td>0.4 to < 0.7</td><td>1.21 (1.05 to 1.40)</td><td>0.009</td><td></td></tr>
<tr><td>≥ 0.7</td><td>0.99 (0.88 to 1.12)</td><td>0.912</td><td></td></tr>
</table>
[a] Adjusted for maternal age.</td><td>There was no association between water fluoridation status and incidence of Down syndrome. (Partial)</td></tr>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>[a])</th></tr>
<tr><td></td><td></td><td></td><td colspan="2">Adjusted incidence rate ratios of Down syndrome, by fluoridation status, England (2012 to 2014)
<table>
<tr><th>Fluoridation Status[a]</th><th>Adjusted IRR (95% CI)[b]</th><th><i>P</i> Value</th></tr>
<tr><td>No</td><td>Ref (1)</td><td>–</td></tr>
<tr><td>Yes</td><td>0.97 (0.89 to 1.07)</td><td>0.596</td></tr>
</table>
[a] No = fluoride level < 0.2 ppm; yes = fluoride level ≥ 2 ppm.
[b] Adjusted for age, gender, ethnicity, and deprivation status.</td><td></td></tr>
</table>

CI = confidence interval; CWF = community water fluoridation; F = fluoride; IRR = incidence rate ratio; NHMRC = National Health and Medical Research Council; NR = not reported; PHE = Public Health England; ppm = parts per million; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

13. Intelligence Quotient and Cognitive Function

Results for IQ and cognitive function are presented in Table 36.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review included one previous SR and identified 11 observational studies (one prospective cohort study, three cross-sectional studies, and seven ecological studies).

The previous SR by McDonagh et al. (2000) included three studies, all assessed to be of low quality. Two reported the relationship of water fluoridation and IQ in children aged 7 to 14 years in China, and one looked at the cognitive function in adults aged 65 years or older. For IQ, one study reported an MD of –7.7, while the other study did not provide an effect estimate. For cognitive function, one study reported a crude RR of 0.93 (confidence intervals not reported). The authors found insufficient evidence of sufficient quality to make any conclusions.

The prospective cohort study of high quality conducted in New Zealand by Broadbent et al. (2014) investigated the relationship between CWF and IQ. The birth cohort between 1972 and 1973 was prospectively followed for 38 years with a 96% retention rate. IQ was measured among participants aged 7 to 13 years and at age 38 years who were residents in areas with CWF (0.7 ppm to 1.0 ppm) and areas without CWF (0.0 ppm to 0.3 ppm). These fluoride levels were similar to the current Canadian levels. Crude IQ scores showed no difference between participants of both age groups living in CWF and non-CWF areas. After adjustment for sex, SES, low birth weight, and breastfeeding, with the addition of educational achievement for adult IQ outcomes, the study found no significant association between CWF and IQ. The authors concluded that it is unlikely that exposure to CWF at fluoride levels of 0.7 ppm to 1.0 ppm is neurotoxic and affects neurological development.

The following studies had limited applicability to the Canadian context and they were presented together based on their findings. Ten studies (two assessed to be of acceptable quality and eight of low quality) provided mixed evidence on the relationship between fluoridated water and IQ. The following studies were conducted in India (Eswar et al. [2011], Trivedi et al. [2012], Saxena et al. [2012], and Singh et al. [2013]), Iran (Karimzade et al. [2014] and Seraj et al. [2012]), China (Fan et al. [2007], Wang et al. [2007], and Choi et al. [2015]), and Mexico (Rocha-Amador et al. [2007]), where the highest naturally occurring water fluoride levels were 3.3- to 13.4-fold higher than the current Canadian optimum level (0.7 ppm). The findings of these studies are summarized as follows:

- Two studies (Eswar et al. [2011]) and Fan et al. [2007]) found no significant difference in the mean IQ scores between high (2.45 ppm, 3.15 ppm) and low (0.29 ppm, 1.03 ppm) water fluoride levels.
- One study (Choi et al. [2015]) found no statistically significant differences between fluoride levels (range: 1.0 ppm to 4.07 ppm; mean 2.2 ppm) for any subtest of cognitive function measurements.
- Five studies (Karimzade et al. [2014], Seraj et al. [2012], Trivedi et al. [2012], Wang et al. [2007], and Saxena et al. [2012]) found significantly lower mean IQ scores among children from high fluoride areas (2.3 ppm to 8.3 ppm) compared with low fluoride areas (0.25 ppm to <1.5 ppm).

- One study (Singh et al. [2013]) provided inconclusive evidence due to the lack of statistical analysis on the differences between IQ scores of children in 6.8 ppm and 1.0 ppm water fluoride areas.

- One study found a significant negative correlation between drinking water fluoride levels (0.8 ppm, 5.3 ppm, 9.4 ppm) and IQ.

Evidence From the Updated Literature Search

The updated literature search identified six additional observational studies (two ecological studies and four cross-sectional studies).

The ecological study of acceptable quality by Aggeborn and Öhman (2017)[76] from Sweden studied the effect of fluoride exposure through the drinking water throughout life on cognitive and non-cognitive ability in participants up to age 18 years, and math test scores in ninth grade students. Fluoride in the community water supply in Sweden is naturally occurring and its level is kept at or below 1.5 ppm. Regression analysis showed that water fluoride levels in Swedish drinking water had no effects on cognitive ability, non-cognitive ability, and math test scores, after adjusting for parent's education, parent's income, father's cognitive and non-cognitive ability, parent immigrant, and cohort mean education (at birth, at school start, and at 16 years age).

The cross-sectional study of low quality by Barberio et al. (2017a)[129] examined the relationship between fluoride exposure and parental- or self-reported diagnosis of a learning disability among a population-based sample of Canadian children aged 3 to 12 years from two surveys: Cycle 2 (2009 to 2011; N = 1,120) and Cycle 3 (2012 to 2013; N = 1,101). Fluoride exposure was determined in Cycle 2 by urine fluoride and in Cycle 3 by fluoride concentration of tap water in addition to urine fluoride. All the analyses were adjusted for age, sex, household income adequacy, and highest attained education in the household. The results are presented in Table 36 and summarized as follows:

- In Cycle 2, self-reported learning disability, self-reported diagnosis of attention-deficit/hyperactivity disorder, and self-reported diagnosis of attention deficit disorder were not significantly associated with fluoride exposure measured as urinary fluoride, creatinine-adjusted urinary fluoride, or specific gravity-adjusted urinary fluoride.
- In Cycle 3, self-reported learning disability was not significantly associated with fluoride exposure measured as urinary fluoride, creatinine-adjusted urinary fluoride, specific gravity-adjusted urinary fluoride, or fluoride concentration of tap water.
- When Cycles 2 and 3 were combined, there was a small significant association between self-reported learning disability and urinary fluoride (OR = 1.02; 95% CI, 1.00 to 1.03). However, the association was not observed with creatinine-adjusted urinary fluoride or specific gravity-adjusted urinary fluoride.

The authors concluded that there was no clear association between fluoride exposure and reported learning disability among Canadian children.

Four cross-sectional studies of low quality, all conducted in India, compared the IQ scores of children aged 6 to 14 years between high (1.2 ppm to 4.99 ppm) and low (0.19 ppm to < 1.2 ppm) groundwater fluoride levels. Three studies (Razdan et al. [2017],[106] Aravind et al. [2016],[130] and Khan et al. [2015][131]) found that children living high fluoride areas had significantly lower mean IQ scores compared with those living in the low fluoride area. These three studies did not adjust for confounding variables in their analyses. A fourth study, after adjustment for age, gender, parental education, and family income, found no association between IQ scores and water fluoride levels (2.0 ppm, 1.2 ppm versus 0.4 ppm).

Summary

Two studies of assessed to be of acceptable quality from New Zealand and Sweden found no association between water fluoridation at the current Canadian levels and IQ or cognitive function in children and adults. One study assessed to be of low quality from Canada found no association between learning disability in children and water fluoridation. The remaining studies, which were assessed to be of low quality and not relevant to the Canadian context, provided mixed evidence. Overall, there was limited evidence for no association between water fluoridation at the current Canadian levels and IQ or cognitive function.

Table 36: IQ and Cognitive Function

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Previous SR and 11 Studies (One Prospective Cohort Study, Three Cross-Sectional Studies, and Seven Ecological Studies)					
McDonagh et al. (2000) UK Previous SR	2 studies (low quality) Two reported the relationship of water fluoridation and IQ in children 7 to 14 years old in China, and one on cognitive impairment in adults 65+ years	NR	NR	IQ MD = –7.7 reported from one study; Estimate not reported in other study Cognitive impairment Crude RR = 0.93	There was no evidence of sufficient quality to make any conclusions.
Broadbent et al. (2014) New Zealand Prospective cohort High	Birth cohort aged 7 to 13 years; N = 992 Birth cohort aged 38 years; N = 942	• CWF (0.85 ppm) • NOF (0.0 ppm to 0.3 ppm)	Mean IQ scores (SD) 7 to 13 years • CWF (0.85 ppm): 100.0 (13.5) • NOF (0.0 ppm to 0.3 ppm): 99.8 (13.0) 38 years • CWF (0.85 ppm): 100.2 (14.2) • NOF (0.0 ppm to 0.3 ppm): 98.1 (13.5)	Beta coefficient (95% CI) 7 to 13 years: –0.14 (–3.49 to 3.20); *P* = 0.93 38 years: 3.00 (0.02 to 5.98); *P* = 0.05 NOF as ref (Adjustment for sex, socio-economic status, low birth weight, and breastfeeding, with the addition of educational achievement for adult IQ outcomes)	There was no difference in the mean IQ scores between CWF (0.7 ppm to 1.0 ppm) and non-CWF. (*Partial*)
Eswar et al. (2011) India Ecological Low	Children aged 12 to 14 years N = 133	NOF • 2.45 ppm • 0.29 ppm	Mean IQ scores (SD) • 2.45 ppm: 88.8 (15.3) • 0.29 ppm: 86.3 (12.8); *P* = 0.30	NR	There was no significant difference in the mean IQ scores between two groups. (*Limited*)

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Karimzade et al. (2014) Iran Ecological Low	Male children aged 9 to 12 years N = 39	NOF • 3.94 ppm • 0.25 ppm	Mean IQ scores (SD) • 3.94 ppm: 81.2 (16.2) • 0.25 ppm: 104.3 (20.7); $P < 0.001$	NR	There were significantly lower mean IQ scores in boys from high fluoride areas compared with low fluoride areas. (*Limited*)
Fan et al. (2007) China Ecological Low	Children aged 7 to 14 years N = 79	NOF • 3.15 ppm • 1.03 ppm	Mean IQ scores (SD) • 3.15 ppm: 96.1 (12.0) • 1.03 ppm: 98.4 (14.8); $P > 0.05$	NR	There was no significant difference in the mean IQ scores between two groups. (*Limited*)
Seraj et al. (2012) Iran Ecological Low	Children aged 6 to 11 years N = 239	NOF • 5.2 ppm • 3.1 ppm • 0.5 ppm to 1 ppm	Mean IQ scores (SD) • 5.2 ppm: 88.6 (16.0) • 3.1 ppm: 89.03 (13.0) • 0.5 ppm to 1 ppm: 97.8 (19.0); $P = 0.001$	NR	There were significantly lower mean IQ scores in children from high and medium fluoride areas (5.2 ppm and 3.1 ppm) compared with low fluoride areas (0.5 to 1 ppm). (*Limited*)
Trivedi et al. (2012) India Ecological Low	Children aged 12 to 13 years N = 84	NOF • 2.30 ppm • 0.84 ppm	Mean IQ scores (SE) All • 2.30 ppm: 92.53 (3.13) • 0.84 ppm: 97.79 (2.54); $P < 0.05$ Males • 2.30 ppm: 94.88 (2.96) • 0.84 ppm: 99.97 (2.10); $P < 0.05$ Females • 2.30 ppm: 90.18 (3.32) • 0.84 ppm: 94.37 (2.98); $P < 0.05$	NR	There were significantly lower mean IQ scores in boys and girls from high fluoride areas compared with low fluoride areas. (*Limited*)
Wang et al. (2007) China Ecological Low	Children aged 8 to 12 years N = 376	NOF (SD) • 8.3 (1.9) ppm • 0.5 (0.2) ppm	Mean IQ scores (SD) • 8.3 ppm: 100.5 (16.2) • 0.5 ppm: 104.8 (20.7); $P < 0.05$	NR	There were significantly lower mean IQ scores in chlidren from high fluoride areas. (*Limited*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>[a])</th></tr>
<tr><td>Saxena et al. (2012)
India
Cross-sectional
Low</td><td>Children aged 12 years
N = 170</td><td>NOF
• > 4.5 ppm
• 3.1 ppm to 4.5 ppm
• 1.5 ppm to 3.0 ppm
• <1.5 ppm</td><td>NR</td><td>Mean “intelligence grade” (lower score = higher intelligence)
• > 4.5 ppm: 4.45
• 3.1 ppm to 4.5 ppm: 4.23
• 1.5 ppm to 3.0 ppm: 3.85
• < 1.5 ppm: 3.16; <i>P</i> < 0.001

No adjustment for confounders</td><td>There was a significant difference in mean intelligence grade between groups.
(<i>Limited</i>)</td></tr>
<tr><td>Rocha-Amador et al. (2007)
Mexico
Cross-sectional
Acceptable</td><td>Children aged 6 to 11 years
N = 132</td><td>NOF
• 9.4 ppm
• 5.3 ppm
• 0.8 ppm</td><td>NR</td><td>Log coefficient
• 9.4 ppm: –6.7; <i>P</i> < 0.001
• 5.3 ppm: –11.2; <i>P</i> < 0.001
• 0.8 ppm: –10.2; <i>P</i> < 0.001

(Adjustment for children’s blood lead level, mother’s education, socio-economic status, height-for-age, and serum transferrin saturation)</td><td>There was a significant negative correlation between drinking water fluoride and IQ.
(<i>Limited</i>)</td></tr>
<tr><td>Singh et al. (2013)
India
Cross-sectional
Low</td><td>Male children aged 9 to 14 years
N = 142</td><td>NOF
• 6.8 ppm
• 1.0 ppm</td><td><table>
<tr><th>IQ</th><th>6.8 ppm</th><th>1.5 ppm</th></tr>
<tr><td>> 130</td><td>0%</td><td>0%</td></tr>
<tr><td>120 to 129</td><td>1.4%</td><td>2.8%</td></tr>
<tr><td>110 to 119</td><td>2.8%</td><td>6.9%</td></tr>
<tr><td>90 to 109</td><td>29.2%</td><td>47.2%</td></tr>
<tr><td>80 to 89</td><td>34.7%</td><td>30.6%</td></tr>
<tr><td>70 to 79</td><td>22.2%</td><td>9.7%</td></tr>
<tr><td><69</td><td>6.9%</td><td>2.8%</td></tr>
</table></td><td>NR</td><td>Inconclusive due to no statistical analyses on the differences between IQ scores.</td></tr>
</table>

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Choi et al. (2015) China Ecological Acceptable	Children aged 6 to 8 years N = 51	NOF (range: 1.0 ppm to 4.07 ppm; mean: 2.2 ppm)	NR	Five neuropsychological tests: • Wide Range Assessment of Memory and Learning • Wechsler Intelligence Scale for Children–Revised • Wide Range Assessment of Visual Motor Ability • Finger Tapping Task • Grooved Pegboard Test Beta coefficient showed no significant correlation between water fluoridation and cognitive function measurements (Adjustment for gender, age, parity, illness < 3 years old, household income, carer's age, and education)	There were no statistically significant differences between fluoride levels for any subtests of cognitive function measurements. (*Limited*)
Evidence From Updated Literature Search: Two Ecological and Four Cross-Sectional Studies					
Aggeborn and Öhman (2017)[76] Sweden Ecological Acceptable	Participants aged ≥ 16 years N = national population	NOF ≤ 1.5 ppm	NR	Beta coefficient (SE); expressed in 0.1 ppm fluoride Cognitive ability (up to age 18) = 0.0058 (0.0041); *NS* *(Cognitive ability increased by 0.058 Stanine points for 1 ppm fluoride; 1 Stanine point = 6 to 8 IQ points)* Non-cognitive ability (up to age 18): 0.0165 (0.0046); *P* < 0.01 *(Non-cognitive ability increased by 0.165 Stanine points for 1 ppm fluoride; 1 Stanine point = 6 to 8 IQ points)*	Water fluoridation had no effect on cognitive ability, non-cognitive ability, and math test. (*Partial*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>[a])</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Math test in the ninth grade:
–0.0205 (0.0088); <i>P</i> < 0.05
<i>(Math test would decrease by less than 0.2 points for 1 ppm fluoride; average number of points on test was 27 points)</i>

(Adjustment for parent’s education, parent’s income, father’s cognitive and non-cognitive ability, parent immigrant, and cohort mean education [at birth, at school start, at 16 years age])</td><td></td></tr>
<tr><td>Barberio et al. (2017a)[129]
Canada
Cross-sectional
Low</td><td>Children aged 3 to 12 years from two surveys
Cycle 2 (2009 to 2011; N = 1,120)
Cycle 3 (2012 to 2013; N = 1,101)</td><td>F exposure determined by:
• urine fluoride (Cycle 2)
• tap water fluoride levels (Cycle 3)</td><td colspan="2">1. For Cycle 2 of the Canadian Health Measures Survey (CHMS)
<table>
<tr><th>Predictor Variable</th><th>Unadjusted OR (95% CI)</th><th>Adjusted OR (95% CI)[a]</th></tr>
<tr><td colspan="3"><i>Parental- or self-reported learning disability among children aged 3 to 12 years</i></td></tr>
<tr><td>Urinary fluoride</td><td>1.01 (0.99 to 1.03)</td><td>1.01 (0.99 to 1.04)</td></tr>
<tr><td>Creatinine-adjusted urinary fluoride</td><td>0.99 (0.87 to 1.13)</td><td>1.04 (0.95 to 1.15)</td></tr>
<tr><td>Specific gravity-adjusted urinary fluoride</td><td>1.00 (0.99 to 1.02)</td><td>1.01 (0.99 to 1.02)</td></tr>
<tr><td colspan="3"><i>Parental- or self-reported diagnosis of ADHD among children aged 3 to 12 years</i></td></tr>
<tr><td>Urinary fluoride</td><td>1.02 (0.97 to 1.08)</td><td>1.02 (0.97 to 1.09)</td></tr>
<tr><td>Creatinine-adjusted urinary fluoride</td><td>0.97 (0.71 to 1.32)</td><td>1.01 (0.85 to 1.21)</td></tr>
<tr><td>Specific gravity-adjusted urinary fluoride</td><td>1.01 (0.97 to 1.05)</td><td>1.01 (0.96 to 1.06)</td></tr>
</table></td><td>• When Cycle 2 data were examined, self-reported learning disability, self-reported diagnosis of ADHD, and self-reported diagnosis of ADD were not significantly associated with fluoride exposure measured as urinary fluoride, creatinine-adjusted urinary fluoride, or specific gravity-adjusted urinary fluoride.
• When Cycle 3 data were examined, self-reported learning disability was not significantly associated with fluoride exposure measured as urinary fluoride, creatinine-adjusted urinary fluoride, specific gravity-</td></tr>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>[a])</th></tr>
<tr><td></td><td></td><td></td><td colspan="2">
<table>
<tr><th>Predictor Variable</th><th>Unadjusted OR (95% CI)</th><th>Adjusted OR (95% CI)[a]</th></tr>
<tr><td colspan="3"><i>Parental- or self-reported diagnosis of ADD among children aged 3 to 12 years</i></td></tr>
<tr><td>Urinary fluoride</td><td>0.98 (0.93 to 1.04)</td><td>0.99 (0.93 to 1.05)</td></tr>
<tr><td>Creatinine-adjusted urinary fluoride</td><td>0.62 (0.47 to 0.83)[b]</td><td>0.79 (0.59 to 1.06)</td></tr>
<tr><td>Specific gravity-adjusted urinary fluoride</td><td>0.97 (0.92 to 1.03)</td><td>0.98 (0.94 to 1.03)</td></tr>
</table>
[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household.
[b] <i>P</i> < 0.01.

2. For Cycle 3 of the CHMS

<table>
<tr><th>Predictor Variable</th><th>Unadjusted OR (95% CI)</th><th>Adjusted OR (95% CI)[a]</th></tr>
<tr><td colspan="3"><i>Parental- or self-reported learning disability among children aged 3 to 12 years</i></td></tr>
<tr><td>Urinary fluoride</td><td>1.01 (0.996 to 1.03)</td><td>1.02 (0.99 to 1.04)</td></tr>
<tr><td>Creatinine-adjusted urinary fluoride</td><td>1.01 (0.77 to 1.34)</td><td>1.03 (0.86 to 1.23)</td></tr>
<tr><td>Specific gravity-adjusted urinary fluoride</td><td>1.01 (0.99 to 1.02)</td><td>1.01 (0.99 to 1.03)</td></tr>
<tr><td>Fluoride concentration of tap water</td><td>1.41 (0.14 to 14.41)</td><td>0.88 (0.068 to 11.33)</td></tr>
</table>
[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household.
</td><td>
adjusted urinary fluoride, or fluoride concentration of tap water.
When Cycles 2 and 3 data were combined, there was a small significant association between self-reported learning disability and urinary fluoride. However, the association was not observed with creatinine-adjusted urinary fluoride or specific gravity-adjusted urinary fluoride.
Overall, there was no clear association between fluoride exposure and reported learning disability among Canadian children. (<i>High</i>)
</td></tr>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(<i>Applicability</i>[a])</th></tr>
<tr><td></td><td></td><td></td><td colspan="2">3. For Cycles 2 and 3 of the CHMS
<table>
<tr><th>Predictor Variable</th><th>Unadjusted OR (95% CI)</th><th>Adjusted OR (95% CI)[a]</th></tr>
<tr><td colspan="3"><i>Parental- or self-reported learning disability among children aged 3 to 12 years</i></td></tr>
<tr><td>Urinary fluoride</td><td>1.01[b] (1.00 to 1.03)</td><td>1.02[c] (1.00 to 1.03)</td></tr>
<tr><td>Creatinine-adjusted urinary fluoride</td><td>1.00 (0.91 to 1.10)</td><td>1.04 (0.98 to 1.10)</td></tr>
<tr><td>Specific gravity-adjusted urinary fluoride</td><td>1.01 (1.00 to 1.02)</td><td>1.01 (1.00 to 1.02)</td></tr>
</table>
[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household
[b] <i>P</i> < 0.1.
[c] <i>P</i> < 0.05.</td><td></td></tr>
<tr><td>Razdan et al. (2017)[106]
India
Cross-sectional
Low</td><td>Children aged 12 to 14 years
N = 219</td><td>NOF
• 4.99 ppm
• 1.70 ppm
• 0.6 ppm</td><td>Mean IQ (95% CI)
• 4.99 ppm: 13.9 (12.8 to 15.1)
• 1.70 ppm: 18.9 (17.9 to 20.0)
• 0.6 ppm: 38.6 (37.1 to 40.1)</td><td>NR</td><td>Children living in the 1.7 ppm and 4.99 ppm fluoride level areas had significantly lower mean IQ scores compared with those in the 0.6 ppm fluoride level area. (<i>Limited</i>)</td></tr>
<tr><td>Aravind et al. (2016)[130]
India
Cross-sectional
Low</td><td>Children aged 10 to 12 years from 3 villages
N = 288</td><td>NOF
• > 2 ppm
• 1.2 ppm to 2 ppm
• < 1.2 ppm</td><td colspan="2">Mean IQ scores
<table>
<tr><th rowspan="2">Fluoride Level</th><th colspan="3">Mean IQ (SD)</th></tr>
<tr><th>All</th><th>Males</th><th>Females</th></tr>
<tr><td>< 1.2 ppm</td><td>41.03 (16.36)[a]</td><td>41.47 (14.93)[a,b]</td><td>40.62 (17.77)[a,b]</td></tr>
<tr><td>1.2 ppm to 2 ppm</td><td>56.68 (14.51)</td><td>56.30 (13.14)</td><td>57.03 (15.78)</td></tr>
<tr><td>> 2 ppm</td><td>31.59 (16.81)</td><td>30.92 (16.09)</td><td>32.24 (17.62)</td></tr>
</table>
[a] <i>P</i> < 0.0001 when compared based on fluoride levels.
[b] NS when comparing males versus females.
Note: Correlation coefficient, <i>r</i> = –0.204, <i>P</i> < 0.0001.</td><td>IQ level was negatively and significantly correlated with fluoride level in drinking water. (<i>Limited</i>)</td></tr>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td>Khan et al. (2015)[131]
India
Cross-sectional
Low</td><td>Children aged 6 to 11 years
N = 429</td><td>NOF
• 2.41 ppm
• 0.19 ppm</td><td colspan="2">Prevalence of different IQ grades at two areas
<table>
<tr><th>IQ Grade</th><th>0.19 ppm; N = 214</th><th>2.41 ppm; N = 215</th></tr>
<tr><td>1</td><td>6 (2.8%)</td><td>0 (0.0%)[a]</td></tr>
<tr><td>2</td><td>160 (74.8%)</td><td>36 (16.7%)[a]</td></tr>
<tr><td>3</td><td>48 (22.4%)</td><td>125 (58.1%)[a]</td></tr>
<tr><td>4</td><td>0</td><td>30 (14.0%)[a]</td></tr>
<tr><td>5</td><td>0</td><td>24 (11.2%)[a]</td></tr>
</table>
[a] P < 0.001</td><td>Children living in the high fluoride area had significantly lower overall IQ compared with those living in low fluoride areas. (Limited)</td></tr>
<tr><td>Sebastien and Sunitha (2015)[109]
India
Cross-sectional
Low</td><td>Children aged 10 to 12 years
N = 405</td><td>NOF
• 2.0 ppm
• 1.2 ppm
• 0.4 ppm</td><td>Mean IQ (SD)
• 2.0 ppm: 80.49 (12.67)[b, c]
• 1.2 ppm: 88.60 (14.01)[d]
• 0.4 ppm: 86.37 (13.58)

[b] P = 0.007 compared with 1.2 ppm
[c] P = 0.03 compared with 0.4 ppm
[d] P = 0.361 compared with 0.4 ppm

In the 2.0 ppm water fluoride area, a higher proportion of children had intellectual capabilities below average or border line (73.3%) compared with 1.2 ppm (54.1%) and 0.4 ppm (63.0%) areas</td><td>Binary regression analysis on IQ scores and water fluoride levels

OR (95% CI)
• 2.0 ppm: 0.59 (0.29 to 1.19)[a]
• 1.2 ppm: 1.74 (1.02 to 2.98)[b]
• 0.4 ppm: ref

[a] P = 0.140 compared with 0.4 ppm
[b] P = 0.044 compared with 0.4 ppm

(Adjustment for age, gender, parental education, and family income)</td><td>There was no clear association between IQ scores and water fluoride levels. (Limited)</td></tr>
</table>

ADD = attention deficit disorder; ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; CWF = community water fluoridation; f = fluoride; IQ = intelligence quotient; MD = mean difference; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; NS = not significant; OR = odds ratio; ppm = parts per million; ref = reference; RR = relative risk; SD = standard deviation; SE = standard error; SR = systematic review.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

14. Thyroid Function

Results for thyroid function are presented in Table 37.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified one cross-sectional study and two ecological studies.

The cross-sectional quality of low quality by Xiang et al. (2009) from China examined thyroid function by measuring total triiodothyronine (T3), total thyroxine (T4), and thyroid-stimulating hormone (TSH) among children aged 8 to 13 years living in high (2.36 ppm) and low (0.36 ppm) fluoride areas. The crude unadjusted results showed significantly higher levels of serum TSH, but not T3 or T4, in children living in high fluoride areas compared with low fluoride areas. However, the mean TSH of children in high fluoride areas (3.88 mlU/mL) and that of children in low fluoride areas (2.54 mlU/mL) were within the normal range, 0.4 mlU/mL to 4.0 mlU/mL, as defined in the NHMRC review.

The ecological study of low quality by Singh et al. (2014) from India found no significant difference in any of the thyroid function tests (free T3, free T4, and TSH) among children 8 to 15 years between groundwater with high (2.7 ppm) and low (1.0 ppm) fluoride levels. Test results were all within the normal range. No confounding variables were adjusted for in the analysis.

The ecological study of low quality by Kutlucan et al. (2013) from Turkey measured total thyroid gland volume among children aged 10 to 12 years in two areas of high naturally occurring water fluoride (4.6 ppm and 2.8 ppm) and one area of low water fluoride (0.19 ppm). The study found no significant difference in mean thyroid volume between groups. However, there was a significantly higher difference in mean echobody index (i.e., thyroid volume adjusted for body surface area) in children living in high fluoride areas compared with low fluoride area (6.94 ± 2.14 versus 6.48 ± 1.53; *P* = 0.003). Confounding variables were not adjusted for in the analysis.

Evidence From the Updated Literature Search

The updated literature search identified four additional observational studies (one case-control study, one ecological study, and two cross-sectional studies).

The case-control study of low quality by Kheradpisheh et al. (2018)[132] from Iran studied the impacts of drinking water fluoride on T3, T4, and TSH among adults aged 20 to 70 years based on two fluoride levels in drinking water; i.e., 0.0 ppm to 0.29 ppm and 0.3 ppm to 0.5 ppm. The crude unadjusted results found a significant difference in TSH, but not T3 or T4, in both cases and controls between fluoride levels. However, after adjustment for gender, family history of thyroid disease, amount of water consumption, exercise, diabetes, and hypertension, multivariable logistic regression analysis showed no association between drinking water fluoride and hypothyroidism (OR = 1.034; 95% CI, 0.7 to 1.53; *P* = 0.86).

The cross-sectional study be of acceptable quality by Barberio et al. (2017b)[133] from Canada examined the relationship between fluoride exposure and thyroid function among a population-based sample of Canadians aged 3 to 79 years living in private households in the ten provinces. Two cycles of the Canadian Health Measures Survey, Cycle 2 (2009 to 2011; N = 2,530) and Cycle 3 (2012 to 2013; N = 2,671) were conducted. Fluoride exposure was determined in Cycle 2 by urine fluoride and in Cycle 3 by fluoride concentration of tap water in addition to urine fluoride. All the analyses were adjusted for age, sex, household income adequacy, and highest attained education in the household. The results were presented in Table 37 and summarized as follows:

- From Cycle 2 and Cycle 3, there was no association between the measures of fluoride exposure (urinary fluoride or fluoride concentration of tap water) and self-reported diagnosis of a thyroid condition.
- From Cycle 3, there was also no association between the measures of fluoride exposure (urinary fluoride or fluoride concentration of tap water) and abnormal (low or high) TSH level compared with normal TSH level.
- Individuals with a thyroid condition and those without did not differ in the mean of urinary fluoride or the mean of fluoride concentration of tap water.

The authors concluded that there was no association between fluoride exposure and impaired thyroid functioning in the Canadian population.

The cross-sectional study of low quality by Khandare et al. (2017)[105] from India compared thyroid function between schoolchildren aged 8 to 15 years living in high fluoride rural areas (1.43 ppm to 3.84 ppm) and older schoolchildren (age not reported) from higher secondary schools living in lower fluoride urban areas (0.32 ppm to 1.18 ppm). The study found no significant differences between groups in T3 and T4, but there were significantly higher levels of parathyroid hormone and lower levels of TSH among children living in high fluoride level areas compared with those in low fluoride areas. However, the values of both groups were within the normal ranges.

The ecological study of low quality by Peckham et al. (2015)[134] examined the association between levels of fluoride in water supplies and hypothyroidism prevalence among adults aged 40 years and over, which was obtained from all general practitioner (GP) practices in England. However, only data from West Midlands (fluoridated) and Greater Manchester (non-fluoridated) of England were selected, instead of from the whole country. The GP practices were divided into two groups: those which recorded high hypothyroidism prevalence (upper tertile) and those which recorded low-to-medium hypothyroidism prevalence (lower two tertiles). Fluoride exposure was classified either according to drinking water fluoride levels (i.e., ≤ 0.3 ppm, > 0.3 ppm to ≤ 0.7 ppm, and > 0.7 ppm) or according to areas (i.e., fluoridated and non-fluoridated). The study found that the adjusted odds of a practice recording high hypothyroidism prevalence was significantly higher in areas with fluoride levels > 0.7 ppm (OR = 1.62; 95% CI, 1.38 to 1.90) and > 0.3 ppm to ≤ 0.7 ppm (OR = 1.37; 95% CI, 1.12 to 1.68) compared with areas with fluoride levels ≤ 0.3 ppm. Also, the adjusted odds of a practice recording high hypothyroidism prevalence in a fluoridated area (> 0.3 ppm) was significantly higher compared with a non-fluoridated area (≤ 0.3 ppm) (OR = 1.94; 95% CI, 1.39 to 2.70). The confounding variables adjusted for were proportion of women registered with the practice, proportion of patients over 40 years old registered with the practice, and IMD.

Summary

One cross-sectional of acceptable quality conducted in Canada (Barberio et al. [2017b][133]) found no association between fluoride exposure and impaired thyroid functioning in the Canadian population. One ecological study of low quality conducted in England (Peckham et al. [2015][134]) found that the odds of a GP practice recording high levels of hypothyroidism was significantly higher in areas with fluoridation compared with areas without fluoridation. The water fluoride levels of the study from England were applicable to the current Canadian levels. The findings of the remaining studies identified from the 2016 NHMRC review and from the updated literature search were assessed to be of limited applicability to the Canadian context due to higher water fluoride levels and substantial methodological limitations. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and thyroid function.

Table 37: Thyroid Function

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Cross-Sectional Study and Two Ecological Studies					
Xiang et al. (2009) China Cross-sectional Low	Children aged 8 to 13 years N = 170	NOF (SD) • 2.36 (0.70) ppm • 0.36 (0.10) ppm	Mean (SD) 2.36 ppm • T3 (ng/mL): 1.47 (0.28) • T4 (mcg/dL): 9.67 (1.76) • TSH (mIU/mL): 3.88 (2.15) 0.36 ppm • T3 (ng/mL): 1.47 (0.33); *P* = 0.394 • T4 (mcg/dL): 9.22 (2.54); *P* = 0.269 • TSH (mIU/mL): 2.54 (2.07); *P* < 0.001	NR	There was significantly higher serum TSH, but not T3 or T4, in high fluoride level areas compared with low fluoride level areas. Although there were significant differences between groups in TSH, the values of both groups were within the normal range. Overall, there was no clear relationship between water fluoride and thyroid function. (*Limited*)
Singh et al. (2014) India Ecological Low	Children aged 8 to 15 years N = 60	NOF • 2.7 ppm • 1.0 ppm	Mean (SD) 2.7 ppm • FT3 (pg/mL): 3.06 (1.10) • FT4 (ng/dL): 1.20 (0.22) • TSH (mIU/mL): 3.71 (1.94) 1.0 ppm • FT3 (pg/mL): 2.50 (0.71); *P* = 0.117 • FT4 (ng/dL): 1.18 (0.22); *P* = 0.796 • TSH (mIU/mL): 2.50 (0.75); *P* = 0.057	NR	There was no significant difference in any of the thyroid function tests between groups. (*Limited*)

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td>Kutlucan et al. (2013)
Turkey
Ecological
Low</td><td>Children aged 10 to 15 years
N = 559</td><td>NOF
4.6 ppm and 2.8 ppm (two areas)
0.19 ppm</td><td>Mean (SD)
Total thyroid volume (ml)
4.6 ppm and 2.8 ppm: 8.60 (3.11)
0.19 ppm: 8.73 (2.75); P = 0.624
Echobody index (ml/m^2)
4.6 ppm and 2.8 ppm: 6.94 (2.14)
0.19 ppm: 6.48 (1.53); P = 0.003</td><td>NR</td><td>There was no significant difference in mean thyroid volume between groups. (Limited)

There was a significantly higher mean echobody index (thyroid volume adjusted for body surface area) in high fluoride areas compared with low fluoride areas. (Limited)</td></tr>
<tr><td colspan="6">Evidence From Updated Literature Search: One Case-Control Study, One Ecological Study, and Two Cross-Sectional Studies</td></tr>
<tr><td>Kheradpisheh et al. (2018)[132]
Iran
Case-control
Low</td><td>Participants aged 20 to 70 years
N = 411 (cases = 198 controls = 213)</td><td>NOF
A: 0.0 ppm to 0.29 ppm
B: 0.3 ppm to 0.5 ppm</td><td>Mean (SD) of T3, ng/dL<table><tr><th></th><th>A</th><th>B</th></tr><tr><td>Case</td><td>115 (22)</td><td>118 (37)</td></tr><tr><td>Control</td><td>135 (18)</td><td>139 (22)</td></tr><tr><td>Normal range</td><td colspan="2">78 to 180</td></tr></table>Mean (SD) of T4, mcg/dL<table><tr><th></th><th>A</th><th>B</th></tr><tr><td>Case</td><td>6.6 (2.2)</td><td>7.6 (4.3)</td></tr><tr><td>Control</td><td>8.5 (1.2)</td><td>8.6 (1.2)</td></tr><tr><td>Normal range</td><td colspan="2">5.5 to 12.5</td></tr></table></td><td>Multivariable logistic regression analysis for factors affecting hypothyroidism in cases and control groups

Drinking water fluoride: 0.3 to 0.5 ppm vs 0.0 to 0.29 ppm
OR = 1.034; 95% CI, 0.7 to 1.53; P = 0.86

0 to 0.29 ppm as Ref

(Adjustment for gender, family history of thyroid disease, amount of water consumption, exercise, diabetes and hypertension)</td><td>There was a significant difference in TSH, but not T3 or T4, in both cases and controls between fluoride levels. (Limited)

Multivariable logistic regression analysis revealed no relationship between drinking water fluoride and hypothyroidism. (Limited)</td></tr>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td></td><td></td><td></td><td>Mean (SD) of TSH, mIU/L
<table>
<tr><th></th><th>A</th><th>B</th></tr>
<tr><td>Case</td><td>11.9 (7)</td><td>20.5 (12.8)[a]</td></tr>
<tr><td>Control</td><td>2.2 (0.95)</td><td>2.8 (0.9)[b]</td></tr>
<tr><td>Normal range</td><td colspan="2">0.17 to 4.5</td></tr>
</table>
[a] P = 0.003.
[b] P = 0.00.</td><td></td><td></td></tr>
<tr><td>Barberio et al. (2017b)[133]
Canada
Cross-sectional
Acceptable</td><td>Participants aged 3 to 79 years from two surveys
Cycle 2 (2009 to 2011; N = 2,530)
Cycle 3 (2012 to 2013; N = 2,671)</td><td>F exposure determined by:
• Urine fluoride (Cycle 2)
• Tap water fluoride levels (Cycle 3)</td><td colspan="2">1. For Cycle 2
<table>
<tr><th>Predictor Variables</th><th>Unadjusted OR (95% CI)</th><th>Adjusted OR (95% CI)[a]</th></tr>
<tr><td colspan="3">Self-reported diagnosis of a thyroid condition</td></tr>
<tr><td>Urinary fluoride</td><td>0.98 (0.94 to 1.03)</td><td>0.98 (0.95 to 1.02)</td></tr>
<tr><td>Creatinine-adjusted urinary fluoride</td><td>NS (data not shown)</td><td>NS (data not shown)</td></tr>
</table>
[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household
2. For Cycle 3
<table>
<tr><th>Predictor Variables</th><th>Unadjusted OR (95% CI)</th><th>Adjusted OR (95% CI)[a]</th></tr>
<tr><td colspan="3">Self-reported diagnosis of a thyroid condition</td></tr>
<tr><td>Urinary fluoride</td><td>1.00 (0.99 to 1.02)</td><td>1.00 (0.99 to 1.01)</td></tr>
<tr><td>Fluoride concentration of tap water</td><td>0.92 (0.22 to 3.94)</td><td>0.98 (0.28 to 3.45)</td></tr>
<tr><td>Predictor variables</td><td>Unadjusted RRR (95% CI)</td><td>Adjusted RRR (95% CI)[a]</td></tr>
<tr><td colspan="3">TSH levels</td></tr>
<tr><td>Urinary fluoride</td><td></td><td></td></tr>
<tr><td>Low TSH</td><td>1.01 (0.99 to 1.04)</td><td>1.01 (0.99 to 1.04)</td></tr>
<tr><td>Normal TSH</td><td>Ref</td><td>Ref</td></tr>
<tr><td>High TSH</td><td>0.99 (0.97 to 1.02)</td><td>0.99 (0.97 to 1.02)</td></tr>
</table></td><td>• There was no association between the measures of fluoride exposure (urinary fluoride or fluoride concentration of tap water) and self-reported diagnosis of a thyroid condition.
• There was also no association between the measures of fluoride exposure (urinary fluoride or fluoride concentration of tap water) and abnormal (low or high) TSH level compared with normal TSH level.
• Individuals with a thyroid condition and those without did not differ in the mean of urinary fluoride or the mean of fluoride concentration of tap water.

Overall, there was no association between fluoride exposure and impaired thyroid</td></tr>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(*Applicability*[a])</th></tr>
<tr><td></td><td></td><td></td><td colspan="2">
<table>
<tr><th>Predictor Variables</th><th>Unadjusted OR (95% CI)</th><th>Adjusted OR (95% CI)[a]</th></tr>
<tr><td colspan="3">Fluoride concentration of tap water</td></tr>
<tr><td>Low TSH</td><td>1.77 (0.20 to 15.86)</td><td>1.38 (0.08 to 24.49)</td></tr>
<tr><td>Normal TSH</td><td>Ref</td><td>Ref</td></tr>
<tr><td>High TSH</td><td>1.38 (0.07 to 27.00)</td><td>1.20 (0.14 to 10.08)</td></tr>
</table>
[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household.
Note: There were no differences between individuals with or without primary hypothyroidism in urinary fluoride (31.78 µmol/L [95% CI, 11.63 to 51.93] vs. 29.23 µmol/L [95% CI, 25.97 to 32.49] and in fluoride concentration of tap water (0.36 ppm [95% CI, 0.16 to 0.57] vs. 0.22 ppm [95% CI, 0.15 to 0.30]).
</td><td>functioning in the Canadian population. (*High*)</td></tr>
<tr><td>Khandare et al. (2017)[105]
India
Cross-sectional
Low</td><td>8 to 15 years old schoolchildren living in high fluoride rural areas (intervention)
Older schoolchildren (age not reported) from higher secondary school living in lower fluoride urban areas (comparator)
N = 824</td><td>NOF
• High (1.43 ppm to 3.84 ppm)
• Low (0.32 ppm to 1.18 ppm)</td><td colspan="2">
<table>
<tr><th></th><th colspan="2">Water Fluoride Level</th><th>Normal Range</th></tr>
<tr><td></td><td>High</td><td>Low</td><td></td></tr>
<tr><td></td><td colspan="2">*mean ± SD*</td><td></td></tr>
<tr><td>PTH (pg/mL)</td><td>49 ± 12[a]</td><td>27 ± 5</td><td>13 to 54</td></tr>
<tr><td>T3 (ng/mL)</td><td>0.63 ± 0.24</td><td>0.68 ± 0.35</td><td>0.8 to 2.0</td></tr>
<tr><td>T4 (mcg/dL)</td><td>16.1 ± 2.9</td><td>16.9 ± 1.6</td><td>6.1 to 11.8</td></tr>
<tr><td>TSH (mIU/L)</td><td>2.9 ± 0.6[a]</td><td>3.4 ± 0.5</td><td>0.3 to 4.0</td></tr>
</table>
[a] $P < 0.05$
</td><td>No significant differences were observed between groups in T3 and T4.
Although there were significant differences between groups in PTH and TSH, the values of both groups were within the normal ranges.

Overall, there was no clear relationship between water fluoride and thyroid function. (*Limited*)</td></tr>
<tr><td>Peckham et al. (2015)[134]
UK
Ecological
Low</td><td>Participants aged ≥ 40 years
N = 7,935 GP practices</td><td>Fluoridated water
• > 0.7 ppm
• > 0.3 ppm to ≤ 0.7 ppm
• ≤ 0.3 ppm</td><td>NR</td><td>OR (95% CI) of upper tertile (high level) hypothyroidism prevalence according to drinking water fluoride levels
• > 0.7 ppm: 1.62 (1.38 to 1.90)
• > 0.3 ppm to ≤ 0.7 ppm: 1.37 (1.12 to 1.68)
• ≤ 0.3 ppm: ref</td><td>The odds of GP practice recording high levels of hypothyroidism was significantly higher in areas with fluoridation compared with areas without fluoridation. (*Partial)*</td></tr>
</table>

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
				OR (95% CI) of upper tertile (high level) hypothyroidism prevalence according to areas • > 0.3 ppm: 1.94 (1.39 to 2.70) • ≤ 0.3 ppm: ref (Adjustment for proportion of women registered with the practice, proportion of patients over 40 years old registered with the practice, and Index of Multiple Deprivation)	

CI = confidence interval; F = fluoride; GP = general practitioner; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; NS = not significant; OR = odds ratio; PTH = parathyroid hormone; ppm = parts per million; ref = reference; RRR = relative risk ratio; SD = standard deviation; T3 = total triiodothyronine; T4 = total thyroxine; FT3 = free total triiodothyronine; FT4 = free thyroxine; TSH = thyroid-stimulating hormone; vs. = versus.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

15. Kidney Stones

Results for kidney stones are presented in Table 38.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review included one previous SR and identified one ecological study.

The previous 2007 NHMRC review included one cross-sectional study assessed to be of low quality from India. The prevalence of kidney stones was compared in an area with endemic skeletal fluorosis (water fluoride level between 3.5 ppm to 4.9 ppm) to a non-endemic area (0.5 ppm). The study found that residents in skeletal fluorosis endemic areas had higher odds of having kidney stones compared with non-endemic area (OR = 4.63; 95%CI, 2.07 to 7.92). No confounding variables were adjusted in the analysis.

The ecological study assessed to be of acceptable quality conducted by PHE investigated the incidence rate of emergency admissions for kidney stones among residents in CWF (0.8 to 1.0 ppm) and non-CWF areas. After adjustment for age, gender, deprivation and ethnicity, the study found that the incidence of emergency admissions for kidney stones was significantly lower in CWF areas compared with areas with no CWF. Difference in incidence rate of emergency admissions for kidney stones was –7.9% (95% CI, –9.6 to –6.2); *P* < 0.001.

Evidence From the Updated Literature Search

One ecological study assessed to be of acceptable quality from England was identified.

PHE (2018)[86] determined the incidence rate of hospital admissions for kidney stones in England from 2007 to 2015. A total of 477,610,000 person-years were included. Fluoride level was stratified from low (< 0.1 ppm) to high (≥ 0.7 ppm), regardless of source. The study found no linear trend between fluoride concentration and incidence of kidney stone hospital admission (*P* = 0.533). At fluoride levels of 0.1 to < 0.2 ppm and 0.2 to < 0.4 ppm, there was a significantly increased risk of kidney stone admission by 22% and 17% compared with fluoride level of < 0.1 ppm. However, there was no association between kidney stone admission and fluoride at higher levels (i.e., 0.4 to < 0.7 ppm and ≥ 0.7 ppm), after adjustment for age, gender, ethnicity and deprivation status. When stratified by fluoridation status (i.e., yes = fluoride level ≥ 0.2 ppm, median = 0.84 ppm in 2005 to 2015; no = fluoride level < 0.2 ppm, median = 0.11 ppm), the risk of hospital admission for kidney stone was 10% lower (95% CI, 2% to 18%) in fluoridation areas than in non-fluoridation areas.

Summary

Two studies of sufficient quality from England, which was partially applicable to the Canadian context, found an inverse relationship between water fluoridation and the incidence of hospital admissions for kidney stones. However, the authors of this study warned that the findings should be interpreted with cautions due to the possibility of residual confounding. A low quality study from India, which had limited applicability to the Canadian context found a positive association between high water fluoride level and kidney stones. Overall, there was limited evidence for an inverse association between water fluoridation at the current Canadian levels and the incidence of kidney stones.

Table 38: Kidney Stones

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td colspan="6">Evidence From the 2016 NHMRC Review: One Previous SR and Ecological Study</td></tr>
<tr><td>NHMRC 2007
Australia
Previous SR</td><td>1 cross-sectional study from India (low quality)</td><td>NOF
• to 4.9 ppm (skeletal fluorosis endemic areas)
• 0.19 ppm (non-endemic area)</td><td>NR</td><td>Prevalence of kidney stones in the endemic area:
OR = 4.63; 95% CI, 2.07 to 7.92

No adjustment for confounders</td><td>Residents in skeletal fluorosis endemic areas had higher odds of having kidney stones compared with non-endemic area (Limited)</td></tr>
<tr><td>PHE (2014)
England
Ecological
Acceptable</td><td>Residents in CWF and non-CWF areas
(N = 312,856,448)</td><td>• CWF (0.8 to 1.0 ppm)
• Non-CWF (F level NR)</td><td>NR</td><td>Difference in incidence rate of emergency admissions for kidney stones = -7.9%; 95% CI, -9.6 to -6.2; P < 0.001

(Adjustment for age, gender, deprivation and ethnicity)</td><td>Incidence of emergency admissions for kidney stones was significantly lower in CWF areas compared with areas with no CWF (Partial)</td></tr>
<tr><td colspan="6">Evidence From the Updated Literature Search: One Ecological Study</td></tr>
<tr><td>PHE 2018[86]
England
Ecological
Acceptable</td><td>Participants aged (NR) for hospital admissions for kidney stone, England 2007 to 2015
N = 477,610,000 person-years</td><td>Fluoride level in water supply (regardless of source):
< 0.1 ppm, 0.1 to < 0.2 ppm, 0.2 to < 0.4 ppm, 0.4 to < 0.7 ppm, ≥ 0.7 ppm</td><td colspan="2">Adjusted incidence rate ratios of kidney stone admissions, by fluoride levels, England 2007 to 2015
<table>
<tr><th>Fluoride Levels</th><th>Adjusted IRR (95% CI)*</th><th>P Value</th><th>P Trend</th></tr>
<tr><td>< 0.1</td><td>Ref (1)</td><td>--</td><td>0.533</td></tr>
<tr><td>0.1 to < 0.2</td><td>1.22 (1.14 to 1.30)</td><td>< 0.001</td><td></td></tr>
<tr><td>0.2 to < 0.4</td><td>1.17 (1.10 to 1.26)</td><td>< 0.001</td><td></td></tr>
<tr><td>0.4 to < 0.7</td><td>1.07 (0.96 to 1.18)</td><td>0.214</td><td></td></tr>
<tr><td>≥ 0.7</td><td>1.01 (0.86 to 1.13)</td><td>0.857</td><td></td></tr>
</table>
* Adjusted for age, gender, ethnicity and deprivation status</td><td>Incidence of kidney stone admissions was significantly lower in fluoridation areas compared with no fluoridation areas (Partial)</td></tr>
</table>

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td></td><td></td><td></td><td colspan="2">Adjusted incidence rate ratios of kidney stone admissions, by fluoridation status, England (2007 to 2015)
<table>
<tr><th>Fluoridation Status[a]</th><th>Adjusted IRR (95% CI)[b]</th><th>P Value</th></tr>
<tr><td>No</td><td>Ref (1)</td><td>--</td></tr>
<tr><td>Yes</td><td>0.90 (0.82 to 0.98)</td><td>0.020</td></tr>
</table>
[a] No = fluoride level < 0.2 ppm; Yes = fluoride level ≥ 2 ppm
[b] Adjusted for age, gender, ethnicity and deprivation status</td><td></td></tr>
</table>

CI = confidence interval; CWF = community water fluoridation; F = fluoride; IRR = incidence rate ratio; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; OR = odds ratio; PHE = Public Health England; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial or low) applicable to the Canadian context, i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

16. Chronic Kidney Disease

Results for chronic kidney disease (CKD) are presented in Table 39.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified one ecological study.

The ecological study assessed to be of low quality by Chandrajith et al. (2011) from Sri Lanka examined the prevalence of CKD among adults (aged > 18 years) in three villages. The mean groundwater water fluoride levels were 1.03 ppm, 1.02 ppm, and 0.74 ppm. The study found no difference in the crude CKD prevalence between the three villages. CKD of unknown etiology was found only in the villages with 1.02 ppm (84%) and 0.74 ppm (96%), but not in the village with 1.03 ppm. No statistical analysis and adjustment for confounding variables were conducted.

Evidence From the Updated Literature Search

One additional cross-sectional study was identified.

The cross-sectional study assessed to be of low quality by Khandare et al. (2017)[105] from India compared mean serum creatinine between schoolchildren aged 8 to 15 years living in high fluoride rural areas (1.43 ppm to 3.84 ppm) and older schoolchildren (age not reported) from higher secondary schools living in lower fluoride urban areas (0.32 ppm to 1.18 ppm). The study found that serum creatinine of children in high fluoride areas was significantly higher than those in the low fluoride areas (0.85 ppm versus 0.45 ppm; $P < 0.05$). However, the values were within the normal range (0.5 ppm to 1.2 ppm). The study had substantial methodological limitations and did not control for confounding variables in the analysis.

Summary

Two studies (one identified by the 2016 NHMRC review and one from the updated literature search), assessed to be of low quality, reported mixed evidence, which had limited applicability to the Canadian context. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and CKD.

Table 39: Chronic Kidney Disease

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: One Ecological Study					
Chandrajith et al. (2011) Sri Lanka Ecological Low	Adults aged > 18 years N = 5,685	NOF • 1.03 ppm • 1.02 ppm • 0.74 ppm	Crude CKD prevalence • 1.03 ppm: 3.2% • 1.02 ppm: 3.7% • 0.74 ppm: 3.9% % of CKDua • 1.03 ppm: 0% • 1.02 ppm: 84% • 0.74 ppm: 96%	NR	There was no association between chronic kidney disease and water fluoridation. (*Limited*)
Evidence From the Updated Literature Search: One Cross-Sectional Study					
Khandare et al. (2017)[105] India Cross-sectional Low	8 to 15 years old schoolchildren living in high fluoride rural areas (intervention) Older schoolchildren (age not reported) from higher secondary school living in lower fluoride urban areas (comparator) N = 824	NOF • High (1.43 ppm to 3.84 ppm) • Low (0.32 ppm to 1.18 ppm)	Mean serum creatinine (SD) • High F: 0.85 (0.35) mg/dL; $P < 0.05$ • Low F: 0.45 (0.16) mg/dL • (normal range: 0.5 to 1.2)	NR	Serum creatinine of individuals in high fluoride areas was significantly higher than those in the low fluoride areas. However, the values were within the normal range. There was no association between water fluoride and kidney function. (*Limited*)

CKD = chronic kidney disease; CKDua = chronic kidney disease of unknown etiology; F = fluoride; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; ppm parts per million; SD = standard deviation.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

17. Gastric Discomfort

Results for gastric discomfort are presented in Table 40.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified two ecological studies, both assessed to be of low quality, from India.

Both studies (Ranjan and Yasmin [2012] and Sharma et al. [2009]) found that the prevalence of gastric discomfort among adults and children was highest in areas with fluoride level > 1.5 ppm. No statistical analysis and adjustment for confounding variables were conducted.

Evidence From the Updated Literature Search

No additional study was identified.

Summary

Two studies identified by the 2016 NHMRC review were assessed to be of low quality and limited applicability to the Canadian context. No additional study was identified from the updated literature search. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and gastric discomfort.

Table 40: Gastric Discomfort

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th colspan="4">Results</th><th>Effect Estimate</th><th>Study Findings
(*Applicability*[a])</th></tr>
<tr><td colspan="9">Evidence From the 2016 NHMRC Review: Two Ecological Studies</td></tr>
<tr><td rowspan="5">Ranjan and Yasmin (2012)
India
Ecological
Low</td><td rowspan="5">Adults and children in 31 villages
N = 2,732</td><td rowspan="5">NOF
• > 1.5 ppm
• 0.4 ppm to 1.5 ppm
• < 0.4 ppm</td><td></td><td>> 1.5 ppm</td><td>0.4 ppm to 1.5 ppm</td><td>< 0.4 ppm</td><td rowspan="5">NR</td><td rowspan="5">Higher prevalence of gastric discomfort among adults and children found in areas with fluoride level > 1.5 ppm.
(<i>Limited</i>)</td></tr>
<tr><td>All</td><td>42.8%</td><td>23.3%</td><td>23.4%</td></tr>
<tr><td>Male adults</td><td>40.4%</td><td>24.1%</td><td>18.4%</td></tr>
<tr><td>Female adults</td><td>41.7%</td><td>24.1%</td><td>17.0%</td></tr>
<tr><td>Children</td><td>50.9%</td><td>19.3%</td><td>48.1%</td></tr>
<tr><td>Sharma et al. (2009)
India
Ecological
Low</td><td>Children aged 6 to 18 years and adults of villages
N = 1,135 children
N = 1,475 adults</td><td>NOF
• High F: > 1.5 ppm
• Medium F: 1.0 ppm to 1.5 ppm
• Low F: < 1.0 ppm</td><td colspan="4">Adults
• High F: 88.8%
• Medium F: 31.7%
• Low F: 24.0%

Children:
• High F: 17.0%
• Medium F: 0.0%
• Low F: 0.0%</td><td>NR</td><td>Highest prevalence of gastric discomfort among adults and children found in areas with fluoride level > 1.5 ppm.
(<i>Limited)</i></td></tr>
<tr><td colspan="9">Evidence From the Updated Literature Search: No Studies Identified</td></tr>
</table>

F = fluoride; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

18. Headache

Results for headache are presented in Table 41.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified two ecological studies, both assessed to be of low quality, from India.

Two studies (Ranjan and Yasmin [2012] and Sharma et al. [2009]) examined the prevalence of headaches among adults and children in villages with high (> 1.5 ppm), medium (0.4 ppm to 1.5 ppm), and low (< 0.4 ppm) water fluoride levels. Both studies found that the prevalence of headache was highest in areas with fluoride level > 1.5 ppm. No statistical analysis and adjustment for confounding variables were conducted.

Evidence From the Updated Literature Search

No additional study was identified.

Summary

Two studies identified by the 2016 NHMRC review were assessed to be of low quality and limited applicability to the Canadian context. No additional study was identified from the updated literature search. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and headaches.

Table 41: Headache

Study Country Design Quality	Population	Exposures	Results				Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Two Ecological Studies								
Ranjan and Yasmin (2012) India Ecological Low	Adults and children in 31 villages N = 2,732	NOF • > 1.5 ppm • 0.4 ppm to 1.5 ppm • < 0.4 ppm		> 1.5 ppm	0.4 ppm to 1.5 ppm	< 0.4 ppm	NR	Higher prevalence of headache found in areas with fluoride level > 1.5 ppm. (*Limited*)
			All	24.9%	10.6%	9.1%		
			Male adults	26.5%	10.4%	5.7%		
			Female adults	27.3%	14.5%	12.7%		
			Children	15.8%	2.4%	8.9%		
Sharma et al. (2009b) India Ecological Low	Adults and children in 29 villages N = 1,145 children N = 1,556 adults	NOF • > 1.5 ppm • 1.0 ppm to 1.5 ppm • < 1.0 ppm		> 1.5 ppm	1.0 ppm to 1.5 ppm	< 1.0 ppm	NR	Higher prevalence of headache found in areas with fluoride level > 1.5 ppm. (*Limited*)
			Adults	31.6%	2.5%	1.6%		
			Children	11.2%	0.0%	0.0%		
Evidence From the Updated Literature Search: No Studies Identified								

NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

19. Insomnia

Results for insomnia are presented in Table 42.

Evidence From the 2016 NHMRC Review

The 2016 NHMRC review identified two ecological studies, both assessed to be of low quality, from India.

Two studies (Ranjan and Yasmin [2012] and Sharma et al. [2009]) examined the prevalence of insomnia among adults and children in villages with high (> 1.5 ppm), medium (0.4 ppm to 1.5 ppm), and low (< 0.4 ppm) water fluoride levels. Both studies found that the prevalence of insomnia was highest in areas with fluoride level > 1.5 ppm. No statistical analyses or adjustment for confounding variables were conducted.

Evidence From the Updated Literature Search

No additional study was identified.

Summary

Two studies identified by the 2016 NHMRC review were assessed to be of low quality and limited applicability to the Canadian context. No additional study was identified from the updated literature search. Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and insomnia.

Table 42: Insomnia

Study Country Design Quality	Population	Exposures	Results				Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: Two Ecological Studies								
Ranjan and Yasmin (2012) India Ecological Low	Adults and children in 31 villages N = 2,732	NOF • > 1.5 ppm • 0.4 ppm to 1.5 ppm • < 0.4 ppm		> 1.5 ppm	0.4 ppm to 1.5 ppm	< 0.4 ppm	NR	Higher prevalence of insomnia among adults found in areas with fluoride level > 1.5 ppm. (*Limited*)
			Adult males	14.0%	4.1%	0.0%		
			Adult females	13.6%	8.6%	4.8%		
			Children	0.0%	0.0%	0.0%		
Sharma et al. (2009b) India Ecological Low	Adults and children in 29 villages N = 1,145 children N = 1,556 adults	NOF • > 1.5 ppm • 1.0 ppm to 1.5 ppm • < 1.0 ppm		> 1.5 ppm	1.0 ppm to 1.5 ppm	< 1.0 ppm	NR	Higher prevalence of insomnia found in areas with fluoride level > 1.5 ppm. (*Limited*)
			Adults	26.7%	1.5%	1.2%		
			Children	11.2%	0.0%	0.0%		
Evidence From the Updated Literature Search: No Studies Identified								

NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

20. Reproductive Outcomes

Results for reproduction are presented in Table 43.

Evidence From the 2016 NHMRC Review

No study was identified from the 2016 NHMRC review.

Evidence From the Updated Literature Search

One cross-sectional study and one ecological study from Iran, both assessed to be of low quality, were identified.

The cross-sectional study by Moghaddam et al. (2018)[135] evaluated the effect of drinking fluoride levels on spontaneous abortion in high and low fluoride regions. Three levels of groundwater fluoride were examined: ≥ 3 ppm, 1.5 ppm to 3.00 ppm, and ≤ 1.5 ppm. The study found that women living in the areas with ≥3 ppm had a significantly higher risk of spontaneous abortion compared with those living in areas with ≤ 1.5 ppm. There was no significant difference in the incidence rate of spontaneous abortion between 1.5 ppm to 3.00 ppm and ≤ 1.5 ppm areas. The study did not adjust for confounding variables in the analysis and had an imbalance in the number of participants between groups (i.e., n = 70, n = 43, and n = 2,488 for ≥ 3 ppm, 1.5 ppm to 3.00 ppm, and ≤ 1.5 ppm, respectively). No participant characteristics were reported.

The ecological study by Yousefi et al. (2017)[136] examined the relationship between drinking water fluoride and (i) fertility, (ii) infertility without known etiology factors, and (iii) abortion without known etiology factors among women living in areas with low (1.90 ppm) and high (8.10 ppm) drinking water fluoride level. The study found a small significant difference in the prevalence of fertility between women living in high and low fluoride areas (difference = 0.4%; $P < 0.001$, favouring high fluoride), and women living in high fluoride areas had significantly higher rates of infertility (difference = 1.1%; $P < 0.001$) and abortion (difference = 10%; $P = 0.011$) than those living in the low fluoride areas. No confounders were identified or adjusted for in the data analysis.

Summary

The updated literature search identified two studies (assessed to be of low quality and limited applicability to the Canadian context) that reported significantly higher rates of abortion, fertility, or infertility in women living in high fluoride areas, which were many times higher than the recommended Canadian level (0.7 ppm). Overall, there was insufficient evidence for an association between water fluoridation at the current Canadian levels and reproduction in women.

Table 43: Reproduction

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td colspan="6">Evidence From the 2016 NHMRC Review: No Study Identified</td></tr>
<tr><td colspan="6">Evidence From the Updated Literature Search: One Cross-Sectional Study and One Ecological Study</td></tr>
<tr><td>Moghaddam et al. 2018[135]
Iran
Cross-sectional
Low</td><td>Pregnant women living in areas having different fluoride levels
N = 2,601</td><td>NOF
• ≥ 3 ppm (n = 70)
• 1.5 ppm to 3.00 ppm (n = 43)
• ≤ 1.5 ppm (n = 2,488)</td><td colspan="2">Rates of spontaneous abortion
<table>
<tr><th>Fluoride level</th><th>IRR (95% CI)</th><th>P Value</th></tr>
<tr><td>≤ 1.5 ppm</td><td>Ref (1)</td><td></td></tr>
<tr><td>1.5 ppm to 3.00 ppm</td><td>0.85 (0.37 to 1.93)</td><td>0.693</td></tr>
<tr><td>≥ 3 ppm</td><td>2.06 (1.11 to 3.83)</td><td>0.022</td></tr>
</table></td><td>High fluoride level was associated with significant risk of spontaneous abortion compared with low fluoride level. (Limited)</td></tr>
<tr><td>Yousefi et al. (2017)[136]
Iran
Ecological
Low</td><td>Women aged 10 to 49 years living in five villages
N = 3,392</td><td>NOF
• 8.10 ppm ± 1.44 ppm (range: 6.00 ppm to 10.30 ppm)
• 1.90 ppm ± 0.37 ppm (range: 1.46 to 2.81 ppm)</td><td colspan="2">Rates of fertility, infertility, and abortion
<table>
<tr><th rowspan="2"></th><th colspan="2">Fluoride level</th><th rowspan="2">Difference</th><th rowspan="2">P Value</th></tr>
<tr><th>1.90 ppm</th><th>8.10 ppm</th></tr>
<tr><td>Fertility</td><td>5.3% (105/1,993)</td><td>5.7% (70/1,224)</td><td>0.4%</td><td>< 0.001</td></tr>
<tr><td>Infertility</td><td>0.9% (17/1,993)</td><td>2.0% (24/1,224)</td><td>1.1%</td><td>< 0.001</td></tr>
<tr><td>Abortion</td><td>5.7% (6/105)</td><td>15.7% (11/70)</td><td>10.0%</td><td>0.011</td></tr>
</table></td><td>There was small and significant difference in fertility between women living in high and low fluoride areas. Women living in high fluoride areas had significantly higher rates of infertility and abortion than those living in the low fluoride areas. (Limited)</td></tr>
</table>

CI = confidence interval; IRR = incidence rate ratio; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

21. Refractive Errors

Refractive errors are vision defects caused by the change in shape of the cornea, a transparent surface that covers the eye ball, leading to improper focus of light rays on the retina. The main types of refractive errors are myopia (nearsightedness), hyperopia (farsightedness), and astigmatism (uneven focusing). Results for refractive errors are presented in Table 44.

Evidence From the 2016 NHMRC Review

No study was identified from the 2016 NHMRC review.

Evidence From the Updated Literature Search

One ecological study from China assessed to be of low quality was identified.

Bin et al. (2016)[137] evaluated the refractive errors and the demographic associations between drinking water with excessive fluoride and normal drinking water. Residents aged ≥ 40 years from four counties in Northern China were divided into two groups: drinking-water-excessive fluoride (1.47 ppm) and control (0.2 ppm). The study found no difference in the prevalence of myopia, hyperopia, and astigmatism among individuals living in high and low water fluoridated areas. Multiple linear regression analysis showed that spherical equivalents from the right eye of the eligible individuals were associated with gender, age, annual income, but not with education ($P = 0.378$), and fluoride levels in drinking water ($P = 0.857$). Participant characteristics were imbalanced between groups. The authors concluded that there was no association between refractive errors and drinking water fluoride levels.

Summary

One ecological study of low quality and of limited applicability to the Canadian context provided insufficient evidence to draw a conclusion regarding the association between water fluoridation at the current Canadian levels and refractive errors.

Table 44: Refractive Errors

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Results</th><th>Effect Estimate</th><th>Study Findings
(*Applicability*[a])</th></tr>
<tr><td colspan="6">**Evidence From the 2016 NHMRC Review: No Studies Identified**</td></tr>
<tr><td colspan="6">**Evidence From the Updated Literature Search: One Cross-Sectional Study**</td></tr>
<tr><td>Bin et al.
(2016)[137]
China
Cross-sectional
Low</td><td>Residents aged ≥ 40 years from four counties in Northern China
N = 1,415</td><td>NOF
• 1.47 ppm
• 0.2 ppm</td><td colspan="2">Prevalence of myopia, hyperopia, and astigmatism among individuals living in high and low water fluoridated areas
<table>
<tr><th rowspan="2"></th><th colspan="2">Prevalence % (95% CI)</th></tr>
<tr><th>1.47 ppm</th><th>0.2 ppm</th></tr>
<tr><td>Myopia</td><td>38.2 (35.7 to 40.8)</td><td>31.7 (29.3 to 34.2)</td></tr>
<tr><td>Hyperopia</td><td>20.6 (18.5 to 22.8)</td><td>27.2 (24.9 to 29.6)</td></tr>
<tr><td>Astigmatism</td><td>43.3 (40.7 to 45.9)</td><td>45.3 (42.7 to 48.0)</td></tr>
</table>
[a] Adjusted for age.

Multiple linear regression analysis showed that spherical equivalents from the right eye of the eligible individuals were associated with gender, age, annual income, but not with education ($P = 0.378$), and fluoride levels in drinking water ($P = 0.857$).</td><td>There was no association between refractive errors and drinking water fluoride levels.
(*Limited*)</td></tr>
</table>

CI = confidence interval; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; ppm = parts per million.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

22. Diabetes

Results for diabetes are presented in Table 45.

Evidence From the 2016 NHMRC Review

No study was identified from the 2016 NHMRC review.

Evidence From the Updated Literature Search

One case-control study assessed to be of low quality from Canada and one ecological study assessed to be of low quality from the US were identified.

Chafe et al. (2018)[138] determined the association between drinking water quality and incidence rates of type 1 diabetes in Newfoundland and Labrador, Canada. The study included children aged 0 to 14 years from communities with and without at least one case of type 1 diabetes. Cases of type 1 diabetes were obtained from the Newfoundland and Labrador Pediatric Diabetes Database. Three levels of analysis were performed: 1) Compared between communities with cases and controls for any difference in each component of water quality (by analysis of variance [ANOVA]); 2) Regression analysis of water quality indicator levels and type 1 diabetes incidence rate at community level; 3) Regression analysis of water quality indicator levels and type 1 diabetes incidence rate at regional level. When comparing communities with cases and controls by ANOVA, levels of ammonia, barium, copper, lead, magnesium, uranium, and zinc were significantly higher in communities that reported cases of type 1 diabetes. However, there was no difference in the level of fluoride or arsenic between communities with cases and controls. Linear regression analyses of water quality indicator and type 1 diabetes incidence rate showed that arsenic (beta coefficient = 0.268; $P = 0.013$) and fluoride (beta coefficient = 0.202; $P = 0.005$) in drinking water were positively associated with higher incidence of type 1 diabetes at the community level, but not at the regional level. No confounding variables were adjusted for in the analysis. The authors conclude that higher levels of arsenic and fluoride were positively associated with higher incidence of type 1 diabetes, but none was found to have a significant association across the three different levels of analysis performed.

Fluegge (2016)[139] examined the associations between added and naturally present fluoride and the prevalence and incidence of diabetes. Participant data were obtained from the County Data Indicators profile of the Diabetes Data and Statistics portal through the Centers for Disease Control and Prevention. Water fluoridation was divided into two groups: added fluoride (0.71 ppm ± 0.31 ppm) and NOF (0.23 ppm ± 0.27 ppm). The fluoride levels under investigation were applicable to the current Canadian levels. Two set of analyses were conducted: adjusted analysis with primary exposure in milligrams of fluoride from tap water consumption and unadjusted analysis with primary exposure in ppm fluoride level. The study found a significant positive relationship between diabetes outcomes (i.e., incidence and prevalence) and added fluoride in the drinking water, after adjusting for physical inactivity, obesity, poverty, log population per square mile, mean number of years fluoridated, and year. Interpretation from the beta coefficient suggests that a 1 mg increase in the amount of added fluoride for an average county would result in 0.23 per 1,000 person increase in diabetes incidence and 0.17% increase in the diabetes prevalence. In the same model, there was a significant inverse relationship between diabetes outcomes (i.e., incidence and prevalence) and fluoride naturally occurring in the drinking water. Similar observations were obtained in unadjusted analysis with primary exposure in ppm. The authors concluded that there was a positive relationship between added fluoride in drinking water, even at optimum levels, and the incidence and prevalence of diabetes. However, the authors stated that "*it is difficult to unequivocally state that these results are the specific consequences of water fluoridation*" due to "*ecological fallacy,*" "*fluoridation is not the only source of exposure to fluoride,*" "*diabetes most likely has a multifactorial etiology, even including epigenetic processes,*" and "*the analyses presented here were limited by the availability of data*" (p.10, 11).[139]

Summary

Due to multifactorial etiology of diabetes and conflicting results, the aforementioned two studies of low quality provided insufficient evidence to draw a conclusion regarding the association between water fluoridation at the current Canadian levels and diabetes.

Table 45: Diabetes

<table>
<tr><th>Study
Country
Design
Quality</th><th>Population</th><th>Exposures</th><th>Effect Estimate</th><th>Study Findings
(Applicability[a])</th></tr>
<tr><td colspan="5">Evidence From the 2016 NHMRC Review: No Study Identified</td></tr>
<tr><td colspan="5">Evidence From the Updated Literature Search: One Case-Control Study and One Ecological Study</td></tr>
<tr><td>Chafe et al. (2018)[138]
Canada
Case-control
Low</td><td>Children aged 0 to 14 years from communities with and without at least one case of type 1 diabetes in Newfoundland and Labrador, Canada

Cases: N = 499
Controls: N = NR</td><td>Components in public water supply including fluoride ion</td><td>There was no difference in the level of fluoride or arsenic between communities with cases and controls (ANOVA)
Linear regression analyses showed a positive association between water components and type 1 diabetes at the community level
Arsenic (beta coefficient = 0.268; P = 0.013)
Fluoride (beta coefficient = 0.202; P = 0.005)
Linear regression analyses showed no association between water components and type 1 diabetes at the regional level
Arsenic (beta coefficient = -0.173; P = 0.458)
Fluoride (beta coefficient = 0.177; P = 0.325)</td><td>Higher levels of arsenic and fluoride were positively associated with higher incidence of type 1 diabetes, but none was found to have a significant association across the three different levels of analysis performed. (High)</td></tr>
<tr><td>Fluegge (2016)[139]
USA
Ecological
Low</td><td>Participant data were from the County Data Indicators profile of the Diabetes Data and statistics portal through the CDC
N = NR</td><td>CWF
0.71 ppm ± 0.31 ppm (added fluoride)
0.23 ppm ± 0.27 ppm (natural fluoride)</td><td>Regression with primary exposure assessed in milligrams (adjusted by county-level per capita tap water consumption) and unadjusted exposure in ppm
<table>
<tr><th rowspan="3">Covariates</th><th colspan="4">Beta Coefficient (SE)</th></tr>
<tr><td colspan="2">Adjusted[a] exposure in mg</td><td colspan="2">Unadjusted exposure in ppm</td></tr>
<tr><td>Incidence</td><td>Prevalence</td><td>Incidence</td><td>Prevalence</td></tr>
<tr><td>Added fluoride</td><td>0.23 (0.06)[c]</td><td>0.17 (0.05)[c]</td><td>0.35 (0.11)[b]</td><td>0.27 (0.09)[c]</td></tr>
<tr><td>Natural fluoride</td><td>–0.23 (0.06)[c]</td><td>–0.15 (0.04)[c]</td><td>–0.73 (0.12)</td><td>–0.55 (0.09)[c]</td></tr>
</table>
[a] Adjusted for physical inactivity, obesity, poverty, log population per square mile, mean of years fluoridated, and year.
[b] P < 0.01.
[c] P < 0.001.</td><td>There was a positive relationship between added fluoride in drinking water, even at optimum level, and the incidence and prevalence of diabetes. (Partial)</td></tr>
</table>

ANOVA = analysis of variance; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CWF = community water fluoridation; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; NR = not reported; ppm = parts per million; SE = standard error.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

23. Myocardial Infarction

Results for myocardial infarction are presented in Table 46.

Evidence From the 2016 NHMRC Review

No study was identified from the 2016 NHMRC review.

Evidence From the Updated Literature Search

One ecological study assessed to be of low quality from Sweden was identified.

Nasman et al. (2016)[140] examined the association between drinking water fluoride exposure and incidence of myocardial infarction in Sweden using nationwide registry data. The study included a large cohort (N = 474,217) born between January 1, 1900, and December 31, 1919, alive and living in municipalities of birth at the time of start of follow-up. Sweden has NOF and the fluoride levels were divided into four groups: ≥ 1.5 ppm, 0.7 ppm to < 1.5 ppm, 0.3 ppm to < 0.7 ppm, and < 0.3 ppm. The last three fluoride levels were applicable to the current Canadian levels. Myocardial infarction was diagnosed according to the International Classification of Diseases, Tenth Revision, Clinical Modification. The study found that there was no significant difference in the risk of myocardial infarction among different water fluoride concentrations, after adjusting for sex, age, calendar period for study entry, geographical area of residence, and water hardness. There was also no significant difference in the risk of myocardial infarction and water fluoride levels when stratified by gender (male or female) or by age (< 65 years or ≥ 65 years). The authors concluded that there was no association between natural drinking water fluoride and myocardial infarction.

Summary

One ecological study of low quality provided insufficient evidence to draw a conclusion regarding the association between water fluoridation at the current Canadian levels and myocardial infarction.

Table 46: Myocardial Infarction

Study Country Design Quality	Population	Exposures	Results	Effect Estimate	Study Findings (*Applicability*[a])
Evidence From the 2016 NHMRC Review: No Study Identified					
Evidence From the Updated Literature Search: One Ecological Study					
Nasman et al. (2016)[140] Sweden Ecological Low	Large cohort (N = 474,217), born between January 1, 1900, and December 31, 1919, alive and living in municipalities of birth at the time of start of follow-up	NOF • ≥ 1.5 ppm • 0.7 ppm to < 1.5 ppm • 0.3 ppm to < 0.7 ppm • < 0.3 ppm	NR	HR (95% CI) • ≥ 1.5 ppm: 1.01 (0.98 to 1.04) • 0.7 ppm to < 1.5 ppm: 1.02 (0.99 to 1.04) • 0.3 ppm to < 0.7 ppm: 1.00 (0.99 to 1.02) • < 0.3 ppm: ref (Adjustment for sex, age, calendar period for study entry, geographical area of residence, and water hardness) There was also no significant difference in the risk of myocardial infarction and water fluoride levels when stratified by gender (male or female) or by age (< 65 years or ≥ 65 years)	There was no association between natural drinking water fluoride and myocardial infarction. (*Partial*)

CI = confidence interval; HR = hazard ratio; NHMRC = National Health and Medical Research Council; NOF = naturally occurring fluoride; ppm = parts per million; ref = reference.

[a] For primary studies that were judged to be (high, partial, or low) applicable to the Canadian context; i.e., based on conditions such as fluoridation level, health and dental care system, and socio-economic characteristics (e.g., household income and education levels).

Summary of Review Findings

Summary of the Review Findings for the Effectiveness of Water Fluoridation in Dental Caries (Question 1)

Dental Caries in Deciduous Teeth

Dental caries in deciduous teeth was assessed by dental outcomes such as dmft, dmfs, caries prevalence (% dmft > 0 or % dmfs > 0), or proportion of caries-free (% dmft = 0 or % dmfs = 0). The numbers of studies reporting those dental outcomes identified in the 2016 NHMRC review and from the updated literature search are listed in Table 47. The quality of the SRs and the primary studies was mixed. All primary studies identified in the NHMRC 2016 review and the updated literature search, with the exception of one, were assessed to be of partial applicability to the Canadian context, judging from the similarity in the fluoride levels and socio-economic parameters.

The review found consistent evidence for an association between water fluoridation and a reduction in the number of dmft, a reduction in the number of dmfs, and a reduction in caries prevalence, as well as an increase in the proportion of caries-free in deciduous teeth in children.

Table 47: Summary of Review Findings for Dental Caries in Deciduous Teeth

Outcomes	Summary of Review Findings		Conclusion
	2016 NHMRC Review	**Updated Literature Search**	
dmft	2 SRs (1 high, 1 low); 3 studies (3 acceptable) • Pooled effect estimate showed a reduction in mean dmft by 1.81 (95% CI, 1.31 to 2.31) in children aged 3 to 12 years in water fluoridation group (SR; 9 studies; N = 44,268) • Median % reduction of dmft was 44% (range 29% to 68%) in children aged 3 to 12 years (SR; 21 studies; N = NR) • An inverse association between mean dmft and percentage lifetime exposure to CWF (beta = –0.66; *P* < 0.001) in children aged 5 to 10 years (1 study; N = 16,857 for total 5 to 16 years) • Significant increase in dmft in children aged 5 to 7 years in non-CWF areas; mean ratio = 2.06, 2.81, 2.23 for year 2008, 2010, 2012, respectively (1 study; N = NR) • Significant reduction in d3mft[a] in children aged 5 years by 0.37 (95% CI 0.27 to 0.48) in fluoridation areas (1 study; N = NR)	2 studies (1 acceptable, 1 low) • Children aged 5 to 10 years in the non-CWF areas had 62% higher risk of dental caries in deciduous teeth (N = 6,318) • Children aged 5 to 7 years living in the pre-fluoridated and non-fluoridated areas had 38% and 53% higher risk of dental caries in deciduous teeth, respectively (N = 2,129)	Consistent evidence for an association between water fluoridation and the reduction in the number of dmft in children.
dmfs	1 SR (low); 4 studies (3 acceptable, 1 low) • Median % reduction of dfs was 33%	No studies	Consistent evidence for an association between water

Outcomes	Summary of Review Findings		Conclusion
	2016 NHMRC Review	Updated Literature Search	
	(range 14% to 66%) in children aged 5 to 11 years (SR; 9 studies; N = NR) • Significantly fewer d2fs in children aged 5 years with higher fluoride intake from drinking water (1 study; N = 575) • Significant reduction in dmfs in children aged 5 to 10 years exposed to CWF (by 34% to 39%) (2 studies, N = 3,620) • A significant inverse association between mean dmfs and fluoride level in drinking water in children aged 6 to 11 years (beta = –2.99; *P* = 0.008) (1 study; N = 2,748)		fluoridation and the reduction in the number of dmfs in children.
Dental caries prevalence and proportion of caries-free of deciduous teeth	1 SR (high); 7 studies (6 acceptable, 1 low) • Pooled effect estimate showed an increase in the proportion of caries-free of deciduous teeth by 15% (95% CI, 11% to 19%) in children aged 3 to 12 years in water fluoridation group (SR; 10 studies; N = 39,966) • Significant reduction in caries prevalence of deciduous teeth in children aged 3 to 11 years in CWF areas (7 studies; N > 17,137). Odds ratios ranged from 0.29 to 0.62 (4 studies). Per cent difference in odds was –28% (1 study). Prevalence ratios ranged from 0.76 to 0.83 (2 studies)	2 studies (2 low) • Significant increase in caries prevalence of deciduous teeth in children aged 5 to 9 years in pre-CWF or non-CWF areas. Odds ratios ranged from 1.54 to 1.86 (2 studies; N = 9,349)	Consistent evidence for an association between water fluoridation and a reduction in caries prevalence and an increase in the proportion of caries-free deciduous teeth in children.

CI = confidence interval; CWF = community water fluoridation; dmfs = decayed, missing, and filled deciduous tooth surfaces; dmft = decayed, missing, and filled deciduous teeth; NHMRC = National Health and Medical Research Council; SR = systematic review.

[a] The “3” in d3mft denotes obvious decay into dentine.

Dental Caries in Permanent Teeth

Dental caries in permanent teeth was assessed by dental outcomes such as DMFT, DMFS, caries prevalence (% DMFT > 0 or % DMFS > 0), proportion of caries-free (% DMFT = 0 or % DMFS = 0), or incidence of caries in permanent teeth. The numbers of studies reporting those dental outcomes identified in the 2016 NHMRC review and from the updated literature search are listed in Table 48. The quality of the SRs and the primary studies was mixed. Most of the primary studies were assessed to be of partial applicability to the Canadian context.

The review found consistent evidence for an association between water fluoridation and a reduction in the number of DMFT, a reduction in the number of DMFS, and a reduction in caries prevalence, as well as an increase in the proportion of caries-free permanent teeth in children and adults. There was insufficient evidence to draw a conclusion about an association between water fluoridation and the decrease in caries incidence of permanent teeth in children.

Table 48: Summary of Review Findings for Dental Caries in Permanent Teeth

Outcomes	Summary of Review Findings		Conclusion
	2016 NHMRC Review	Updated Literature Search	
DMFT	3 SRs (1 high, 2 low); 6 studies (5 acceptable, 1 low) • Pooled effect estimate showed a reduction in mean DMFT by 1.16 (95% CI, 0.72 to 1.61) in children aged 8 to 11 years in water fluoridation group (SR; 10 studies; N = 78,764) • Median % reduction of mean DMFT was 37% (range 5% to 85%) in participants aged 8 to 51 years (SR; 37 studies; N = NR) • Pooled effect estimate showed a 35% reduction in mean DMFT in adults aged ≥ 20 years (RR: 0.65, 95% CI, 0.49 to 0.87) (SR; 9 studies; N = 7,853) • An inverse association between mean DMFT and exposure to CWF (beta ranged from –0.10 to –2.58; $P < 0.05$) in children and adults aged 11 to ≥ 15 years (3 studies; N > 20,636) • Significantly lower in mean D3MFT[a] in children aged 12 years in CWF areas (mean difference –0.19; 95% CI, –0.27 to –0.11) (1 study; N = NR) • Significant reduction in mean DMFT in adolescents and young adults aged 13 to 21 years living in CWF (by 42% to 44%) (2 studies; N = 1,560)	5 studies (2 acceptable, 3 low) • An inverse association between water fluoride levels and a decrease in filled teeth (FT) among participants aged ≥ 16 years (beta = –0.0583; $P < 0.01$; expressed in 0.1 ppm fluoride) (1 study; N = national population of Sweden) • Significantly lower in mean DMFT among children aged 8 years (by 73%) and 11 years (by 40%) living in CWF areas (1 study; N = 1,411) • A positive relationship between mean DMFT and outside capital cities (mean lifetime fluoride exposure = 42.3%) compared with capital cities (lifetime exposure = 59.1%) in participants aged ≥ 15 years (beta = 0.8; $P = 0.01$ (1 study; N = 3,770) • Significant increase in mean DMFT (over 100%) in children aged 6 to 15 years living in non-CWF areas (1 study; N = 8,377) • Significant increase in mean DMFT (by 39%) in adults aged 20 to 59 years having < 50% LAFW compared with > 75% LAFW (1 study; N = 209)	Consistent evidence that water fluoridation reduced caries in permanent teeth (measured using DMFT) in both children and adults.
DMFS	1 SR (low); 4 studies (3 acceptable, 1 low) • Median % reduction of mean DMFS was 29% (range 0% to 50%) in participants aged 5 to 35 years (14 studies; N = NR) • Significant decrease in mean DMFS (from 24% to 37%) in children aged 8 to 14 years having full lifetime exposure to CWF (2 studies; N = 5,797) • An inverse relationship between water fluoride levels or lifetime exposure to fluoridated water and mean DMFS in participants aged 6 to 17 years (2 studies; N = 6,527)	3 studies (1 acceptable, 2 low) • Full 100% LAFW was associated with significantly lower in mean DMFS (by 21% to 33%) in children, and young and middle-aged adults up to 45 years old (2 studies; N = 5,310) • Significant reduction in mean DMFS in children aged 8 years (by 72%) and 11 years (by 40%) in CWF areas (1 study; N = 1,411)	Consistent evidence that water fluoridation reduced caries in permanent teeth (measured using DMFS) in both children and adults.
Dental caries prevalence and proportion of caries-free of permanent teeth	1 SR (high); 10 studies (7 acceptable, 3 low) • Pooled effect estimate showed an increase in the proportion of caries-free permanent teeth by 14% (95% CI	2 studies (2 low) • Significant increase in caries prevalence of permanent teeth in participants aged 6 to 19 years living in non-CWF areas. Odds ratios	Consistent evidence that water fluoridation at the current Canadian levels reduced caries

Outcomes	Summary of Review Findings		Conclusion
	2016 NHMRC Review	Updated Literature Search	
	5% to 23%) in children aged 5 to 17 years in water fluoridation group (SR; 9 studies; N = 63,538) - No significant differences in dental caries prevalence between CWF and no CWF in children aged 8 to 12 years (3 studies, N > 25,043) - Significant reduction in caries prevalence in permanent teeth in participants aged 6 to 21 years (7 studies; N > 14,093). Per cent difference in odds was –21% (95% CI, –29% to –12%) (1 study; N = NR). Odds ratios ranged from 0.30 to 0.60 (4 studies; N = 3,620). Prevalence ratios were 0.67 and 0.90 (2 studies; N = 10,473)	ranged from 1.42 to 1.62 (2 studies; N = 19,086)	prevalence and increased the proportion of caries-free permanent teeth in children and adolescents.
Incidence of first molar occlusal caries in permanent teeth	1 study (acceptable) - No significant reduction in incidence of first molar occlusion caries upon exposure to fluoride in drinking water (OR 0.32; 95% CI, 0.10 to 1.02; *P* = 0.056) (1 study; N = 523)	No study	Insufficient evidence to draw a conclusion about an association between water fluoridation and the decrease in caries incidence of permanent teeth in children.

CI = confidence interval; CWF = community water fluoridation; DMFS = decayed, missing, and filled permanent tooth surfaces; DMFT = decayed, missing, and filled permanent teeth; LAFW = lifetime access to fluoridated water; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; ppm = parts per million; RR = rate ratio; SR = systematic review.

[a] The “3” in d3mft denotes obvious decay into dentine.

Dental Caries in Mixed Dentition

Dental caries in mixed dentition was assessed using combined measures of both dmft and DMFT. Three primary studies identified from the 2016 NHMRC review were of acceptable quality and assessed to be of partial or high applicability to the Canadian context. No additional studies were identified from the updated literature search (Table 49).

The review found insufficient evidence for an association between water fluoridation and a decrease in dental caries in mixed dentition.

Table 49: Summary of Review Findings for Dental Caries in Mixed Dentition

Outcomes	Quantity of research available		Conclusion
	2016 NHMRC Review	**Updated Literature Search**	
Combined dmft and DMFT	1 SR (NR); 3 studies (3 acceptable) • Median of proportion of caries-free in mixed dentition in children aged 5 to 14 years increased by 14.6% in fluoridated areas (interquartile range: 5.05% to 22.1%) (SR; 9 studies; N = NR) • Non-significant inverse relationship between mean dmft and DMFT and water fluoridation (beta coefficient ranged from –1.16 to –0.18; $P > 0.05$) (2 studies; N = 1,237) • Non-significant difference in caries prevalence in mixed dentition in children aged 3 to 12 years between CWF and non-CWF areas (OR = 0.81; 95% CI, 0.46 to 1.43) (1 study; N = 434)	No study	Insufficient evidence for an association between water fluoridation and a decrease in dental caries in mixed dentition.

CI = confidence interval; CWF = community water fluoridation; dmft = decayed, missing, and filled deciduous teeth; DMFT = decayed, missing, and filled permanent teeth; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; SR = systematic review.

Disparities in Dental Outcomes

The effect of water fluoridation on the change of disparities in dental outcomes (i.e., dmft, DMFT, caries prevalence) was examined between levels of SES, Indigenous status, and deprivation. The numbers of studies reporting disparities in dental outcomes identified in the 2016 NHMRC review and from the updated literature search are listed in Table 50. The quality of the primary studies was mixed. All primary studies were assessed to be of partial applicability to the Canadian context.

The review found:

- insufficient evidence for an association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth between levels of SES
- limited evidence for no association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth by Indigenous status
- limited evidence for an association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth and hospital admissions for caries-related dental extractions between levels of deprivation.

Table 50: Summary of Review Findings for the Effect of Community Water Fluoridation on Disparities in Dental Outcomes

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	Updated Literature Search	
Disparities in caries	1 SR (NR); 4 studies (2 acceptable, 2 low) • Water fluoridation did not reduce the disparity in the proportion of caries-free, but reduced the disparity in dmft and DMFT in children aged 5 to 16 years between social classes (SR; 15 studies; N = NR) • Water fluoridation reduced the disparity in caries experience (measured using DMFT) between social classes (1 study; N = 1,783) • The impact of CWF exposure on tooth loss at birth was larger for adults of lower SES compared with those of higher SES (race and education) (1 study; N = NR) • Water fluoridation did not reduce the gap in dental caries experience (measured using the proportion of caries-free of both deciduous and permanent teeth) between Indigenous and non-Indigenous children aged 5 to 15 years (1 study; N = NR) • An association between fluoridation and mean dmft and DMFT, as well as caries prevalence and hospital admissions for caries in children 1 to 12 years in the most deprived quintile group compared with the other four least deprived quintiles (1 study, N = NR)	4 studies (1 acceptable, 3 low) • A stronger association between water fluoridation and a decrease in caries prevalence, as well as hospital admissions for caries-related dental extractions in children aged 5 years of the most deprivation compared with those of the least deprivation group (1 study; N = 111,455) • No significant association between water fluoridation and a reduction in tooth decay in children aged 5 months to 5 years from low-income families (beta = 0.177; *P* = 0.561) (1 study; N = 388) • A non-significant inverse relationship between dmft or DMFT and water fluoridation among Indigenous children aged 5 to 10 years (dmft; beta = –0.10) and aged 6 to 15 years (DMFT; beta = –0.02) (1 study; N = NR) • Water fluoridation did not reduce the gap in dental caries experience (measured using mean dmft or DMFT and proportion of caries-free of both deciduous and permanent teeth) between Indigenous (Māori) and non-Indigenous children aged 5 years (N = 417,318) and 12 to 13 years (N = 417,333)	Insufficient evidence for an association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth between levels of SES. Limited evidence for no association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth by Indigenous status. Limited evidence for an association between water fluoridation and a reduction in the disparity in dental caries experience in deciduous and permanent teeth and hospital admissions for caries-related dental extractions between levels of deprivation.

CI = confidence interval; CWF = community water fluoridation; dmft = decayed, missing, and filled deciduous teeth; DMFT = decayed, missing, and filled permenant teeth; NHMRC = National Health and Medical Research Council; NR = not reported; OR = odds ratio; SES = socio-economic status; SR = systematic review.

Other Dental Outcomes

Other dental outcomes included tooth loss (or functional dentition), delayed tooth eruption, tooth wear, hospital admissions for caries-related dental extractions, and dental clinic visits. The numbers of studies reporting other dental outcomes identified in the 2016 NHMRC review and from the updated literature search are listed in Table 51. The quality of the primary studies was mixed. Most of the primary studies were assessed to be of limited applicability to the Canadian context.

The review found:

- limited evidence for an association between water fluoridation and a reduction of tooth loss or an increase in functional dentition in children and adults
- limited evidence for an association between water fluoridation and a reduction in hospital admissions for extraction of decayed teeth under a general anesthetic in children
- insufficient evidence for an association between water fluoridation and delayed tooth eruption, and between water fluoridation and a reduction in dental care visits, and between water fluoridation and tooth wear.

Table 51: Summary of Review Findings for Other Dental Outcomes

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	**Updated Literature Search**	
Tooth loss	5 studies (4 acceptable, 1 low) • A significantly inverse relationship between fluoridated water exposure and the number of missing permanent teeth in children and adults (beta ranged from –0.26 to –0.33; *P* < 0.05) (2 studies; N > 92,701) • A non-significant relationship between higher lifetime exposure to fluoridated water (≥ 50% versus < 50%) and a reduction in tooth loss in participants aged 15 to 45 years (1 study; N = 466) • A significantly greater prevalence of missing teeth in adolescents aged 15 to 19 years in non-CWF areas. Prevalence ratio was 1.40 (95% CI, 1.34 to 1.46) (1 study; N = 16,833) • Significantly higher functional dentition in adults aged 35 to 44 years with at least 5 years of exposure to CWF. Odds ratios were 1.88 (95% CI, 1.20 to 2.95) for 5 to 9 years and 1.78 (1.32 to 2.40) for ≥ 10 years (1 study; N = 10,625)	2 studies (2 low) • Significantly higher prevalence of functional dentition in adults aged 35 to 44 years living in CWF areas, measured by four oral health outcomes (FDWHO, WDT, FDclass5, and FDclass6). Prevalence ratios (95% CI) were 1.18 (1.10 to 1.27), 1.21 (1.12 to 1.31), 1.20 (1.04 to 1.38), and 1.22 (1.05 to 1.41), respectively (1 study; N = 9,564) • Significantly higher risk of tooth loss in adults aged 20 to 59 years with shorter exposure to CWF (13 years versus 27 years). Odds ratio was 1.02 (95% CI, 1.01 to 1.02) (1 study, N = 720)	Limited evidence for an association between water fluoridation and a reduction of tooth loss or an increase in functional dentition.
Delayed tooth eruption	2 studies (1 acceptable, 1 low) • No significant difference in mean number of erupted permanent teeth in children aged 5 to 17 years living in areas of < 0.3 ppm, 0.3 ppm to < 0.7 ppm, and 0.7 ppm to 1.2 ppm (*P* = 0.12) (1 study; N = 13,348) • Conclusion could not be drawn due to lacking of statistical analysis (1 study; N = 70)	No study	Insufficient evidence for an association between water fluoridation and delayed tooth eruption.
Tooth wear	1 study (acceptable) • Conclusion could not be drawn due to lacking of statistical analysis (1 study; N = 2,556)	No study	Insufficient evidence for an association between water fluoridation and tooth wear.

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	Updated Literature Search	
Hospital admissions	1 study (acceptable) • Significant reduction in incidence rate of hospital admissions for caries in children aged 1 to 4 years in CWF areas. Difference in rate was –55% (95% CI, –73% to –27%) (1 study; N = NR)	1 study (acceptable) • Significant decrease in hospital admissions for caries-related dental extractions in children and adolescents aged 0 to 19 years living in areas with fluoride levels above 0.1 ppm in England from 2007 to 2015 (1 study; N = 114,530,000 persons-year)	Limited evidence for an association between water fluoridation and the reduction in hospital admissions for extraction of decayed teeth under a general anesthetic in children.
Dental clinic visits	No study	2 studies (1 acceptable, 1 low) • A negatively non-significant association between dental clinic visit and drinking water fluoride of 1.0 ppm (beta = –0.044; NS) (1 study; N = NR) • A significant inverse relationship between dental care visit and CWF (beta = –0.029; *P* = 0.043) (1 study; N = 472,250)	Insufficient evidence for an association between water fluoridation and a reduction in dental care visits.

CI = confidence interval; CWF = community water fluoridation; FDclass5 = functional dentition classified by aesthetics and occlusion; FDclass6 = functional dentition classified by aesthetics, occlusion, and periodontal status; FDWHO = WHO functional dentition; NHMRC = National Health and Medical Research Council; NR = not reported; NS = not significant; ppm = parts per million; WDT = well-distributed teeth.

Summary of the Review Findings for the Impact of Community Water Fluoridation Cessation on Dental Caries (Question 2)

Impact of Community Water Fluoridation Cessation on Dental Caries in Deciduous Teeth

The impact of CWF cessation on dental caries in deciduous teeth was examined by comparing the dental outcomes (i.e., dmft or deft, dmfs or defs, and caries prevalence of deciduous teeth) between before and after the cessation of a CWF or between a CWF cessation community and a CWF continued community. The 2016 McLaren and Singhal review included 12 studies, two of which provided usable data for quantitative synthesis of dmft. The updated literature search identified two primary studies, one from Canada and one from England, which were assessed to be of high and partial applicability to the Canadian context (Table 52).

The review found:

- insufficient evidence for an association between CWF cessation and an increase in dental caries in children (measured as dmft, deft, or defs)
- limited evidence for a non-association between CWF cessation and an increase caries prevalence of deciduous teeth.

Table 52: Summary of Review Findings for the Impact of Community Water Fluoridation Cessation on Dental Caries in Deciduous Teeth

Outcomes	Quantity of research available		Conclusion
	2016 McLaren and Singhal Review	Updated Literature Search	
dmft or deft	SR of 2 studies (N = 3,947) - Pooled effect estimates on mean deft in children aged 2.5 to 5 years from two studies without a comparison community provided mixed evidence from different analyses	2 studies (1 acceptable, 1 low) - Significant increase in mean deft in children aged 7 years living in CWF cessation city compared with those in the CWF continued city. Rate ratio of mean deft > 0 was 1.34 (95% CI, 1.23 to 1.46) (1 study; N = 11,689) - No significant difference in mean dmft between post- and pre-cessation in children aged 5 years. Mean difference of dmft > 0 was +0.31; *P* = 0.21(1 study; N = 1,873)	Insufficient evidence for an association between CWF cessation and an increase in dental caries in children (measured as dmft or deft).
dmfs or defs	No study	1 study (acceptable) - Significant increase mean defs (all tooth surfaces or smooth surfaces) in children aged 7 years living in CWF cessation city compared with those in the CWF continued city (1 study; N=12,581) ○ All tooth surfaces: Rate ratio of mean defs > 0 was 1.6 (95% CI, 1.4 to 1.8) ○ Smooth surfaces: Rate ratio of mean defs > 0 was 1.7 (95% CI, 1.5 to 2.0)	Insufficient evidence for an association between CWF cessation and an increase in dental caries in children (measured as defs).
Dental caries prevalence and proportion of caries-free deciduous teeth	No study	2 studies (1 acceptable, 1 low) - No significant difference in caries prevalence in children aged 7 years between the CWF cessation city and the CWF continued city. Odds ratio was 1.18 (95% CI, 0.92 to 1.51) (1 study; N = 11,689) - No significant increase in caries prevalence between pre- and post-cessation. Difference in prevalence was +0.9%; *P* = 0.51(1 study; N = 1,873)	Limited evidence for a non-association between CWF cessation and an increase caries prevalence of deciduous teeth.

CI = confidence interval; CWF = community water fluoridation; defs = decayed, extracted, and filled deciduous tooth surfaces; deft = decayed, extracted, and filled deciduous teeth; dmfs = decayed, missing, and filled deciduous tooth surfaces; dmft = decayed, missing, and filled deciduous teeth; SR = systematic review.

Impact of Community Water Fluoridation Cessation on Dental Caries in Permanent Teeth

The impact of CWF cessation on dental caries in permanent teeth was examined by comparing the dental outcomes (i.e., DMFT, DMFS, caries prevalence of permanent teeth, and complete dental caries care) between before and after the cessation of a CWF or between a CWF cessation community and a CWF continued community. The 2016 McLaren and Singhal review included three studies for quantitative synthesis of DMFT, and the updated literature search identified two reports from the same study of acceptable quality from Canada (Table 53).

The review found insufficient evidence for an association between CWF cessation and mean DMFT, mean DMFS, caries prevalence of permanent teeth, and complete dental caries care in children.

Table 53: Summary of Review Findings for the Impact of Community Water Fluoridation Cessation on Dental Caries in Permanent Teeth

Outcomes	Quantity of Research Available		Conclusion
	2016 McLaren and Singhal Review	Updated Literature Search	
DMFT	• SR of 3 studies (N = 9,503) • Pooled effect estimates on mean DMFT in children aged 6 to 16 years from three studies without a comparison community provided mixed evidence from different analyses • SR of 3 studies (N = 111,436) • Pulled effect estimates on mean DMFT in children aged 6 to 15 years from three studies with a comparison community provided mixed evidence from different analyses	1 study (acceptable) • Significant decrease in decrease in mean DMFT (overall), but not mean DMFT (those with DMFT > 0) in children aged 7 years in the CWF cessation city compared with the CWF continued city (1 study; N = 11,689)	Insufficient evidence for an association between CWF cessation and an increase in mean DMFT in children.
DMFS	No study	1 study (acceptable) • No significant differences in mean DMFS (measured from all tooth surfaces or smooth surfaces only) between CWF cessation and CWF continued cities (1 study; N = 12,581)	Insufficient evidence for an association between CWF cessation and an increase in mean DMFS in children.
Dental caries prevalence and proportion of caries-free permanent teeth	No study	1 study (acceptable) • Significant decrease in caries prevalence of permanent teeth in children aged 7 years in CWF cessation city compared with CWF continued city. Odds ratio was 0.37 (95% CI, 0.28 to 0.49) (1 study; N = 11,689)	Insufficient evidence for an association between CWF cessation and a decrease in dental caries prevalence of permanent teeth in children.
Dental caries care	No study	1 study (acceptable) • Significant increase in the proportion of complete caries care in children aged 7 years in CWF cessation city compared with CWF continued city. Odds ratio was 2.53 (95% CI, 2.04 to 3.13) (1 study; N = 11,689)	Insufficient evidence for an association between CWF cessation and an increase in complete caries care in children.

CI = confidence interval; CWF = community water fluoridation; DMFS = decayed, missing, and filled permanent tooth surfaces; DMFT = decayed, missing, and filled permenant teeth; NHMRC = National Health and Medical Research Council; SR = systematic review.

Impact of Community Water Fluoridation Cessation on Disparities in Dental Outcomes

The impact of CWF cessation on the change of disparities in dental outcomes (i.e., dmft, DMFT, caries prevalence) was examined between levels of deprivation. The updated literature search identified two primary studies, one from Canada and one from England, which were assessed to be of high and partial applicability to the Canadian context, respectively (Table 54).

The review found limited evidence for no association between CWF cessation and a change in disparities in dental caries in children by levels of deprivation.

Table 54: Summary of Review Findings for the Impact of Community Water Fluoridation Cessation on Disparities in Dental Outcomes

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	Updated Literature Search	
Disparities in caries	No study	2 studies (1 acceptable, 1 low) • No significant difference in caries experience (measured as deft, DMFT, and 2 or more deciduous or permanent teeth with untreated decay) in children aged 7 years between CWF cessation and CWF continued cities among different levels of deprivation (1 study; N = 3,787) • No significant difference in mean dmft and caries prevalence within disparity groups between pre- and post-cessation (1 study; N = 1,010)	Limited evidence for a non-association between CWF cessation and a change in disparities in dental caries in children by levels of deprivation.

CWF = community water fluoridation; deft = decayed, extracted, and filled deciduous teeth; dmft = decayed, missing, and filled deciduous teeth; DMFT = decayed, missing, and filled permenant teeth; NHMRC = National Health and Medical Research Council.

Summary of the Review Findings for the Effects of Community Water Fluoridation on Other Health Outcomes (Question 3)

The 2016 NHMRC review and the updated literature search identified a total of 23 other health outcomes, including dental fluorosis. Each study quality was assessed for internal and external validity and the applicability of the findings of each study were categorized as high, partial, or limited based on the comparison of water fluoride level and socio-economic parameters to the Canadian context. The numbers of studies reporting other health outcomes identified in the 2016 NHMRC review and from the updated literature search are listed in Table 55. The quality of most primary studies was low. The findings of most studies were assessed to be of limited applicability to the Canadian context.

The review found:

- consistent evidence for an association between an increase in the level of fluoride in drinking water and an increase in the overall prevalence of dental fluorosis (any severity)
- consistent evidence for no association between water fluoridation at the current Canadian levels and the incidence of bone cancer, total cancer and cancer-related mortality, and hip fracture

- limited evidence for no association between water fluoridation at the current Canadian levels and Down syndrome, and IQ and cognitive function
- limited evidence for an inverse association between water fluoridation at the current Canadian levels and kidney stones
- insufficient evidence for an association between water fluoridation at the current Canadian levels and all-cause mortality, atherosclerosis, hypertension, skeletal fluorosis, osteoporosis, musculoskeletal pain, newborn’s height and weight, thyroid function, CKD, gastric discomfort, headache, insomnia, reproductive outcomes, refractive errors, diabetes, and myocardial infarction.

Table 55: Summary of Review Findings for the Effects of Community Water Fluoridation on Other Health Outcomes

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	Updated Literature Search	
Dental fluorosis	3 SRs (2 NR, 1 high) • Dental fluorosis prevalence increased with water fluoride levels. Prevalence of dental fluorosis of any level of severity at 1 ppm was 48% (95% CI, 40 to 75), of which 12.5% (95% CI, 7.0 to 21.5) had fluorosis of aesthetic concern (SR; 88 studies; N = NR) • A fourfold higher risk in the development of overall dental fluorosis and fluorosis of aesthetic concern in optimal water fluoridation compared with non-CWF. The absolute increase in prevalence was 26% and 5%, respectively (SR; 10 studies ; N = NR) • Dental fluorosis prevalence of any level at 0.7 ppm was 40%, of which 12% had fluorosis of aesthetic concern (SR; 90 studies; N = 59,630)	21 studies (1 acceptable, 19 low) • In all studies, dental fluorosis prevalence and its severity increased with increased water fluoride levels (21 studies; N = 35,374). The majority of evidence (17 out of 21 studies) derived from countries where water fluoride levels were many folds higher than the current Canadian levels.	Consistent evidence for an association between an increase in the level of fluoride in drinking water and an increase in the prevalence of dental fluorosis.
All-cause mortality	1 study (acceptable) • A small reduction in incidence rate of all-cause mortality in CWF areas. Difference in rate was –1.3% (95% CI, –2.4% to –0.1%) (1 study; N = 208,570,962)	No study	Insufficient evidence for an association between water fluoridation at the current Canadian levels and all-cause mortality.
Atherosclerosis	1 study (low) • Significantly higher risk of carotid artery atherosclerosis in adults in areas with high fluoride levels (> 1.2 ppm) (1 study; N = 500)	No study	Insufficient evidence for an association between water fluoridation at the current Canadian levels and carotid artery atherosclerosis.
Hypertension	3 studies (3 low) • Mixed findings from studies of low quality and derived from countries were fluoride levels were many times higher than the current Canadian levels (3 studies; N > 160,637)	2 studies (2 low) • Mixed findings from studies of low quality and from countries where fluoride levels were many folds higher than the current Canadian levels (2 studies; N = 3,224)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and hypertension.
Bone cancer	2 SRs (2 NR); 6 studies (3 acceptable, 3 low) • No clear association between water fluoridation and the incidence rate of osteosarcoma (SR; 8 studies; N = NR) • Higher exposure to fluoridated	2 studies (2 acceptable) • Two studies with partial applicability to the Canadian context showed no significant difference in incidence rate of osteosarcoma in children and adults between high and low fluoride level areas (2 studies; N = 1,663 and	Consistent evidence for no association between water fluoridation at the current Canadian levels and the incidence of bone cancer.

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	**Updated Literature Search**	
	water was associated with a higher risk of developing osteosarcoma in males, but not in females (SR; 1 study; N = 318) • Five studies with partial applicability to the Canadian context showed no significant difference in the incidence rate of osteosarcoma in children and adults between high and low exposure to water fluoridation (5 studies; N > 253,768,952) • A conclusion could not be drawn from a low quality study from India with high risk of bias (1 study; N = 20)	N = 710,260,000 person-years)	
Total cancer incidence and mortality	2 SRs (2 NR); 2 studies (2 acceptable) • No clear association between water fluoridation and overall cancer incidence (2 SR; 13 studies; N = NR) • No significant difference in the incidence of all cancer between CWF and non-CWF (1 study; N = 208,770,962). Significantly lower incidence rate of invasive bladder cancer in CWF. Difference in rate –8.0% (95% CI, –9.9% to –6.0%) (1 study; N = 555,127,448) • An inverse correlation between the percentage of the population receiving fluoridated water and incidence of eye cancer (*r* = –0.45; *P* = 0.002) (1 study; N = NR)	1 study (acceptable) • Incidence of bladder cancer was lower in fluoridation areas. Odds ratio was 0.94 (95% CI, 0.90 to 0.98) (1 study; N = 827,660,000 person-years)	Consistent evidence for no association between water fluoridation at the current Canadian levels and the overall incidence of cancer or cancer-related mortality.
Skeletal fluorosis	1 SR (NR); 2 studies (2 low) • Skeletal fluorosis found only in areas of high fluoride levels (3.8 ppm to 8.0 ppm) (SR; 1 study; N = NR) • No clear relationship between water fluoride level and prevalence of skeletal fluorosis (2 studies; N = 2,816)	2 studies (2 low) • Mixed findings from studies of low quality and from countries where fluoride levels were many folds higher that the current Canadian levels (2 studies; N = 1,595)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and skeletal fluorosis.
Hip fracture	2 SRs (2 NR); 2 studies (2 acceptable) • No clear association between water fluoridation and hip fracture incidence in adults (2 SRs; 19 studies; N = NR)	1 study (acceptable) • A weak association between water fluoridation and hip fracture observed in females, but not in males (1 study; N = 477,610,000 person-years)	Consistent evidence for no association between water fluoridation and hip fracture.

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	Updated Literature Search	
	• No increased risk of hip fracture from water fluoridation exposure (2 studies; N = 313,329,725)		
Osteoporosis	1 SR (NR); 1 study (low) • Addition of fluoride to drinking water at the level of 1 ppm did not associate with a decrease in bone mineral density compared with non-fluoridated water (SR; 27 studies; N = NR)	No study	Insufficient evidence for an association between water fluoridation at the current Canadian levels and osteoporosis.
Musculoskeletal pain	2 studies (2 low) • Increased risk of lower back pain and joint pain associated with higher fluoride levels (2 studies; N = 3,266) • The results were from studies of low quality and from countries where socio-economic parameters differed than those in Canada	No study	Insufficient evidence for an association between water fluoridation at the current Canadian levels and musculoskeletal pain.
Newborns' height and weight	1 study (low) • Mothers exposed to drill water with a fluoride level of 4.7 ppm had higher risk to have low birth weight newborns (1 study; N = 324)	1 study (low) • A positive correlation between babies' height ($r = 0.69$; $P < 0.001$) or babies' weight ($r = 0.44$; $P < 0.001$) and drinking water fluoride (1 study; N = 492)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and newborns' weight or newborns' height.
Down syndrome	2 SRs (2 NR); 1 study (acceptable) • No clear association between water fluoridation and Down syndrome (2 SRs; N = NR) • No significant difference in the incidence rate of Down syndrome between CWF and non-CWF (1 study; N = 2,272,300)	1 study (acceptable) • No significant difference in the incidence rate of Down syndrome by fluoridation status (1 study; N = 2,020,259)	Limited evidence for no association between water fluoridation at the current Canadian levels and Down syndrome.
IQ and cognitive function	1 SR (NR); 11 studies (1 high, 2 acceptable, 8 low) • No evidence of sufficient quality to make any conclusions for a relationship between water fluoridation and IQ in children or cognitive impairment in adults (SR; 2 studies; N = NR) • No difference in mean IQ scores of children and adults between fluoridated water (0.7 ppm to 1.0 ppm) and naturally occurring water fluoride (0.0 ppm to 0.3 ppm) (1 study; N = 942) • (A study with acceptable quality and partial applicability to the Canadian context) • Mixed findings on the relationship between water fluoridation and	6 studies (1 acceptable, 5 low) • No effect of water fluoride on cognitive ability, non-cognitive ability, and math test in participants aged ≥ 16 years in Sweden (1 study; N = NR) • No clear association between fluoride exposure and reported learning disability among Canadian children aged 3 to 12 years (1 study; N = 2,220) • Mixed findings from studies of low quality and with limited applicability to the Canadian context (4 studies; N = 1,341)	Limited evidence for no association between water fluoridation at the current Canadian levels and IQ or cognitive function.

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	**Updated Literature Search**	
	IQ or cognitive function from low-quality studies with limited applicability to the Canadian context (10 studies; N = 1,445)		
Thyroid function	3 studies (3 low) • Mixed findings from studies of low quality and with limited applicability the Canadian context (4 studies; N=789)	4 studies (1 acceptable, 3 low) • No association between fluoride exposure and impaired thyroid functioning in the Canadian population (1 study, N = 5,201) • Significantly higher odds of GP practice recording high levels of hypothyroidism in areas with fluoridation compared with areas without fluoridation in the US (1 study; N = 7,935 GP practices) • No clear relationship between water fluoride and thyroid function from studies of low quality and with limited applicability to the Canadian context (2 studies; N = 1,037)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and thyroid function.
Kidney stones	1 SR (NR), 1 study (acceptable) • Higher prevalence of kidney stones in skeletal fluorosis endemic areas, from a study of low quality with limited applicability to the Canadian context (1 study; N = NR) • Lower incidence of emergency admissions for kidney stones in CWF areas in England. Difference in rate was –7.9% (95% CI, –9.6 to –6.2) (1 study; N = 312,856,448)	1 study (acceptable) • Lower incidence of emergency admissions for kidney stones in CWF areas in England. Incidence rate ratio was 0.90 (95% CI, 0.82 to 0.98) (1 study; N = 47,610,000 person-years)	Limited evidence for an inverse association between water fluoridation at the current Canadian levels and the incidence of kidney stones.
Chronic kidney disease	1 study (low) • No conclusion could be drawn due to significant methodological limitations and lack of statistical analysis (1 study; N = 5,685)	1 study (low) • No conclusion could be drawn due to significant methodological limitations and lack of statistical analysis (1 study; N = 824)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and chronic kidney disease.
Gastric discomfort	2 studies (2 low) • No conclusion could be drawn due to significant methodological limitations and lack of statistical analysis (2 study; N = 5,342)	No study	Insufficient evidence for an association between water fluoridation at the current Canadian levels and gastric discomfort.
Headache	2 studies (2 low) • No conclusion could be drawn due to significant methodological limitations and lack of statistical analysis (2 study; N=5,342)	No study	Insufficient evidence for an association between water fluoridation at the current Canadian levels and headache.
Insomnia	2 studies (2 low) • No conclusion could be drawn due to significant methodological limitations and lack of statistical analysis (2 study; N = 5,342)	No study	Insufficient evidence for an association between water fluoridation at the current Canadian levels and insomnia.

Outcomes	Quantity of Research Available		Conclusion
	2016 NHMRC Review	Updated Literature Search	
Reproduction	No study	2 studies (2 low) • No clear relationship between water fluoride level and rates of abortion and fertility due to lack of controlling for confounders, from studies of low quality and of limited applicability to the Canadian context (2 studies; N = 5,993)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and reproduction in women.
Refractive errors	No study	1 study (low) • No difference in prevalence of refractive errors (myopia, hyperopia, astigmatism) between high and low water fluoride levels (1 study; N = 1,415)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and refractory errors.
Diabetes	No study	2 studies (2 low) • No convincing evidence for an association between water fluoride levels and incidence of type 1 diabetes in Canada (1 study; N = NR) • A positive relationship between added fluoride in drinking water, even at optimum level, and the incidence and prevalence of diabetes in the US (1 study; N = NR)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and diabetes.
Myocardial infarction	No study	1 study (low) • No significant difference in the risk of myocardial infarction and water fluoride levels in Sweden (1 study; N = 474,217)	Insufficient evidence for an association between water fluoridation at the current Canadian levels and myocardial infarction.

CI = confidence interval; CWF = community water fluoridation; IQ = intelligence quotient; GP = general practitioner; NHMRC = National Health and Medical Research Council; NR = not reported; ppm = parts per million; SR = systematic review.

Discussion

Summary of Overall Findings

Review of Dental Caries and Other Health Outcomes

Effectiveness of Water Fluoridation

There was consistent evidence that water fluoridation at the current Canadian levels was associated with the reduction in dental caries experience in children and adults in terms of both severity (measured as mean dmft, dmfs, DMFT, and DMFS) and prevalence (measured as the proportion of individuals with dmft, dmfs, DMFT, and DMFS greater than 0). The impact of CWF in dental caries reduction has been noted particularly more in children and adolescents than in adults. There was limited evidence that water fluoridation resulted in a reduction of tooth loss and in increased functional dentition prevalence in children and adults. Two published studies showed that the rates of hospital admissions for caries-related dental procedures under general anesthetic in children were lower in areas with water fluoridation. There was insufficient evidence for an association between water fluoridation and a reduction in dental care visits. Limited evidence suggested that water fluoridation might reduce the disparity gap in dental caries experience between levels of deprivation. Identified studies found no evidence that water fluoridation could reduce disparities in dental caries by Indigenous status.

Impact of Community Water Fluoridation Cessation

There was insufficient evidence to suggest that the water fluoridation cessation had any significant impact on dental caries in deciduous and permanent teeth in children. There was no information regarding the impact of CWF cessation on dental caries in adults. There was limited evidence to suggest a non-association between CWF cessation and a change in dental caries disparities by levels of deprivation.

Effect of Community Water Fluoridation on Other Health Outcomes

There was consistent evidence that the risk of dental fluorosis increased with increasing fluoride levels in the drinking water. The 2015 Cochrane review[62] found that 12.5% of people exposed to a fluoride level of 1 ppm would have dental fluorosis “of aesthetic concern,” which was broadly categorized as “mild” to “severe,” according to the Dean’s index. In Canada, less than 0.3% of children have teeth that are classified as “moderate” or “severe” fluorosis.[2]

There was consistent evidence for a non-association between water fluoridation at the current Canadian levels and both cancer and hip fracture. There was limited evidence for a non-association between water fluoridation at the current Canadian levels and both Down syndrome, and IQ and cognitive function.

There was limited evidence for an inverse association between water fluoridation at the current Canadian levels and the incidence of kidney stones.

There was insufficient evidence for an association between water fluoridation at the current Canadian levels and all-cause mortality, atherosclerosis, hypertension, skeletal fluorosis, osteoporosis, musculoskeletal pain, newborns’ height and weight, thyroid function, CKD, self-reported health outcomes (gastric discomfort, headache, insomnia), reproduction (fertility, abortion), refractory errors, diabetes, and myocardial infarction.

Interpretation

The evidence for the effectiveness of water fluoridation on dental caries came from three SRs (a total of 77 studies included), 25 primary studies identified by the 2016 NHMRC review,[60] and 17 additional primary studies identified from the updated literature search. Findings in the recent studies identified from the updated literature search were consistent with those reported in the 2016 NHMRC review.[60] This suggests that CWF continues to have a protective effect against dental caries in both deciduous and permanent teeth in children and in permanent teeth in adults, despite the widespread availability and use of fluoridated toothpaste in the current settings. Likewise, the review found that the rates of tooth loss, dental clinic visits, and hospital admissions related to dental caries tended to be lower in areas with water fluoridation. In the current review, the findings for the effect of CWF on disparity in dental outcomes by Indigenous status and by levels of deprivation were also consistent with those found in the 2016 NHMRC review;[60] that is, water fluoridation seems to reduce the gap of disparity in dental caries experience between levels of deprivation, but not by Indigenous status.

The evidence for the impact of CWF cessation on dental caries came from the 2016 McLaren and Singhal review,[52] with a limited number of studies included in the quantitative analysis and two additional primary studies identified from the updated literature search. The studies collectively provided mixed evidence on the effect of CWF cessation on dental caries in both deciduous and permanent teeth in children. The pre-post cross-sectional study of acceptable quality by McLaren et al. (2017)[92] found that short-term fluoridation cessation (2 to 3 years) in Calgary was associated with a significant increase in dental caries experience measured in deft or defs, but not in DMFT or DMFS, in children aged seven years living in Calgary (CWF cessation in 2011) compared with Edmonton (CWF continued). Meanwhile, the prevalence of complete caries care (defined as no untreated decay, but one or more fillings or extractions) was significantly higher in Calgary compared with Edmonton, suggesting that dental treatment was increased after CWF cessation. On the other hand, the pre-post cross-sectional study without a comparison community and adjustment for confounding variables by PHE (2015)[93] found no significant increase in mean dmft and caries prevalence between post- and pre-cessation; the period of water fluoridation cessation was five to six years. Collectively, there was insufficient evidence that CWF cessation has any significant effect on dental caries in children. Both studies also found that CWF cessation did not change in disparities in dental caries in children by levels of deprivation.

The evidence for the effect of water fluoridation on dental fluorosis came from the Cochrane review by Iheozor-Ejiofor et al. (2015)[62] identified by the 2016 NHMRC review[60] and 21 additional primary studies reporting dental fluorosis identified from the updated literature search. The Cochrane review included 135 primary studies, of which 19 studies and 40 studies provided sufficient data in the analysis for all severities of dental fluorosis and fluorosis of aesthetic concern, respectively.[62] The findings in the recent studies identified from the updated literature search were consistent with those reported in the Cochrane review[62] — that dental fluorosis prevalence and its severity increased with increased water fluoride levels. The majority of evidence came from studies conducted in countries where water fluoride levels were many times higher than the current Canadian levels. Of note, the Cochrane review[62] included studies with fluoride levels much higher than the current Canadian levels in its dose-dependent analysis and the definition of dental fluorosis of "aesthetic" concern seems to be quite broad which covered from "mild" to "severe" on the Dean's index. No Canadian study on dental fluorosis could be identified from the updated literature search. According to the Canadian Health Measures Survey (2007 to 2009),[2] the prevalence of dental fluorosis of “aesthetic” concern in Canadian children, which was defined as “moderate” or “severe,” was rare and less than 0.3%.

The evidence for the effect of water fluoridation on 22 other health outcomes came from 41 primary studies identified by the 2016 NHMRC review[60] and 20 additional primary studies identified from the updated literature search. Most studies were of low quality and their findings were assessed to be of limited applicability to the Canadian context. Two large ecological studies conducted by PHE (2014[141] and 2018[86]), which were of acceptable quality and relevant to the Canadian context, found no association between water fluoridation and the incidence of bone cancer, total cancer, hip fracture, and Down syndrome.

The 2016 NHMRC review[60] identified 11 primary studies, including one prospective cohort study of high quality by Broadbent et al. (2014)[142] from New Zealand that provided the evidence for the effect of water fluoridation on IQ and cognitive function. A previous meta-analysis by Choi et al. (2012)[143] on the neurotoxic effect of water fluoride came to the attention of the 2016 NHMRC review,[60] but did not meet its inclusion criteria in selecting only primary studies. The Choi meta-analysis found that high fluoride exposure (up to 11.5 ppm) lowered IQ scores in children with a pooled estimate of the standardized weighted MD of –0.45 (95% CI, –0.56 to –0.35) when compared with low fluoride levels (range, 0.24 ppm to 2.84 ppm).[143] All of the 27 included cross-sectional studies were conducted in poor and rural areas in China and Iran having high naturally occurring water fluoride levels and exposure levels greater than the Canadian target range, and did not properly identify and control for confounding variables such as exposure to known neurotoxicants (e.g., lead, arsenic, or iodine), SES, nutritional status, and parental education that could potentially affect children’s IQ.[60] The updated literature search identified an additional six primary studies, including two relevant ecological studies, by Aggeborn and Öhman (2017)[76] from Sweden and by Barberio et al. (2017a)[129] from Canada. The rest of the studies had significant limitations in methodological quality, not controlling for confounding variables, and were conducted in rural areas in China, India, and Iran, where naturally occurring water fluoride levels were much higher than the current Canadian levels. Results from studies in New Zealand, Sweden, and Canada found no evidence that water fluoridation at the recommended level could affect IQ and cognitive function in children and adults.

The updated literature search identified two relevant studies, one study from Canada by Barberio et al. (2017b)[133] and one from the UK by Peckham et al. (2015).[134] The two studies provided mixed results on the effect of water fluoridation on thyroid function. The Canadian study found no association between fluoride exposure and impaired thyroid functioning in the Canadian population, while the UK study found that the odds of a GP practice reporting high prevalence of hypothyroidism (i.e., upper tertile) was significantly higher in areas with fluoridation compared with areas without fluoridation. It was unclear why a focus on practices with high hypothyroidism prevalence was chosen as an outcome instead of the actual prevalence in CWF and non-CWF communities in the UK study. This study was scientifically critiqued for various reasons, including an unclear prior hypothesis, inadequate control for the potential confounding variables, and arbitrary cut-offs of categorized variables that deviate from normal practice.[144,145]

The updated literature search also identified two relevant studies on diabetes, both poor in methodology quality, one from Canada by Chafe et al. (2018)[138] and one from the US by Fluegge (2016).[139] Without sufficient controlling for diabetes-related confounding variables, both studies found a positive relationship between water fluoride and diabetes. Due to multifactorial etiology of diabetes, these low-quality studies provided insufficient evidence to draw a conclusion regarding the association between water fluoridation at the current Canadian levels and diabetes. There was also insufficient evidence to draw a conclusion for an association between water fluoridation and the remaining health outcomes.

Strengths

This review has been developed utilizing a robust methodology. A detailed protocol was prepared, *a priori*; reviewed by stakeholders external to CADTH; registered with the PROSPERO database; and the final version is publicly available.

The literature search was performed by an information specialist, using a peer-reviewed search strategy. Through our initial systematic scoping, two previously published SRs were identified as the most recent, comprehensive, and relevant to our policy question. The methodological quality of these reviews was considered sufficient to utilize as the base knowledge and to update with more current relevant literature. Details of methods and results are reported transparently and comprehensively as to facilitate the updating process.

Extensive search through multiple databases and websites retrieved 3,395 citations, including published and grey literature, which after application of including and excluding criteria resulted in 60 articles and reports. The report of findings was prepared in consideration of relevant reporting guidelines for SRs (i.e., PRISMA).[69]

The QA of included studies was done using NICE checklists.[72] For the interpretation of the results, the evidence of each outcome is presented together with the risk of bias and the applicability of the included studies to the Canadian context. Comparability with the Canadian context was based on the levels of fluoride in fluoridated and non-fluoridated water, socio-economic factors, and similarity to dental and health care systems in Canada.

The current review on the effects of water fluoridation on dental caries and other health outcomes was built on evidence identified from the previous 2016 NHMRC review,[60] which updated its own review in 2007[61] and conducted an overview of SRs and an SR of primary studies. In its overview of SRs, a Cochrane review by Iheozor-Ejiofor et al. in 2015[62] was identified, which updated a previous review by McDonagh et al. in 2000.[64] The evidence evaluation of the current review was also supplemented with evidence from SRs of primary studies published between 2014 and 2018. Thus, a large body of evidence presented in this review included both previous and contemporary evidence identified since the review by McDonagh et al. (2000).[64]

The current review applied the same selection criteria for identification of studies as in the 2016 NHMRC review;[60] to select all comparative studies with no restriction to study design that allowed capturing contemporary evidence from all observational studies. Similarly, the current review updated the evidence from the 2016 McLaren and Singhal[52] review for the impact of water fluoridation cessation on dental caries using the same criteria. For dental caries outcomes, only observational studies that controlled for confounding were included to limit the potential for issues with measurement of exposures and outcomes. For the effects of water fluoridation on other health outcomes, including dental fluorosis, no restriction was applied to the water fluoride levels with the aim to capture all possible adverse health outcomes that could be associated with fluoride levels beyond the current Canadian levels.

Limitations

The literature search for this review was limited to documents added to the databases since January 1, 2014, in order to capture studies after the literature searches for NHMRC 2016[60] and McLaren and Singhal 2016[52] had been conducted. Also, the search strategy was limited to Cochrane recommendations and CADTH subscription databases. There is a possibility, though rare, to miss on any relevant literature published before January 2014 and not included in the two identified SRs.

A limitation for updating a previous SR is that the reviewers rely on study selection, data extraction, quality assessment and reporting of the findings of that SR without directly reviewing the included primary studies that may introduce the risk of selection and ascertainment bias. It is fortunate that the comprehensive data extraction and QA results of the included studies were made available in the Technical Report of the 2016 NHMRC review,[146] and were kindly provided by authors of the fluoridation cessation review.[52] During data extraction, the reviewers of the current review also referred to previous SRs included in the 2016 NHMRC review (i.e., McDonagh et al. [2000],[64] NHMRC 2007,[61] and Iheozor-Ejiofor et al. [2015]).[62]

Conference abstracts were excluded from the search results as complete information on those studies was not available; however, regular alerts were established to update the searches until the publication of the final report.

For studies included in the review, any study with a water fluoridation level of < 0.4 ppm was considered non-fluoridated. One can argue that less than 0.4 ppm of fluoride in water is not non-fluoridated; especially when newer studies have suggested fluoridation in the range of 0.5 ppm to 0.8 ppm to establish a trade-off between dental caries and dental fluorosis.[147,148] Also, the average fluoride level in fluoridated water across Canada ranges between 0.46 ppm (not much higher than 0.4 ppm) and 1.1 ppm. However, this level was considered to be in alignment with previous reviews, such as the 2016 NHMRC review[60] and the 2015 Cochrane review.[62]

This review did not assess the impact of fluoridated salt or milk or fluoride supplements, the reason being that in Canada only water is being fluoridated as a population health intervention to reduce the burden of dental caries.

The type of fluoride compound (powder or liquid form and the source of the compound) used for water fluoridation is not considered in this review, for the scientific reason that once the fluoride compound is mixed with the water, it is dissociated as F^-, irrespective of the compound used.

In terms of dental caries outcomes in the included studies, none of the studies to date have used the International Caries Detection and Assessment System, which assess both cavitated and non-cavitated lesions. Along with reducing the prevalence, fluoride also helps in diminishing the severity of dental decay, and indexes such as the International Caries Detection and Assessment System can be more sensitive tools for detecting the effects of CWF.

Not many studies have been conducted to assess the impact of CWF on reducing the disparities in dental caries. Studies among Indigenous populations are even fewer and those that have been conducted are all from Australia.

Not many studies have been conducted to assess the impact of prenatal fluoride exposure to reduce dental caries, and for the potential development of other unintended health outcomes.

In regards to CWF cessation, all studies focused on children; although, studying the cessation impact on other vulnerable populations such as the elderly, in terms of root caries, would also be valuable. Also, the evidence on the equity implications of discontinuing CWF is limited.

Evidence in this review came from observational studies, mostly, of ecological and cross-sectional designs, which only provide possible correlation, but not causation, between an intervention and an outcome. Since water fluoridation is a public health intervention, measurement of fluoride exposure could only be attained at the population level, and not at the individual level, often comparing water fluoride levels of different areas. The fluoride exposure can be from various sources; controlling other sources of fluoride is also logistically difficult. And most importantly, there is enough literature to document the effectiveness of fluoridated water in reducing the burden of dental caries. With these considerations, the ecological and cross-sectional studies may be sufficient to provide evidence on the effects of water fluoridation as long as a proper control is used and adjustment for confounding variables is carried out.

Many studies included in this review had significant limitations in methodology with high risk of bias and lack or insufficient control for confounding variables. Many studies of other health outcomes had a small sample size; lack of power calculation; and poor or insufficient reporting about study characteristics, participant demographics, and results.

For the effect of water fluoridation on many health outcomes and on disparities in caries health outcomes, evidence came from few studies, which made the interpretation difficult. Also, few Canadian studies were identified in the current review, particularly in the evaluation of the impact of water fluoridation cessation on dental caries, and the effect of water fluoridation on IQ and thyroid function. Caution is therefore needed when attempting to generalize the scarce evidence to other populations or settings.

Directions for Future Research

Further research is needed to assess the impact on populations varying in age, SES, education, ethnicity, and migration status. Researchers are encouraged to follow the recommendations proposed by Singhal et al. (2017)[149] regarding the methodological considerations in designing the study to observe the effects of CWF cessation on dental caries.

As approximately 5% of the Canadian population is Indigenous, with higher proportions in some juridictions,[150] it is crucial to work in partnership with First Nations, Inuit, and Metis communities to undertake studies to assess the impact of fluoridated water on dental health of the Canadian Indigenous population. However, for this to occur, federal funds need to be invested to ensure that communities have the necessary water treatment facility infrastructure to deliver CWF. Many Canadian Indigenous communities do not have this, with many currently on boil water alerts.

Also, more research is required to assess the impact of prenatal fluoride exposure for effectiveness in reducing dental decay and other unintended health outcomes in primary teeth.

Ultimately, more studies need to be conducted in Canada to effectively generalize the findings within the national jurisdictions. It is imperative that future studies be of high quality in methodological design, and that they include proper adjustment for confounding variables in the analysis.

Additional Studies Identified From Alerts (Updated Searches)

Seven additional studies were identified from the alerts following the initial literature search until December 2018 (Appendix 10). Four studies continued to find caries-preventive benefit of CWF in children and adolescents.[151-154] One study found that prevalence of dental fluorosis was highest in the youngest and lowest in the oldest age group of adults with lifetime exposure to water fluoridation, suggesting that the aesthetic impact of fluorosis seems to decrease with age.[155] Two studies found no evidence for an association between water fluoride (at optimal level or at levels twice the optimum) and bone cancer, any cancer, asthma, and cardiovascular events, despite a decrease in dental caries and increase in prevalence of dental fluorosis.[156,157] The findings in the additional studies were in line with those identified in the main literature search.

Conclusions

This report describes the Review of Dental Caries and Other Health Outcomes. As noted, separate reports on the assessment of economic considerations,[56] implementation issues,[57] environmental impact,[58] and ethical considerations[59] for CWF are available as part of the full HTA review on this topic.

The evidence in this review supports the protective effect of CWF in reducing dental caries in both deciduous and permanent teeth in children and in permanent teeth in adults, despite the widespread availability and use of fluoridated toothpaste in the current settings. There was limited evidence that water fluoridation is associated with a reduction in caries-related hospital admissions. Evidence on the impact of CWF cessation on dental caries and the effect of water fluoridation on disparities in dental health outcomes remains to be determined. Dental fluorosis prevalence may increase with increasing water fluoride levels, but dental fluorosis of “aesthetic concern” among Canadian children is rare. There was evidence that there may be no association between water fluoridation at the current Canadian levels and bone cancer, total cancer incidence, hip fracture, Down syndrome, and IQ and cognitive function. There was insufficient evidence to draw a conclusion for an association between water fluoridation at the current Canadian levels and other reported health outcomes. Several limitations of the evidence in the current review were identified, and, therefore, caution is warranted in interpreting the evidence.

References

1. Behrman RE, Kliegman RM, Arvin AM, editors. *Nelson textbook of pediatrics.* 15th ed. Philadelphia (PA): W.B. Saunders Co.; 1996.
2. Health Canada. Report on the findings of the oral health component of the Canadian Health Measures Survey 2007-2009. Ottawa (ON): Government of Canada; 2010: http://publications.gc.ca/collections/collection_2010/sc-hc/H34-221-2010-eng.pdf. Accessed 2018 Aug 2.
3. Ripa LW. A half-century of community water fluoridation in the United States: review and commentary. *J Public Health Dent.* 1993;53(1):17-44.
4. Locker D, Matear D. *Oral disorders, systemic health, well-being and the quality of life: a summary of recent research evidence.* Toronto (ON): University of Toronto; 2000.
5. Low W, Tan S, Schwartz S. The effect of severe caries on the quality of life in young children. *Pediatr Dent.* 1999;21(6):325-326.
6. Ayhan H, Suskan E, Yildirim S. The effect of nursing or rampant caries on height, body weight and head circumference. *J Clin Pediatr Dent.* 1996;20(3):209-212.
7. Jackson SL, Vann WF, Jr., Kotch JB, Pahel BT, Lee JY. Impact of poor oral health on children's school attendance and performance. *Am J Public Health.* 2011;101(10):1900-1906. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3222359. Accessed 2017 Oct 31.
8. Gift HC, Reisine ST, Larach DC. The social impact of dental problems and visits. *Am J Public Health.* 1992;82(12):1663-1668. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1694558. Accessed 2017 Oct 31.
9. Clarke M, Locker D, Berall G, Pencharz P, Kenny DJ, Judd P. Malnourishment in a population of young children with severe early childhood caries. *Pediatr Dent.* 2006;28(3):254-259.
10. Offenbacher S, Katz V, Fertik G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. *J Periodontol.* 1996;67(10 Suppl):1103-1113.
11. Dasanayake AP. Poor periodontal health of the pregnant woman as a risk factor for low birth weight. *Ann Periodontol.* 1998;3(1):206-212.
12. National health expenditure trends, 1975 to 2018. Ottawa (ON): Canadian Institute for Health Information; 2018: https://www.cihi.ca/sites/default/files/document/nhex-trends-narrative-report-2018-en-web.pdf. Accessed 2019 Jan 15.
13. The state of oral health in Canada. Ottawa (ON): Canadian Dental Association; 2017: https://www.cda-adc.ca/stateoforalhealth/_files/TheStateofOralHealthinCanada.pdf. Accessed 2018 Mar 3.
14. Water fluoridation: questions & answers. Toronto (ON): University of Toronto, Faculty of Dentistry, Dental Public Health program; 2012: http://www.caphd.ca/sites/default/files/WaterFluoridationQA.pdf. Accessed 2017 Oct 31.
15. Health Canada. Guidelines for Canadian drinking water quality: guideline technical document -- fluoride. Ottawa (ON): Health Canada, Healthy Environments and Consumer Safety Branch, Water, Air and Climate Change Bureau; 2010: https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/water-fluoride-fluorure-eau/alt/water-fluoride-fluorure-eau-eng.pdf. Accessed 2017 Oct 31.
16. Hutton WL, Linscott BW, Williams DB. The Brantford fluorine experiment. Interim report after five years of water fluoridation. *Can J Public Health.* 1951;42(3):81-87.
17. Connor RA. Editorial. Twenty-fifth anniversary of fluoridation. A public health success story. *Can J Public Health.* 1970;61(4):283-284.
18. Dunton EA. Two fluoridation health surveys in Ontario. *Can J Public Health.* 1967;58(7):319-323.
19. Smith AG. The Brantford fluorine experiment. *J Can Dent Assoc.* 1946;12:11-14.
20. Featherstone JD. Prevention and reversal of dental caries: role of low level fluoride. *Community Dent Oral Epidemiol.* 1999;27(1):31-40.
21. Singh KA, Spencer AJ, Armfield JM. Relative effects of pre- and posteruption water fluoride on caries experience of permanent first molars. *J Public Health Dent.* 2003;63(1):11-19.
22. Singh KA, Spencer AJ. Relative effects of pre- and post-eruption water fluoride on caries experience by surface type of permanent first molars. *Community Dent Oral Epidemiol.* 2004;32(6):435-446.
23. Singh KA, Spencer AJ, Brennan DS. Effects of water fluoride exposure at crown completion and maturation on caries of permanent first molars. *Caries Res.* 2007;41(1):34-42.
24. Newbrun E, editor. *Fluorides and dental caries.* Springfield (IL): Charles C. Thomas; 1986.
25. Groeneveld A, Van Eck AA, Backer DO. Fluoride in caries prevention: is the effect pre- or post-eruptive? *J Dent Res.* 1990;69 Spec No:751-755.
26. Hamilton IR. Biochemical effects of fluoride on oral bacteria. *J Dent Res.* 1990;69 Spec No:660-667.
27. Lambrou D, Larsen MJ, Fejerskov O, Tachos B. The effect of fluoride in saliva on remineralization of dental enamel in humans. *Caries Res.* 1981;15(5):341-345.
28. Kamel MS, Thomson WM, Drummond BK. Fluoridation and dental caries severity in young children treated under general anaesthesia: an analysis of treatment records in a 10-year case series. *Community Dent Health.* 2013;30(1):15-18.

29. Centers for Disease Control and Prevention (CDC). Water fluoridation and costs of Medicaid treatment for dental decay--Louisiana, 1995-1996. *MMWR Morb Mortal Wkly Rep.* 1999;48(34):753-757. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4834a2.htm. Accessed 2017 Oct 31.

30. Seaman S, Thomas FD, Walker WA. Differences between caries levels in 5-year-old children from fluoridated Anglesey and non-fluoridated mainland Gwynedd in 1987. *Community Dent Health.* 1989;6(3):215-221.

31. Evans DJ, Rugg-Gunn AJ, Tabari ED. The effect of 25 years of water fluoridation in Newcastle assessed in four surveys of 5-year-old children over an 18-year period. *Br Dent J.* 1995;178(2):60-64.

32. Rugg-Gunn AJ, Carmichael CL, Ferrell RS. Effect of fluoridation and secular trend in caries in 5-year-old children living in Newcastle and Northumberland. *Br Dent J.* 1988;165(10):359-364.

33. Downer MC, Blinkhorn AS, Attwood D. Effect of fluoridation on the cost of dental treatment among urban Scottish schoolchildren. *Community Dent Oral Epidemiol.* 1981;9(3):112-116.

34. Chippendale I, Storey E. Declining attendances for general anaesthesia and tooth extractions in children following the fluoridation of Melbourne. *Aust Dent J.* 1988;33(5):415-419.

35. Whitford GM. The metabolism and toxicity of fluoride. *Monographs in oral science, vol. 16 (book 16)*. Basel (CH): S. Karger; 1996.

36. Whitford GM. Fluoride metabolism and excretion in children. *J Public Health Dent.* 1999;59(4):224-228.

37. Fluoride. *Nutrient reference values for Australia and New Zealand*. Version 1.1 ed. Canberra (AU): Australian Government, National Health and Medical Research Council; 2017.

38. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Washington (DC): National Academy Press; 1997: https://www.ncbi.nlm.nih.gov/books/NBK109825/pdf/Bookshelf_NBK109825.pdf. Accessed 2017 Oct 31.

39. Public Health Agency of Canada. The state of community water fluoridation across Canada: 2017 report. Ottawa (ON): Government of Canada; 2017: https://www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/community-water-fluoridation-across-canada-2017/community-water-fluoridation-across-canada-2017-eng.pdf. Accessed 2018 Mar 29.

40. Perrella AM, Kiss SJ. Risk perception, psychological heuristics and the water fluoridation controversy. *Can J Public Health.* 2015;106(4):e197-e203.

41. Podgorny PC, McLaren L. Public perceptions and scientific evidence for perceived harms/risks of community water fluoridation: an examination of online comments pertaining to fluoridation cessation in Calgary in 2011. *Can J Public Health.* 2015;106(6):e413-e425.

42. Quinonez CR, Locker D. Public opinions on community water fluoridation. *Can J Public Health.* 2009;100(2):96-100.

43. Peckham S, Awofeso N. Water fluoridation: a critical review of the physiological effects of ingested fluoride as a public health intervention. *ScientificWorldJournal.* 2014;2014:293019. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3956646. Accessed 2017 Sep 20.

44. Mork N, Griffin S. Perceived safety and benefit of community water fluoridation: 2009 HealthStyles survey. *J Public Health Dent.* 2015;75(4):327-336. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4813797/. Accessed 2017 Nov 22.

45. School dental health - Calgary zone. Edmonton (AB): Alberta Health Services; 2018: https://www.albertahealthservices.ca/services/page13173.aspx. Accessed 2018 Jul 10.

46. Dental oral health. Regina (SK): Government of Saskatchewan; 2018: https://www.saskatchewan.ca/residents/health/wellness-and-prevention/dental-oral-health. Accessed 2018 Jul 10.

47. Resolution on fluoride varnish programs for children at risk for dental caries. Fergus (ON): Wellington-Dufferin-Guelph Public Health; 2017: https://wdgpublichealth.ca/sites/default/files/bh.01.may0317.r12_resolution_on_fluoride_varnish_programs_for_children_at_risk_for_dental_caries_access.pdf. Accessed 2017 Oct 31.

48. McLaren L, McIntyre L. Drinking water fluoridation in Canada: review and synthesis of published literature. Calgary (AB): University of Calgary, Department of Health Sciences; 2011: http://www.albertahealthservices.ca/poph/hi-poph-surv-phids-drinking-water-fluoridation.pdf. Accessed 2018 Aug 2.

49. Cheng KK, Chalmers I, Sheldon TA. Adding fluoride to water supplies. *BMJ.* 2007;335(7622):699-702.

50. Cohen H, Locker D. The science and ethics of water fluoridation. *J Can Dent Assoc.* 2001;67(10):578-580. http://www.cda-adc.ca/jcda/vol-67/issue-10/578.html. Accessed 2018 Jan 29.

51. McNally M, Downie J. The ethics of water fluoridation. *J Can Dent Assoc.* 2000;66(11):592-593. http://www.cda-adc.ca/jcda/vol-66/issue-11/592.html. Accessed 2017 Nov 24.

52. McLaren L, Singhal S. Does cessation of community water fluoridation lead to an increase in tooth decay? A systematic review of published studies. *J Epidemiol Community Health.* 2016;70(9):934-940. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013153. Accessed 2017 Oct 31.

53. Moncton to debate return of fluoride in drinking water. Moncton (NB): CBC News; 2016: http://www.cbc.ca/news/canada/new-brunswick/moncton-fluoride-water-meeting-1.3900235. Accessed 2017 Oct 31.

54. Cromwell A. Saint John councillor says province should pay for water fluoridation. Saint John (NB): Global News; 2016: https://globalnews.ca/news/2980007/saint-john-councillor-says-province-should-pay-for-water-fluoridation/. Accessed 2017 Oct 31.

55. Community water fluoridation programs: a health technology assessment — review of dental caries and other health outcomes. *(CADTH Technology review no.12)*. Ottawa (ON): CADTH; 2019.

56. Community water fluoridation programs: a health technology assessment — budget impact analysis. *(CADTH Technology review no.13)*. Ottawa (ON): CADTH; 2019.

57. Community water fluoridation programs: a health technology assessment — implementation issues analysis. *(CADTH Technology review no.15)*. Ottawa (ON): CADTH; 2019.

58. Community water fluoridation programs: a health technology assessment — environmental assessment. *(CADTH Technology review no.14)*. Ottawa (ON): CADTH; 2019.

59. Community water fluoridation programs: a health technology assessment — ethical considerations. *(CADTH Technology review no.16)*. Ottawa (ON): CADTH; 2019.

60. Jack B, Ayson M, Lewis S, Irving A, Agresta B, Ko H. *Health effects of water fluoridation: evidence evaluation report.* Sydney (AU): The University of Sydney; 2016.

61. National Health and Medical Research Council. *A systematic review of the efficacy and safety of fluoridation. Part A: review of methodology and results.* Canberra (AU): Australian Government; 2007.

62. Iheozor-Ejiofor Z, Worthington HV, Walsh T, et al. Water fluoridation for the prevention of dental caries. *Cochrane Database Syst Rev.* 2015(6):CD010856.

63. *Fluoride in drinking water: a scientific review of EPA's standards.* Washington (DC): The National Academies Press; 2006.

64. McDonagh M, Whiting P, Bradley M, Cooper J, Sutton A, Chestnutt I. *A systemic review of public water fluoridation.* York (GB): University of York; 2000.

65. Griffin SO, Regnier E, Griffin PM, Huntley V. Effectiveness of fluoride in preventing caries in adults. *J Dent Res.* 2007;86(5):410-415.

66. Rugg-Gunn AJ, Do L. Effectiveness of water fluoridation in caries prevention. *Community Dent Oral Epidemiol.* 2012;40 Suppl 2:55-64.

67. Robinson KA, Chou R, Berkman ND, et al. Integrating bodies of evidence: existing systematic reviews and primary studies. *Methods guide for effectiveness and comparative effectiveness reviews*. Rockville (MD): Agency for Healthcare Research and Quality; 2015: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0077778/pdf/PubMedHealth_PMH0077778.pdf. Accessed 2018 Jan 15.

68. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.

69. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6(7):e1000100.

70. Higgins PT, Green S, editors. Cochrane handbook for systematic reviews of interventions. *Version 5.1.0*. London (GB): The Cochrane Collaboration; 2011: http://handbook-5-1.cochrane.org/. Accessed 2017 Nov 10.

71. Community water fluoridation programs: a health technology assessment protocol. *(CADTH Health technology assessment)*. Ottawa (ON): CADTH; 2018 Feb: https://cadth.ca/sites/default/files/pdf/HT0022-Community%20Water%20Fluoridation_Protocol.pdf. Accessed 2018 Aug 2.

72. Methods for the development of NICE public health guidance. *(Process and methods; no. 4)*. 3rd ed. London (GB): National Institute for Health and Care Excellence (NICE); 2012: https://www.nice.org.uk/process/pmg4/chapter/about-this-document. Accessed 2017 Oct 31.

73. Arrow P. Oral health of schoolchildren in Western Australia. *Aust Dent J.* 2016;61(3):333-341.

74. Blinkhorn AS, Byun R, Johnson G, Metha P, Kay M, Lewis P. The dental health of primary school children living in fluoridated, pre-fluoridated and non-fluoridated communities in New South Wales, Australia. *BMC Oral Health.* 2015;15:9.

75. Crouchley K, Trevithick R. *Dental health outcomes of children residing in fluoridated and non-fluoridated areas of western Australia.* Perth (AU): Government of Western Australia; 2016.

76. Aggeborn L, Öhman M. The effects of fluoride in the drinking water. *Working paper 2017:20*. Uppsala (SE): Institute for Evaluation of Labour Market and Education Policy; 2017: https://www.ifau.se/globalassets/pdf/se/2017/wp2017-20-the-effects-of-fluoride-in-the-drinking-water.pdf. Accessed 2018 Mar 1.

77. Crocombe LA, Brennan DS, Slade GD. Does lower lifetime fluoridation exposure explain why people outside capital cities have poor clinical oral health? *Aust Dent J.* 2016;61(1):93-101.

78. Kim HN, Kim JH, Kim SY, Kim JB. Associations of community water fluoridation with caries prevalence and oral health inequality in children. *Int J Environ Res Public Health.* 2017;14(6).

79. Peres MA, Peres KG, Barbato PR, Hofelmann DA. Access to fluoridated water and adult dental caries: a natural experiment. *J Dent Res.* 2016;95(8):868-874.

80. Do L, Ha D, Peres MA, Skinner J, Byun R, Spencer AJ. Effectiveness of water fluoridation in the prevention of dental caries across adult age groups. *Community Dent Oral Epidemiol.* 2017;45(3):225-232.

81. Spencer AJ, Liu P, Armfield JM, Do LG. Preventive benefit of access to fluoridated water for young adults. *J Public Health Dent.* 2017;77(3):263-271.

82. Aguiar VR, Pattussi MP, Celeste RK. The role of municipal public policies in oral health socioeconomic inequalities in Brazil: a multilevel study. *Community Dent Oral Epidemiol.* 2017;46(3):245-250.

83. Heima M, Ferretti M, Qureshi M, Ferretti G. The effect of social geographic factors on the untreated tooth decay among head start children. *J Clin Exp Dent.* 2017;9(10):e1224-e1229.

84. Ha DH, Lalloo R, Jamieson LM, Giang DL. Trends in caries experience and associated contextual factors among indigenous children. *J Public Health Dent.* 2016;76(3):184-191.

85. Schluter PJ, Lee M. Water fluoridation and ethnic inequities in dental caries profiles of New Zealand children aged 5 and 12-13 years: analysis of national cross-sectional registry databases for the decade 2004-2013. *BMC Oral Health.* 2016;16:21.

86. Water fluoridation: health monitoring report for England 2018. London (GB): Public Health England; 2018: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/692754/Water_Fluoridation_Health_monitoring_report_for_England_2018_final.pdf. Accessed 2018 Mar 23.

87. Chalub LL, Martins CC, Ferreira RC, Vargas AM. Functional dentition in Brazilian adults: an investigation of social determinants of health (SDH) using a multilevel approach. *PLoS ONE.* 2016;11(2):e0148859.

88. Barbato PR, Peres MA, Hofelmann DA, Peres KG. Contextual and individual indicators associated with the presence of teeth in adults. *Rev Saude Publica.* 2015;49:27.

89. Virtanen JI, Bloigu RS, Larmas MA. Timing of eruption of permanent teeth: standard Finnish patient documents. *Community Dent Oral Epidemiol.* 1994;22(5 Pt 1):286-288.

90. Leroy R, Bogaerts K, Lesaffre E, Declerck D. The effect of fluorides and caries in primary teeth on permanent tooth emergence. *Community Dent Oral Epidemiol.* 2003;31(6):463-470.

91. Cho MS, Han KT, Park S, Moon KT, Park EC. The differences in healthcare utilization for dental caries based on the implementation of water fluoridation in South Korea. *BMC Oral Health.* 2016;16(1):119.

92. McLaren L, Patterson S, Thawer S, et al. Exploring the short-term impact of community water fluoridation cessation on children's dental caries: a natural experiment in Alberta, Canada. *Public Health.* 2017;146:56-64.

93. Dental health impact of water fluoridation in children living in Bedford Borough Council in 2008, 2009 and 2015. London (GB): Public Health England; 2015: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/473931/9Bedford_OSC.pdf. Accessed 2018 Mar 1.

94. McLaren L, Patterson S, Thawer S, et al. Measuring the short-term impact of fluoridation cessation on dental caries in Grade 2 children using tooth surface indices. *Community Dent Oral Epidemiol.* 2016;44(3):274-282.

95. McLaren L, McNeil DA, Potestio M, et al. Equity in children's dental caries before and after cessation of community water fluoridation: differential impact by dental insurance status and geographic material deprivation. *Intern J Equity Health.* 2016;15:24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4750250/pdf/12939_2016_Article_312.pdf. Accessed 2018 Aug 10.

96. Smith GE. Fluoride and fluoridation. *Soc Sci Med.* 1988;26(4):451-462.

97. Cutress TW, Suckling GW. Differential diagnosis of dental fluorosis. *J Dent Res.* 1990;69 Spec No:714-720.

98. Fejerskov O, Manji F, Baelum V. The nature and mechanisms of dental fluorosis in man. *J Dent Res.* 1990;69 Spec No:692-700.

99. Burt BA. The changing patterns of systemic fluoride intake. *J Dent Res.* 1992;71(5):1228-1237.

100. Arora S, Kumar JV, Moss ME. Does water fluoridation affect the prevalence of enamel fluorosis differently among racial and ethnic groups? *J Public Health Dent.* 2018;78(2):95-99.

101. Bal IS, Dennison PJ, Evans RW. Dental fluorosis in the Blue Mountains and Hawkesbury, New South Wales, Australia: policy implications. *J Investig Clin Dent.* 2015;6(1):45-52.

102. Pretty IA, Boothman N, Morris J, et al. Prevalence and severity of dental fluorosis in four English cities. *Community Dent Health.* 2016;33(4):292-296.

103. Balmer R, Toumba KJ, Munyombwe T, Duggal MS. A comparison of the presentation of molar incisor hypomineralisation in two communities with different fluoride exposure. *Eur Arch Paediatr Dent.* 2015;16(3):257-264.

104. Peckham S. Slaying sacred cows: is it time to pull the plug on water fluoridation? *Crit Public Health.* 2012;22(2):159-177.

105. Khandare AL, Gourineni SR, Validandi V. Dental fluorosis, nutritional status, kidney damage, and thyroid function along with bone metabolic indicators in school-going children living in fluoride-affected hilly areas of Doda District, Jammu and Kashmir, India. *Environ Monit Assess.* 2017;189(11):579.

106. Razdan P, Patthi B, Kumar JK, Agnihotri N, Chaudhari P, Prasad M. Effect of fluoride concentration in drinking water on intelligence quotient of 12-14-year-old children in Mathura District: a cross-sectional study. *J Int Soc Prev Community Dent.* 2017;7(5):252-258.

107. Mahantesha T, Dixit UB, Nayakar RP, Ashwin D, Ramagoni NK, Kamavaram E, V. Prevalence of dental fluorosis and associated risk factors in Bagalkot District, Karnataka, India. *Int J Clin Pediatr Dent.* 2016;9(3):256-263.

108. Sebastian ST, Soman RR, Sunitha S. Prevalence of dental fluorosis among primary school children in association with different water fluoride levels in Mysore District, Karnataka. *Indian J Dent Res.* 2016;27(2):151-154.

109. Sebastian ST, Sunitha S. A cross-sectional study to assess the intelligence quotient (IQ) of school going children aged 10-12 years in villages of Mysore District, India with different fluoride levels. *J Indian Soc Pedod Prev Dent.* 2015;33(4):307-311.

110. Punitha VC, Sivaprakasam P, Elango R, Balasubramanian R, Midhun Kumar GH, Sudhir Ben Nelson BT. Prevalence of dental fluorosis in a non-endemic district of Tamil Nadu, India. *Biosciences Biotechnology Research Asia.* 2014;11(1):159-163.

111. Sukhabogi JR, Parthasarathi P, Anjum S, Shekar B, Padma C, Rani A. Dental fluorosis and dental caries prevalence among 12 and 15-year-old school children in Nalgonda District, Andhra Pradesh, India. *Ann Med Health Sci Res.* 2014;4(Suppl 3):S245-S252.

112. Bonola-Gallardo I, Irigoyen-Camacho ME, Vera-Robles L, Campero A, Gomez-Quiroz L. Enzymatic activity of glutathione S-transferase and dental fluorosis among children receiving two different levels of naturally fluoridated water. *Biological Trace Element Research.* 2017;176(1):40-47.

113. Garcia-Perez A, Irigoyen-Camacho ME, Borges-Yanez SA, Zepeda-Zepeda MA, Bolona-Gallardo I, Maupome G. Impact of caries and dental fluorosis on oral health-related quality of life: a cross-sectional study in schoolchildren receiving water naturally fluoridated at above-optimal levels. *Clin Oral Investig.* 2017;21(9):2771-2780.

114. Irigoyen-Camacho ME, García Pérez A, Mejia González A, Huizar AR. Nutritional status and dental fluorosis among schoolchildren in communities with different drinking water fluoride concentrations in a central region in Mexico. *Sci Total Environ.* 2016;541:512-519.

115. Moimaz SA, Saliba O, Marques LB, Garbin CA, Saliba NA. Dental fluorosis and its influence on children's life. *Pesqui Odontol Bras.* 2015;29(1):1-7.

116. Rango T, Vengosh A, Jeuland M, Whitford GM, Tekle-Haimanot R. Biomarkers of chronic fluoride exposure in groundwater in a highly exposed population. *Sci Total Environ.* 2017;596-597(2017):1-11.

117. Rango T, Vengosh A, Jeuland M, et al. Fluoride exposure from groundwater as reflected by urinary fluoride and children's dental fluorosis in the Main Ethiopian Rift Valley. *Sci Total Environ.* 2014;496:188-197.

118. Ibiyemi O, Zohoori FV, Valentine RA, Kometa S, Maguire A. Prevalence and extent of enamel defects in the permanent teeth of 8-year-old Nigerian children. *Community Dent Oral Epidemiol.* 2017:1-9.

119. Ramadan AM, Ghandour IA. Dental fluorosis in two communities in Khartoum State, Sudan, with potable water fluoride levels of 1.36 and 0.45 mg/L. *Fluoride.* 2016;Part(4):509-520.

120. Wong HM, McGrath C, King NM. Diffuse opacities in 12-year-old Hong Kong children--four cross-sectional surveys. *Community Dent Oral Epidemiol.* 2014;42(1):61-69.

121. Khandare AL, Validandi V, Gourineni SR, Gopalan V, Nagalla B. Dose-dependent effect of fluoride on clinical and subclinical indices of fluorosis in school going children and its mitigation by supply of safe drinking water for 5 years: an Indian study. *Environ Monit Assess.* 2018;190(3):110.

122. Yousefi M, Yaseri M, Nabizadeh R, et al. Association of hypertension, body mass index, and waist circumference with fluoride intake; water drinking in residents of fluoride endemic area, Iran. *Biol Trace Elem Res.* 2018;185(2):282-288.

123. Aghaei M, Karimzade S, Yaseri M, Khorsandi H, Zolfi E, Mahvi AH. Hypertension and fluoride in drinking water: case study from West Azerbaijan, Iran. *Fluoride.* 2015;48(3):252-258.

124. Archer NP, Napier TS, Villanacci JF. Fluoride exposure in public drinking water and childhood and adolescent osteosarcoma in Texas. *Cancer Causes Control.* 2016;27(7):863-868.

125. Krishnamachari KA. Skeletal fluorosis in humans: a review of recent progress in the understanding of the disease. *Prog Food Nutr Sci.* 1986;10(3-4):279-314.

126. Mohammadi AA, Yousefi M, Yaseri M, Jalilzadeh M, Mahvi AH. Skeletal fluorosis in relation to drinking water in rural areas of West Azerbaijan, Iran. *Sci Rep.* 2017;7(1):17300.

127. Shruthi MN, Santhuram AN, Arun HS, Kishore Kumar BN. A comparative study of skeletal fluorosis among adults in two study areas of Bangarpet taluk, Kolar. *Indian J Public Health.* 2016;60(3):203-209.

128. Aghaei M, Derakhshani R, Raoof M, Dehghani M, Mahvi AH. Effect of fluoride in drinking water on birth height and weight: an ecological study in Kerman Province, Zarand county, Iran. *Fluoride.* 2015;48(2):160-168.

129. Barberio AM, Quinonez C, Hosein FS, McLaren L. Fluoride exposure and reported learning disability diagnosis among Canadian children: implications for community water fluoridation. *Can J Public Health.* 2017;108(3):e229-e239.

130. Aravind A, Dhanya RS, Narayan A, Sam G, Adarsh VJ, Kiran M. Effect of fluoridated water on intelligence in 10-12-year-old school children. *J Int Soc Prev Community Dent.* 2016;6(Suppl 3):S237-S242.

131. Khan SA, Singh RK, Navit S, et al. Relationship between dental fluorosis and intelligence quotient of school going children in and around Lucknow District: a cross-sectional study. *J Clin Diagn Res.* 2015;9(11):ZC10-ZC15.

132. KheradPisheh Z, Mirzaei M, Mahvi AH, et al. Impact of drinking water fluoride on human thyroid hormones: a case-control study. *Sci Rep.* 2018;8(1):2674.

133. Barberio AM, Hosein FS, Quinonez C, McLaren L. Fluoride exposure and indicators of thyroid functioning in the Canadian population: implications for community water fluoridation. *J Epidemiol Community Health.* 2017;71(10):1019-1025.

134. Peckham S, Lowery D, Spencer S. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water. *J Epidemiol Community Health.* 2015;69(7):619-624.

135. Moghaddam VK, Yousefi M, Khosravi A, et al. High concentration of fluoride can be increased risk of abortion. *Biol Trace Elem Res.* 2018;185(2):262-265.

136. Yousefi M, Mohammadi AA, Yaseri M, Mahvi AH. Epidemiology of drinking water fluoride and its contribution to fertility, infertility, and abortion: an ecological study in West Azerbaijan Province, Poldasht County, Iran. *Fluoride.* 2017;50(3):343-353.

137. Bin G, Liu H, Zhao C, et al. Refractive errors in Northern China between the residents with drinking water containing excessive fluorine and normal drinking water. *Biological Trace Element Research.* 2016;173(2):259-267.

138. Chafe R, Aslanov R, Sarkar A, Gregory P, Comeau A, Newhook LA. Association of type 1 diabetes and concentrations of drinking water components in Newfoundland and Labrador, Canada. *BMJ Open Diabetes Res Care.* 2018;6(1):e000466.

139. Fluegge K. Community water fluoridation predicts increase in age-adjusted incidence and prevalence of diabetes in 22 states from 2005 and 2010. *J Water Health.* 2016;14(5):864-877.

140. Nasman P, Granath F, Ekstrand J, Ekbom A, Sandborgh-Englund G, Fored CM. Natural fluoride in drinking water and myocardial infarction: a cohort study in Sweden. *Sci Total Environ.* 2016;562:305-311.

141. *Water fluoridation health monitoring report for England.* London (GB): Public Health England; 2014.

142. 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.

143. Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environ Health Perspect.* 2012;120(10):1362-1368.

144. Newton JN, Verne J, Dancox M, Young N. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? Comments on the authors' response to earlier criticism. *J Epidemiol Community Health.* 2017;71(4):315-316.

145. Newton JN, Young N, Verne J, Morris J. Water fluoridation and hypothyroidism: results of this study need much more cautious interpretation. *J Epidemiol Community Health.* 2015;69(7):617-618.

146. Jack B, Ayson M, Lewis S, Irving A, Agresta B, Ko H. *Health effects of water fluoridation: technical report.* Sydney (AU): The University of Sydney; 2016.

147. Frazao P, Peres MA, Cury JA. Drinking water quality and fluoride concentration. *Rev Saude Publica.* 2011;45(5):964-973.

148. Bergamo ET, Barbana M, Terada RS, Cury JA, Fujimaki M. Fluoride concentrations in the water of Maringa, Brazil, considering the benefit/risk balance of caries and fluorosis. *Braz Oral Res.* 2015;29:47.

149. Singhal S, Farmer J, McLaren L. Methodological considerations for designing a community water fluoridation cessation study. *Community Dent Oral Epidemiol.* 2017;45(3):193-200.

150. Aboriginal peoples in Canada: key results from the 2016 census. Ottawa (ON): Statistics Canada; 2017: https://www150.statcan.gc.ca/n1/daily-quotidien/171025/dq171025a-eng.htm. Accessed 2018 Jul 10.

151. Cruz M, Narvai PC. Caries and fluoridated water in two Brazilian municipalities with low prevalence of the disease. *Rev Saude Publica.* 2018;52:28.

152. Firmino RT, Bueno AX, Martins CC, Ferreira FM, Granville-Garcia AF, Paiva SM. Dental caries and dental fluorosis according to water fluoridation among 12-year-old Brazilian schoolchildren: a nation-wide study comparing different municipalities. *J Public Health.* 2018;26(5):501-507.

153. Slade GD, Grider WB, Maas WR, Sanders AE. Water fluoridation and dental caries in U.S. children and adolescents. *J Dent Res.* 2018;97(10):1122-1128.

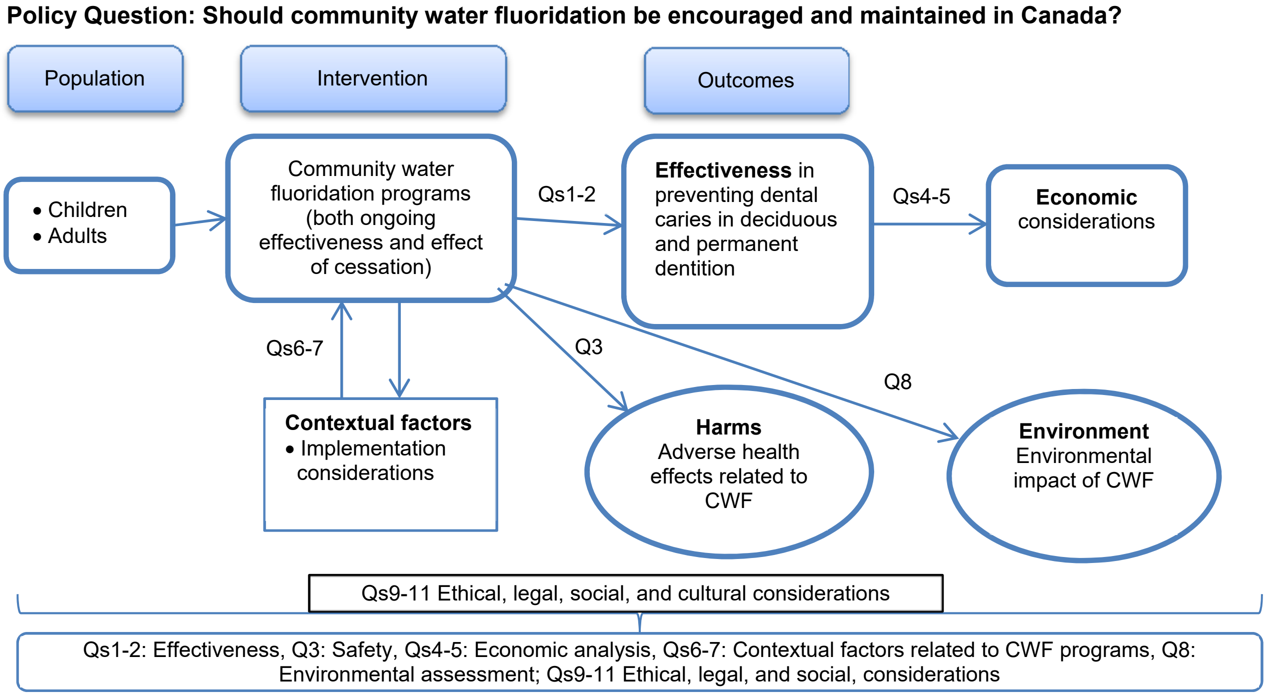
154. Spencer AJ, Do LG, Ha DH. Contemporary evidence on the effectiveness of water fluoridation in the prevention of childhood caries. *Community Dent Oral Epidemiol.* 2018;46(4):407-415.

155. Macey R, Tickle M, MacKay L, McGrady M, Pretty IA. A comparison of dental fluorosis in adult populations with and without lifetime exposure to water fluoridation. *Community Dent Oral Epidemiol.* 2018.

156. Crnosija N, Choi M, Meliker JR. Fluoridation and county-level secondary bone cancer among cancer patients 18 years or older in New York State. *Environ Geochem Health.* 2018.

157. Sezgin BI, Onur SG, Mentes A, Okutan AE, Haznedaroglu E, Vieira AR. Two-fold excess of fluoride in the drinking water has no obvious health effects other than dental fluorosis. *J Trace Elem Med Biol.* 2018;50:216-222.

Appendix 1: Analytical Framework



Research Questions	Methods
Q1. What is the effectiveness of community water fluoridation compared with non-fluoridated drinking water in the prevention of dental caries in children and adults?	Update of two published systematic reviews
Q2. What are the effects of community water fluoridation cessation compared with continued community water fluoridation, the period before cessation of water fluoridation, or non-fluoridated communities on dental caries in children and adults?	
Q3. What are the negative effects of community water fluoridation (at a given fluoride level) compared with non-fluoridated drinking water (fluoride level < 0.4 parts per million) or fluoridation at different levels on human health outcomes?	
Q4. What is the budget impact of introducing water fluoridation in a Canadian municipality without an existing community water fluoridation program from a societal perspective?	Budget impact analyses
Q5. What is the budget impact of ceasing water fluoridation in a Canadian municipality that presently has a community water fluoridation program from a societal perspective?	
Q6. What are the main challenges, considerations, and enablers to implementing or maintaining community water fluoridation programs in Canada?	Consultations with targeted experts and stakeholders Narrative summary of the published and grey literature Survey on implementation issues related to CWF
Q7. What are the main challenges, considerations, and enablers to the cessation of community water fluoridation programs in Canada?	
Q8. What are the potential environmental (toxicological) risks associated with community water fluoridation?	Narrative summary of the published and grey literature Qualitative risk assessment
Q9. What are the major ethical issues raised by the implementation of community water fluoridation?	Review of the bioethics literature and

Research Questions	Methods
Q10. What are the broader legal, social, and cultural considerations to consider for implementation and cessation?	analysis of ethical issues raised by reports answering Qs1-8.
Q11. What are the major ethical issues raised by the cessation of community water fluoridation?	

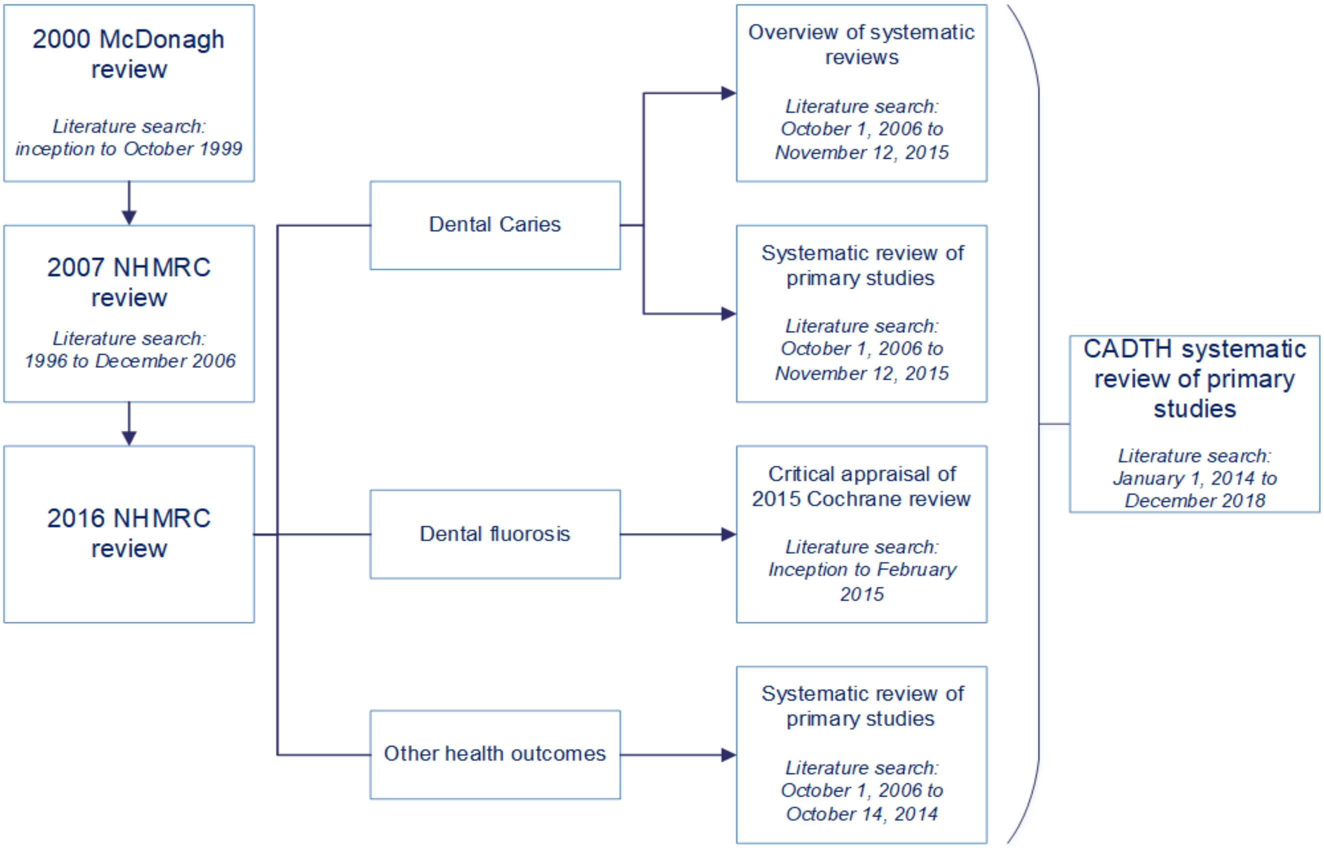
Appendix 2: Quality Assessment of the Updated Systematic Reviews

AMSTAR 2 Checklist	Jack et al., 2016	McLaren and Singhal 2016
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	NA	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NA	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes

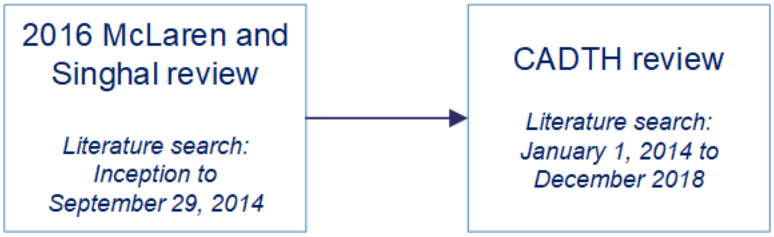
NA = not applicable.

Appendix 3: Flow Diagrams of Sources of Evidence

Questions 1 and 3:



Question 2:



Appendix 4: Literature Search Strategy

Database Search for the Review of Dental Caries and Other Health Outcomes

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials August 2017 EBM Reviews - Cochrane Database of Systematic Reviews 2005 to September 26, 2017 Embase 1974 to 2017 October 02 Ovid MEDLINE(R) ALL 1946 to October 02, 2017 **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 18, 2017
Alerts:	Bi-weekly search updates until project completion
Study Types:	No filter
Limits:	Publication years 2014-current Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Author keyword heading word (MEDLINE)
.kw	Keyword heading (MEDLINE)
.kw	Author keyword (Embase)
medall	Ovid database code; Medline ALL
cctr	Ovid database code; Cochrane Central Register of Controlled Trials
coch	Ovid database code; Cochrane Database of Systematic Reviews
oemezd	Ovid database cose; Embase 1974 to present

SYNTAX GUIDE

#	Searches
	Water Fluoridation Concept (Medline & The Cochrane Library)
1	Fluoridation/
2	(antifluorid* or defluorid* or defluorin* or deflurin* or deflurid* or fluoridation* or nonfluorid* or nonfluorin* or nonflurin* or nonflurid*).ti,ab,kf,kw.
3	or/1-2
4	exp Fluorides/
5	(fluorid* or fluorin* or flurin* or flurid*).ti,ab,kf,kw.

SYNTAX GUIDE	
#	**Searches**
6	or/4-5
7	exp Water supply/
8	Drinking Water/
9	Water Quality/
10	(water* or groundwater* or ground-water*).ti,ab,kf,kw.
11	or/7-10
12	3 or (6 and 11)
13	exp animals/
14	exp animal experimentation/ or exp animal experiment/
15	exp models animal/
16	nonhuman/
17	exp vertebrate/ or exp vertebrates/
18	or/13-17
19	exp humans/
20	exp human experimentation/ or exp human experiment/
21	or/19-20
22	18 not 21
23	12 not 22
24	23 use medall
25	limit 24 to yr="2014 -Current"
26	(201408* or 201409* or 20141* or 2015* or 2016* or 2017* or 2018*).dc,ed,ep.
27	24 and 26
28	25 or 27
29	limit 12 to yr="2014 -Current"
30	29 use cctr
31	29 use coch
	Water Fluoridation Concept (Embase)
32	Fluoridation/
33	(antifluorid* or defluorid* or defluorin* or deflurin* or deflurid* or fluoridation* or nonfluorid* or nonfluorin* or nonflurin* or nonflurid*).ti,ab,kw.
34	or/32-33
35	Fluoride/
36	(fluorid* or fluorin* or flurin* or flurid*).ti,ab,kw.
37	or/35-36
38	Water supply/
39	Drinking Water/
40	Water Quality/
41	(water* or groundwater* or ground-water*).ti,ab,kw.
42	or/38-41
43	34 or (37 and 42)
44	43 not 22
45	44 use oemezd

SYNTAX GUIDE	
#	**Searches**
46	(201408* or 201409* or 20141* or 2015* or 2016* or 2017* or 2018*).dd.
47	limit 45 to yr="2014 -Current"
48	45 and 46
49	or/47-48
50	49 not conference abstract.pt.
	All Clinical Results (Duplicates removed)
51	28 or 30 or 31 or 50
52	remove duplicates from 51
46	(201408* or 201409* or 20141* or 2015* or 2016* or 2017* or 2018*).dd.
47	limit 45 to yr="2014 -Current"

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.
Scopus (Elsevier)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Scopus platform.

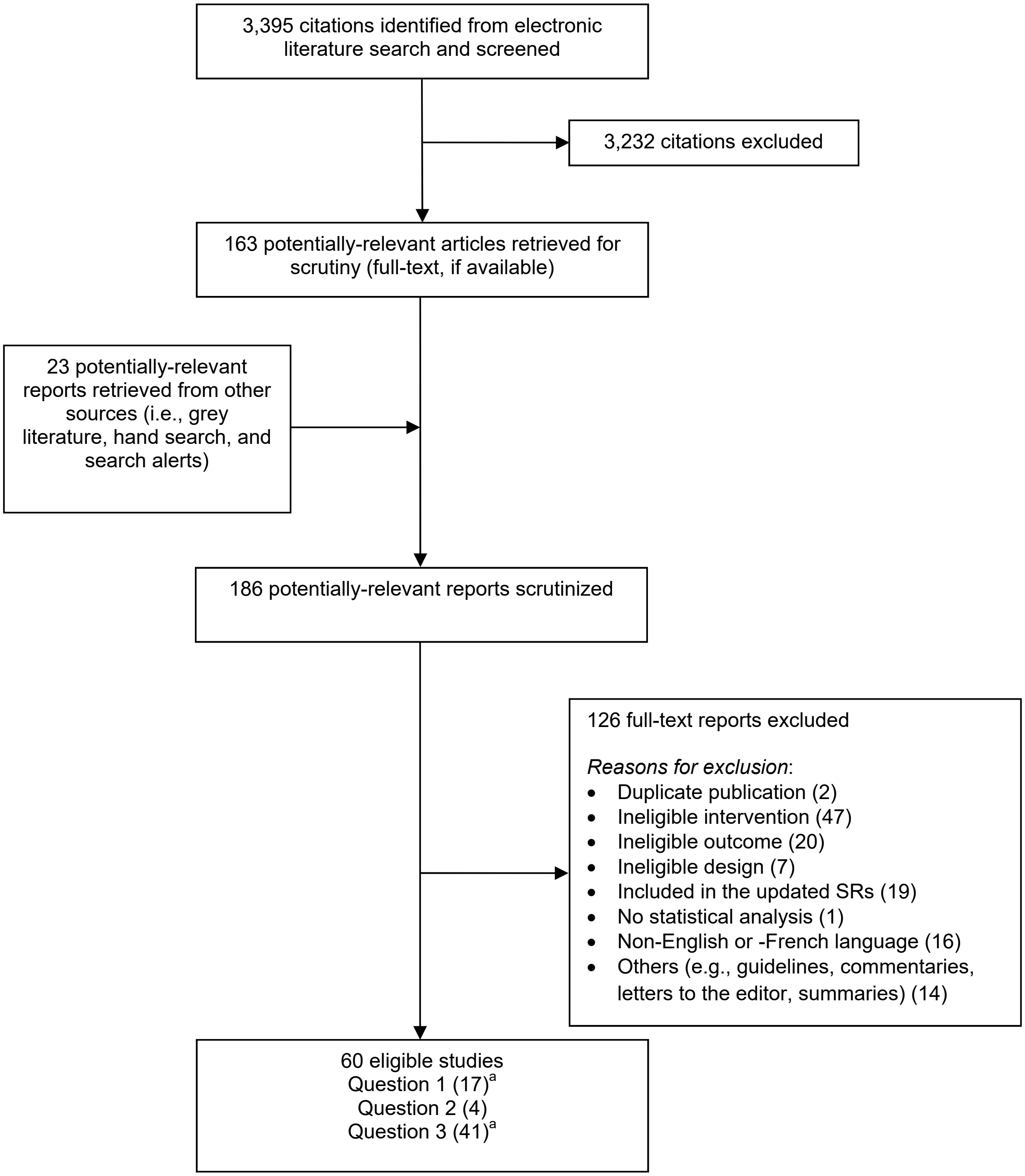
Grey Literature

Dates for Search:	Nov-Dec 2017
Keywords:	Included terms for fluoridation or fluoride in water
Limits:	English or French language

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals

Appendix 5: Flow Diagram of Study Selection From the Updated Literature Search



3,395 citations identified from electronic literature search and screened

3,232 citations excluded

163 potentially-relevant articles retrieved for scrutiny (full-text, if available)

23 potentially-relevant reports retrieved from other sources (i.e., grey literature, hand search, and search alerts)

186 potentially-relevant reports scrutinized

126 full-text reports excluded

Reasons for exclusion:
- Duplicate publication (2)
- Ineligible intervention (47)
- Ineligible outcome (20)
- Ineligible design (7)
- Included in the updated SRs (19)
- No statistical analysis (1)
- Non-English or -French language (16)
- Others (e.g., guidelines, commentaries, letters to the editor, summaries) (14)

60 eligible studies
Question 1 (17)[a]
Question 2 (4)
Question 3 (41)[a]

[a] Two of the included sixty studies addressed both questions 1 and 3.

Appendix 6: List of Included Primary Studies — Review of Dental Caries and Other Health Outcomes

Table 56: Included Primary Studies Identified From the Updated Literature Search for Research Question 1

Study (First author, year)	Citation
2018	
PHE 2018	Water fluoridation: health monitoring report for England 2018 [Internet]. London: Public Health England; 2018. [cited 2018 Mar 23].
2017	
Aggeborn 2017	Aggeborn L, Öhman M. The effects of fluoride In the drinking water [Internet]. Uppsala (SE): Institute for Evaluation of Labour Market and Education Policy; 2017. [cited 2018 Jan 3]. (Working paper 2017:20). *(Dental outcomes)*
Aguiar 2017	Aguiar VR, Pattussi MP, Celeste RK. The role of municipal public policies in oral health socioeconomic inequalities in Brazil: a multilevel study. Community Dent Oral Epidemiol. 2017 Dec 7.
Do 2017	Do L, Ha D, Peres MA, Skinner J, Byun R, Spencer AJ. Effectiveness of water fluoridation in the prevention of dental caries across adult age groups. Community Dent Oral Epidemiol. 2017 Jun;45(3):225-32.
Heima 2017	Heima M, Ferretti M, Qureshi M, Ferretti G. The effect of social geographic factors on the untreated tooth decay among head start children. J Clin Exp Dent [Internet]. 2017 Oct [cited 2017 Dec 20];9(10):e1224-e1229
Kim 2017	Kim HN, Kim JH, Kim SY, Kim JB. Associations of Community Water Fluoridation with Caries Prevalence and Oral Health Inequality in Children. Int J Environ Res Public Health [Internet]. 2017 Jun 13 [cited 2017 Nov 7];14.
Spencer 2017	Spencer AJ, Liu P, Armfield JM, Do LG. Preventive benefit of access to fluoridated water for young adults. J Public Health Dent. 2017 Jun;77(3):263-71.
2016	
Arrow 2016	Arrow P. Oral health of schoolchildren in Western Australia. Aust Dent J. 2016 Sep;61(3):333-41.
Chalub 2016	Chalub LL, Martins CC, Ferreira RC, Vargas AM. Functional dentition in Brazilian adults: an investigation of social determinants of health (SDH) using a multilevel approach. PLoS ONE [Internet]. 2016 [cited 2017 Nov 6];11(2):e0148859.
Cho 2016	Cho MS, Han KT, Park S, Moon KT, Park EC. The differences in healthcare utilization for dental caries based on the implementation of water fluoridation in South Korea. BMC Oral Health [Internet]. 2016 Nov 8 [cited 2017 Nov 6];16(1):119.
Crocombe 2016	Crocombe LA, Brennan DS, Slade GD. Does lower lifetime fluoridation exposure explain why people outside capital cities have poor clinical oral health? Aust Dent J. 2016;61(1):93-101.
Crouchley 2016	Crouchley K, Trevithick R. Dental health outcomes of children residing in fluoridated and non-fluoridated areas of western Australia. Perth (AU): Government of Western Australia; 2016
Ha 2016	Ha DH, Lalloo R, Jamieson LM, Giang DL. Trends in caries experience and associated contextual factors among indigenous children. J Public Health Dent. 2016 Jun;76(3):184-91.
Peres 2016	Peres MA, Peres KG, Barbato PR, Hofelmann DA. Access to Fluoridated Water and Adult Dental Caries: A Natural Experiment. J Dent Res. 2016 Jul;95(8):868-74.
Schluter 2016	Schluter PJ, Lee M. Water fluoridation and ethnic inequities in dental caries profiles of New Zealand children aged 5 and 12-13 years: analysis of national cross-sectional registry databases for the decade 2004-2013. BMC Oral Health [Internet]. 2016 Feb 18 [cited 2017 Nov 6];16:21.
2015	
Barbato 2015	Barbato PR, Peres MA, Hofelmann DA, Peres KG. Contextual and individual indicators associated with the presence of teeth in adults. Rev Saude Publica [Internet]. 2015 [cited 2017 Nov 7];49:27.
Blinkhorn 2015	Blinkhorn AS, Byun R, Johnson G, Metha P, Kay M, Lewis P. The Dental Health of primary school children living in fluoridated, pre-fluoridated and non-fluoridated communities in New South Wales, Australia. BMC Oral Health [Internet]. 2015 Jan 21 [cited 2017 Nov 6];15:9.

Table 57: Included Primary Studies Identified From the Updated Literature Search for Research Question 2

Study (First author, year)	Citation
2017	
McLaren 2017	McLaren L, Patterson S, Thawer S, Faris P, McNeil D, Potestio ML, et al. Exploring the short-term impact of community water fluoridation cessation on children's dental caries: a natural experiment in Alberta, Canada. Public Health. 2017 May;146:56-64.
2016	
McLaren 2016a	McLaren L, Patterson S, Thawer S, Faris P, McNeil D, Potestio M, et al. Measuring the short-term impact of fluoridation cessation on dental caries in Grade 2 children using tooth surface indices. Community Dent Oral Epidemiol [Internet]. 2016 Jun [cited 2017 Nov 7];44(3):274-82.
McLaren 2016b	McLaren L, McNeil DA, Potestio M, Patterson S, Thawer S, Faris P, et al. Equity in children's dental caries before and after cessation of community water fluoridation: differential impact by dental insurance status and geographic material deprivation. Intern J Equity Health [Internet].
2015	
PHE 2015	Dental health impact of water fluoridation in children living in Bedford Borough Council in 2008, 2009 and 2015 [Internet]. London: Public Health England; 2015. [cited 2018 Jan 3].

Table 58: Included Primary Studies Identified From the Updated Literature Search for Research Question 3

Study (First author, year)	Citation
2018	
Chafe 2018	Chafe R, Aslanov R, Sarkar A, Gregory P, Comeau A, Newhook LA. Association of type 1 diabetes and concentrations of drinking water components in Newfoundland and Labrador, Canada. BMJ Open Diabetes Res Care [Internet]. 2018 [cited 2018 Mar 20];6(1):e000466.
Khandare 2018	Khandare AL, Validandi V, Gourineni SR, Gopalan V, Nagalla B. Dose-dependent effect of fluoride on clinical and subclinical indices of fluorosis in school going children and its mitigation by supply of safe drinking water for 5 years: an Indian study. Environ Monit Assess. 2018 Feb 2;190(3):110
Kheradpisheh 2018	Kheradpisheh Z, Mirzaei M, Mahvi AH, Mokhtari M, Azizi R, Fallahzadeh H, et al. Impact of drinking water fluoride on human thyroid hormones: a case- control study. Sci Rep [Internet]. 2018 Feb 8 [cited 2018];8(1):2674
Moghaddam 2018	Moghaddam VK, Yousefi M, Khosravi A, Yaseri M, Mahvi AH, Hadei M, et al. High concentration of fluoride can be increased risk of abortion. Biol Trace Elem Res. 2018 Mar 14.
PHE 2018	Water fluoridation: health monitoring report for England 2018 [Internet]. London: Public Health England; 2018. [cited 2018 Mar 23].
Yousefi 2018	Yousefi M, Yaseri M, Nabizadeh R, Hooshmand E, Jalilzadeh M, Mahvi AH, et al. Association of hypertension, body mass index, and waist circumference with fluoride intake; water drinking in residents of fluoride endemic areas, Iran. Biol Trace Elem Res. 2018 Mar 14.
2017	
Aggeborn 2017	Aggeborn L, Öhman M. The effects of fluoride In the drinking water [Internet]. Uppsala (SE): Institute for Evaluation of Labour Market and Education Policy; 2017. [cited 2018 Jan 3]. (Working paper 2017:20).
Arora 2017	Arora S, Kumar JV, Moss ME. Does water fluoridation affect the prevalence of enamel fluorosis differently among racial and ethnic groups? J Public Health Dent. 2017 Nov 24.
Barberio 2017a	Barberio AM, Quinonez C, Hosein FS, McLaren L. Fluoride exposure and reported learning disability diagnosis among Canadian children: Implications for community water fluoridation. Can J Public Health. 2017 Sep 14;108(3):e229-e239.
Barberio 2017b	Barberio AM, Hosein FS, Quinonez C, McLaren L. Fluoride exposure and indicators of thyroid functioning in the Canadian population: implications for community water fluoridation. J Epidemiol Community Health [Internet]. 2017 Oct [cited 2017 Nov 7];71(10):1019-25.

Study (First author, year)	Citation
Bonola-Gallardo 2017	Bonola-Gallardo I, Irigoyen-Camacho ME, Vera-Robles L, Campero A, Gomez-Quiroz L. Enzymatic activity of glutathione S-transferase and dental fluorosis among children receiving two different levels of naturally fluoridated water. Biol Trace Elem Res. 2017;176(1):40-7.
Garcia-Perez 2017	Garcia-Perez A, Irigoyen-Camacho ME, Borges-Yanez SA, Zepeda-Zepeda MA, Bolona-Gallardo I, Maupome G. Impact of caries and dental fluorosis on oral health-related quality of life: a cross-sectional study in schoolchildren receiving water naturally fluoridated at above-optimal levels. Clin Oral Investig. 2017 Mar 1.
Ibiyemi 2017	Ibiyemi O, Zohoori FV, Valentine RA, Kometa S, Maguire A. Prevalence and extent of enamel defects in the permanent teeth of 8-year-old Nigerian children. Community Dent Oral Epidemiol. 2017 Sep 11;1-9.
Khandare 2017	Khandare AL, Gourineni SR, Validandi V. Dental fluorosis, nutritional status, kidney damage, and thyroid function along with bone metabolic indicators in school-going children living in fluoride-affected hilly areas of Doda district, Jammu and Kashmir, India. Environ Monit Assess. 2017 Oct 23;189(11):579.
Mohammadi 2017	Mohammadi AA, Yousefi M, Yaseri M, Jalilzadeh M, Mahvi AH. Skeletal fluorosis in relation to drinking water in rural areas of West Azerbaijan, Iran. Sci Rep [Internet]. 2017 Dec 11 [cited 2018 Jan 9];7(1):17300.
Rango 2017	Rango T, Vengosh A, Jeuland M, Whitford GM, Tekle-Haimanot R. Biomarkers of chronic fluoride exposure in groundwater in a highly exposed population. Science of the Total Environment. 2017;596-597(2017):1-11.
Razdan 2017	Razdan P, Patthi B, Kumar JK, Agnihotri N, Chaudhari P, Prasad M. Effect of Fluoride Concentration in Drinking Water on Intelligence Quotient of 12-14-Year-Old Children in Mathura District: A Cross-Sectional Study. J Int Soc Prev Community Dent [Internet]. 2017 Sep [cited 2017 Nov 7];7(5):252-8.
Yousefi 2017	Yousefi M, Mohammadi AA, Yaseri M, Mahvi AH. Epidemiology of drinking water fluoride and its contribution to fertility, infertility, and abortion: an ecological study in West Azerbaijan Province, Poldasht County, Iran. Fluoride. 2017;50(3):343-53. *(Reproduction)*
2016	
Aravind 2016	Aravind A, Dhanya RS, Narayan A, Sam G, Adarsh VJ, Kiran M. Effect of fluoridated water on intelligence in 10-12-year-old school children. J Int Soc Prev Community Dent [Internet]. 2016 Dec [cited 2017 Nov 7];6(Suppl 3):S237-S242.
Archer 2016	Archer NP, Napier TS, Villanacci JF. Fluoride exposure in public drinking water and childhood and adolescent osteosarcoma in Texas. Cancer Causes Control. 2016 Jul;27(7):863-8.
Bin 2016	Bin G, Liu H, Zhao C, Zhou G, Ding X, Zhang N, et al. Refractive errors in Northern China between the residents with drinking water containing excessive fluorine and normal drinking water. Biol Trace Elem Res. 2016;173(2):259-67.
Fluegge 2016	Fluegge K. Community water fluoridation predicts increase in age-adjusted incidence and prevalence of diabetes in 22 States from 2005 and 2010. Journal of Water and Health [Internet]. 2016 [cited 2017 Nov 7];14(5):864-77.
Irigoyen-Camacho 2016	Irigoyen-Camacho ME, García Pérez A, Mejia González A, Huizar AR. Nutritional status and dental fluorosis among schoolchildren in communities with different drinking water fluoride concentrations in a central region in Mexico. Sci Total Environ. 2016 Jan 15;541:512-9.
Mahantesha 2016	Mahantesha T, Dixit UB, Nayakar RP, Ashwin D, Ramagoni NK, Kamavaram E, V. Prevalence of Dental Fluorosis and associated Risk Factors in Bagalkot District, Karnataka, India. Int J Clin Pediatr Dent [Internet]. 2016 Jul [cited 2017 Nov 7];9(3):256-63.
Nasman 2016	Nasman P, Granath F, Ekstrand J, Ekbom A, Sandborgh-Englund G, Fored CM. Natural fluoride in drinking water and myocardial infarction: A cohort study in Sweden. Science of the Total Environment. 2016;562:305-11.
Pretty 2016	Pretty IA, Boothman N, Morris J, MacKay L, Liu Z, McGrady M, et al. Prevalence and severity of dental fluorosis in four English cities. Community Dent Health. 2016 Dec;33(4):292-6.
Ramadan 2016	Ramadan AM, Ghandour IA. Dental fluorosis in two communities in Khartoum State, Sudan, with potable water fluoride levels of 1.36 and 0.45 mg/L. Fluoride. 2016;Part(4):509-20.

Study (First author, year)	Citation
Sebastian 2016	Sebastian ST, Soman RR, Sunitha S. Prevalence of dental fluorosis among primary school children in association with different water fluoride levels in Mysore district, Karnataka. Indian J Dent Res. 2016 Mar;27(2):151-4.
Shruthi 2016	Shruthi MN, Santhuram AN, Arun HS, Kishore Kumar BN. A comparative study of skeletal fluorosis among adults in two study areas of Bangarpet taluk, Kolar. Indian J Public Health. 2016 Jul;60(3):203-9.
2015	
Aghaei 2015a	Aghaei M, Derakhshani R, Raoof M, Dehghani M, Mahvi AH. Effect of fluoride in drinking water on birth height and weight: an ecological study in Kerman Province, Zarand county, Iran. Fluoride [Internet]. 2015 [cited 2017 Nov 6];48(2):160-8.
Aghaei 2015b	Aghaei M, Karimzade S, Yaseri M, Khorsandi H, Zolfi E, Mahvi AH. Hypertension and fluoride in drinking water: Case study from West Azerbaijan, Iran. Fluoride [Internet]. 2015 [cited 2017 Nov 6];48(3):252-8.
Bal 2015	Bal IS, Dennison PJ, Evans RW. Dental fluorosis in the Blue Mountains and Hawkesbury, New South Wales, Australia: policy implications. J Investig Clin Dent. 2015 Feb;6(1):45-52.
Balmer 2015	Balmer R, Toumba KJ, Munyombwe T, Duggal MS. A comparison of the presentation of molar incisor hypomineralisation in two communities with different fluoride exposure. Eur Arch Paediatr Dent. 2015 Jun;16(3):257-64.
Khan 2015	Khan SA, Singh RK, Navit S, Chadha D, Johri N, Navit P, et al. Relationship between dental fluorosis and intelligence quotient of school going children in and around Lucknow District: a cross-sectional study. J Clin Diagn Res [Internet]. 2015 Nov [cited 2017 Nov 7];9(11):ZC10-ZC15.
Moimaz 2015	Moimaz SA, Saliba O, Marques LB, Garbin CA, Saliba NA. Dental fluorosis and its influence on children's life. Pesqui Odontol Bras [Internet]. 2015 [cited 2017 Nov 6];29.
Peckham 2015	Peckham S, Lowery D, Spencer S. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water. J Epidemiol Community Health. 2015 Jul;69(7):619-24.
Sebastian 2015	Sebastian ST, Sunitha S. A cross-sectional study to assess the intelligence quotient (IQ) of school going children aged 10-12 years in villages of Mysore district, India with different fluoride levels. J Indian Soc Pedod Prev Dent. 2015 Oct;33(4):307-11.
2014	
Punitha 2014	Punitha VC, Sivaprakasam P, Elango R, Balasubramanian R, Midhun Kumar GH, Sudhir Ben Nelson BT. Prevalence of dental fluorosis in a non-endemic district of Tamil Nadu, India. Biosciences Biotechnology Research Asia [Internet]. 2014 [cited 2017 Nov 16];11(1):159-63.
Rango 2014	Rango T, Vengosh A, Jeuland M, Tekle-Haimanot R, Weinthal E, Kravchenko J, et al. Fluoride exposure from groundwater as reflected by urinary fluoride and children's dental fluorosis in the Main Ethiopian Rift Valley. Sci Total Environ. 2014 Oct 15;496:188-97.
Sukhabogi 2014	Sukhabogi JR, Parthasarathi P, Anjum S, Shekar B, Padma C, Rani A. Dental fluorosis and dental caries prevalence among 12 and 15-year-old school children in Nalgonda District, Andhra Pradesh, India. Ann Med Health Sci Res [Internet]. 2014 Sep [cited 2017 Nov 6];4(Suppl 3):S245-S252. *(Dental fluorosis)*
Wong 2014	Wong HM, McGrath C, King NM. Diffuse opacities in 12-year-old Hong Kong children--four cross-sectional surveys. Community Dent Oral Epidemiol. 2014 Feb;42(1):61-9.

Appendix 7: List of Excluded Studies and Reasons for Exclusion — Review of Dental Caries and Other Health Outcomes

Citation	Reason for exclusion
2018	
Aghapour S, Bina B, Tarrahi MJ, Amiri F, Ebrahimi A. Distribution and health risk assessment of natural fluoride of drinking groundwater resources of Isfahan, Iran, using GIS. Environ Monit Assess. 2018 Feb 13;190(3):137.	Irrelevant outcomes
Dehbandi R, Moore F, Keshavarzi B. Geochemical sources, hydrogeochemical behavior, and health risk assessment of fluoride in an endemic fluorosis area, central Iran. Chemosphere. 2018;193:763-76.	No useful outcome data
Fallahzadeh RA, Miri M, Taghavi M, Gholizadeh A, Anbarani R, Hosseini-Bandegharaei A, et al. Spatial variation and probabilistic risk assessment of exposure to fluoride in drinking water. Food Chem Toxicol. 2018 Feb 6.	Irrelevant outcomes
Khandare AL, Validandi V, Boiroju N. Fluoride Alters Serum Elemental (Calcium, Magnesium, Copper, and Zinc) Homeostasis Along with Erythrocyte Carbonic Anhydrase Activity in Fluorosis Endemic Villages and Restores on Supply of Safe Drinking Water in School-Going Children of Nalgonda District, India. Biol Trace Elem Res. 2018 Feb 17.	Irrelevant outcomes
2017	
Andegiorgish AK, Weldemariam BW, Kifle MM, Mebrahtu FG, Zewde HK, Tewelde MG, et al. Prevalence of dental caries and associated factors among 12 years old students in Eritrea. BMC Oral Health [Internet]. 2017 Dec 29 [cited 2018 Jan 9];17(1):169.	No comparison between F levels in drinking water
Arulkumar M, Vijayan R, Penislusshiyan S, Sathishkumar P, Angayarkanni J, Palvannan T. Alteration of paraoxonase, arylesterase and lactonase activities in people around fluoride endemic area of Tamil Nadu, India. Clin Chim Acta. 2017 Aug;471:206-15.	No useful outcome data
Guissouma W, Hakami O, Al-Rajab AJ, Tarhouni J. Risk assessment of fluoride exposure in drinking water of Tunisia. Chemosphere. 2017 Jun;177:102-8.	No useful outcome data
Kumar RP, Vijayalakshmi B. Assessment of fluoride concentration in ground water in Madurai district, Tamil Nadu, India. Research Journal of Pharmacy and Technology. 2017;10(1):309-10.	No useful outcome data
Ma Q, Huang H, Sun L, Zhou T, Zhu J, Cheng X, et al. Gene-environment interaction: Does fluoride influence the reproductive hormones in male farmers modified by ER□ gene polymorphisms? Chemosphere. 2017 Dec;188:525-31.	Exposure measured by urine fluoride levels
Malek Mohammadi T, Derakhshani R, Tavallaie M, Hasheminejad N, Haghdoost AA. Analysis of Ground Water Fluoride Content and its Association with Prevalence of Fluorosis in Zarand/Kerman: (Using GIS). J Dent Biomater [Internet]. 2017 Jun [cited 2017 Nov 7];4(2):379-86.	No useful outcome data
Manthra Prathoshni SM, Vishnu Priya V, Sohara Parveen N. Awareness of dental fluorosis among children - A survey. Journal of Pharmaceutical Sciences and Research [Internet]. 2017 [cited 2017 Nov 7];9(4):459-61.	No useful outcome data
Meena C, Dwivedi S, Rathore S, Gonmei Z, Toteja GS, Bala K, et al. Assessment of skeletal fluorosis among children in two blocks of rural area, Jaipur District, Rajasthan, India. Asian Journal of Pharmaceutical and Clinical Research. 2017;10(9):322-5.	No statistical analysis
Meena C, Rathore S, Dwivedi S, Gonmei Z, Toteja GS, Bala K, et al. Assessment of dental fluorosis in children of Jaipur district, Rajasthan, India. Asian Journal of Pharmaceutical and Clinical Research. 2017;10(8):161-4.	No statistical analysis
McLaren L, Patterson S, Thawer S, Faris P, McNeil D, Potestio M. Fluoridation cessation: More science from Alberta. Community Dent Oral Epidemiol. 2017 Oct 10.	Letter to editor
Mondal D, Gupta S, Reddy DV, Dutta G. Fluoride enrichment in an alluvial aquifer with its subsequent effect on human health in Birbhum district, West Bengal, India. Chemosphere. 2017 Feb;168:817-24.	No comparator and no useful outcome data
Patel PP, Patel PA, Zulf MM, Yagnik B, Kajale N, Mandlik R, et al. Association of dental and skeletal fluorosis with calcium intake and serum vitamin D concentration in adolescents from a region endemic for fluorosis. Indian J Endocrinol Metab. 2017 Jan;21(1):190-5.	Irrelevant intervention

Citation	Reason for exclusion
Pérez-Pérez P, Irigoyen-Camacho ME, Boges-Yañez AS. Factors affecting dental fluorosis in low socioeconomic status children in Mexico. Community Dent Health. 2017 Jun;34(2):66-71.	No comparison between F levels in drinking water
Plaka K, Ravindra K, Mor S, Gauba K. Risk factors and prevalence of dental fluorosis and dental caries in school children of North India. Environmental Monitoring and Assessment. 2017;189(1).	No comparison between F levels in drinking water
Ramesh M, Malathi N, Ramesh K, Aruna RM, Kuruvilla S. Comparative Evaluation of Dental and Skeletal Fluorosis in an Endemic Fluorosed District, Salem, Tamil Nadu. J Pharm Bioallied Sci [Internet]. 2017 Nov [cited 2018 Jan 9];9(Suppl 1):S88-S91.	No comparison between F levels in drinking water
Rustagi N, Rathore AS, Meena JK, Chugh A, Pal R. Neglected health literacy undermining fluorosis control efforts: a pilot study among schoolchildren in an endemic village of rural Rajasthan, India. J Family Med Prim [Internet]. 2017 Jul [cited 2018];6(3):533-7.	No comparison between F levels in drinking water
Sahu BL, Banjare GR, Ramteke S, Patel KS, Matini L. Fluoride contamination of groundwater and toxicities in Dongargaon Block, Chhattisgarh, India. Exposure and Health. 2017;9(2):143-56.	No comparator and no useful outcome data
Spittle B. The effect of the fluoride ion on reproductive parameters and an estimate of the safe daily dose of fluoride to prevent female infertility and miscarriage, and foetal neurotoxicity. Fluoride. 2017;50(3):287-91	Commentary
Ugran V, Desai NN, Chakraborti D, Masali KA, Mantur P, Kulkarni S, et al. Groundwater fluoride contamination and its possible health implications in Indi taluk of Vijayapura District (Karnataka State), India. Environ Geochem Health. 2017 Oct;39(5):1017-29.	No useful outcome data
Valdez Jimenez L, Lopez Guzman OD, Cervantes Flores M, Costilla-Salazar R, Calderon Hernandez J, Alcaraz Contreras Y, et al. In utero exposure to fluoride and cognitive development delay in infants. Neurotoxicology. 2017 Mar;59:65-70.	No comparison between F levels in drinking water
Wickramarathna S, Balasooriya S, Diyabalanage S, Chandrajith R. Tracing environmental aetiological factors of chronic kidney diseases in the dry zone of Sri Lanka-A hydrogeochemical and isotope approach. J Trace Elem Med Biol. 2017 Dec;44:298-306.	No comparison between F levels in drinking water
Zhang LE, Huang D, Yang J, Wei X, Qin J, Ou S, et al. Probabilistic risk assessment of Chinese residents' exposure to fluoride in improved drinking water in endemic fluorosis areas. Environ Pollut. 2017 Mar;222:118-25.	No useful outcome data
2016	
Afzal S, Durrani S, Malghani AK, Khan M, Sajjad N, Tariq N. Concentrations of fluoride in drinking water and tea samples and associations with dental fluorosis. Pakistan Journal of Nutrition. 2016;15(1):85-9.	Irrelevant intervention (water and tea as F sources)
Antonijevic E, Mandinic Z, Curcic M, Djukic-Cosic D, Milicevic N, Ivanovic M, et al. "Borderline" fluorotic region in Serbia: correlations among fluoride in drinking water, biomarkers of exposure and dental fluorosis in schoolchildren. Environ Geochem Health. 2016 Jun;38(3):885-96.	No comparison between F levels in drinking water
Bhagavatula P, Levy SM, Broffitt B, Weber-Gasparoni K, Warren JJ. Timing of fluoride intake and dental fluorosis on late-erupting permanent teeth. Community Dent Oral Epidemiol [Internet]. 2016 Feb [cited 2017 Nov 7];44(1):32-45.	No comparison between F levels in drinking water
Blakey K, McNally RJ. Fluoridation may not be linked with adverse health outcomes. J Evid-Based Dent Pract. 2016 Sep;16(3):209-12.	Summary
Celeste RK, Luz PB. Independent and additive effects of different sources of fluoride and dental fluorosis. Pediatr Dent. 2016;38(3):233-8.	No comparison between F levels in drinking water
Das K, Mondal NK. Dental fluorosis and urinary fluoride concentration as a reflection of fluoride exposure and its impact on IQ level and BMI of children of Laxmisagar, Simlapal Block of Bankura District, W.B., India. Environmental Monitoring and Assessment. 2016;188(4).	No comparison between F levels in drinking water
Del Carmen AF, Javier FH, Aline CC. Dental fluorosis, fluoride in urine, and nutritional status in adolescent students living in the rural areas of Guanajuato, Mexico. J Int Soc Prev Community Dent [Internet]. 2016 Nov [cited 2017 Nov 7];6(6):517-22.	No comparison between F levels in drinking water
Duan L, Zhu J, Wang K, Zhou G, Yang Y, Cui L, et al. Does fluoride affect serum testosterone and androgen binding protein with age-specificity? A population-based cross-sectional study in Chinese male farmers. Biol Trace Elem Res. 2016;174(2):294-9.	No comparison between F levels in drinking water
Hirzy JW, Connett P, Xiang Q, Spittle BJ, Kennedy DC. Developmental neurotoxicity of fluoride: A quantitative risk analysis towards establishing a safe daily dose of fluoride for children. Fluoride.	Irrelevant outcome. Re-analysis of previous studies

Citation	Reason for exclusion
2016;Part(4):379-400.	
Kebede A, Retta N, Abuye C, Whiting SJ, Kassaw M, Zeru T, et al. Dietary fluoride intake and associated skeletal and dental fluorosis in school age children in rural Ethiopian Rift Valley. International Journal of Environmental Research and Public Health [Internet]. 2016 [cited 2017 Nov 7];13(8).	No comparison between F levels in drinking water
Jin HJ, Lee MK, Lee JH. The oral health status and behavior of middle school students according to fluoridation area. International Journal of Bio-Science and Bio-Technology. 2016;8(2):279-86.	No multivariable analysis
Li M, Gao Y, Cui J, Li Y, Li B, Liu Y, et al. Cognitive impairment and risk factors in elderly people living in fluorosis areas in China. Biol Trace Elem Res. 2016;172(1):53-60.	No comparison between F levels in drinking water
Mondal D, Dutta G, Gupta S. Inferring the fluoride hydrogeochemistry and effect of consuming fluoride-contaminated drinking water on human health in some endemic areas of Birbhum district, West Bengal. Environ Geochem Health. 2016 Apr;38(2):557-76.	No comparison between F levels in drinking water
Narbutaite J, Virtanen JI, Vehkalahti MM. Variation in fluorosis and caries experience among Lithuanian 12 year olds exposed to more than 1 ppm F in tap water. J Investig Clin Dent. 2016 May;7(2):187-92.	No comparison between F levels in drinking water
Nawsherwan, Kaur CR, Arif M, Nauman AM, Wasila H, Ulhaq I, et al. Risk factors associated with teeth discoloration in Malakand District, Pakistan. Fluoride. 2016;Part(3):253-62.	Irrelevant outcome
Nørrisgaard PE, Qvist V, Ekstrand K. Prevalence, risk surfaces and inter-municipality variations in caries experience in Danish children and adolescents in 2012. Acta Odontol Scand. 2016;74(4):291-7.	No comparison between F levels in drinking water
Oznurhan F, Ekci ES, Ozalp S, Deveci C, Delilbasi AE, Bani M, et al. Time and sequence of eruption of permanent teeth in Ankara, Turkey. Pediatric Dental Journal. 2016;26(1):1-7.	No comparison between F levels in drinking water
Ramesh M, Narasimhan M, Krishnan R, Chalakkal P, Aruna RM, Kuruvilah S. The prevalence of dental fluorosis and its associated factors in Salem district. Contemp Clin Dent [Internet]. 2016 Apr [cited 2017 Nov 7];7(2):203-8.	No comparison between F levels in drinking water
Sami E, Vichayanrat T, Satitvipawee P. Caries with Dental Fluorosis and Oral Health Behaviour Among 12-Year School Children in Moderate-Fluoride Drinking Water Community in Quetta, Pakistan. J Coll Physicians Surg Pak. 2016 Sep;26(9):744-7.	No comparison between F levels in drinking water
Susheela AK, Gupta R, Mondal NK. Anaemia in adolescent girls: An intervention of diet editing and counselling. Natl Med J India [Internet]. 2016 Jul [cited 2017 Nov 7];29(4):200-4.	No comparison between F levels in drinking water
Wasana HM, Aluthpatabendi D, Kularatne WM, Wijekoon P, Weerasooriya R, Bandara J. Drinking water quality and chronic kidney disease of unknown etiology (CKDu): synergic effects of fluoride, cadmium and hardness of water. Environ Geochem Health. 2016 Feb;38(1):157-68.	Irrelevant intervention
Zhou GY, Ren LJ, Hou JX, Cui LX, Ding Z, Cheng XM, et al. Endemic fluorosis in Henan province, China: ER□ gene polymorphisms and reproductive hormones among women. Asia Pac J Clin Nutr. 2016 Dec;25(4):911-9.	Irrelevant outcomes
2015	
Asawa K, Singh A, Bhat N, Tak M, Shinde K, Jain S. Association of temporomandibular joint signs & symptoms with dental fluorosis & skeletal manifestations in endemic fluoride areas of Dungarpur District, Rajasthan, India. J Clin Diagn Res [Internet]. 2015 Dec [cited 2017 Nov 7];9(12):ZC18-ZC21.	No comparison between F levels in drinking water
Blinkhorn AS, Byun R, Mehta P, Kay M. A 4-year assessment of a new water-fluoridation scheme in New South Wales, Australia. Int Dent J. 2015 Jun;65(3):156-63.	Included in NHMCR review
Broadbent JM, Thomson WM, Ramrakha S, Moffitt TE, Zeng J, Foster Page LA, et al. Community water fluoridation and intelligence: prospective study in New Zealand. Am J Public Health [Internet]. 2015 Jan [cited 2017 Nov 6];105(1):72-6.	Included in NHMCR review
Choi AL, Zhang Y, Sun G, Bellinger DC, Wang K, Yang XJ, et al. Association of lifetime exposure to fluoride and cognitive functions in Chinese children: a pilot study. Neurotoxicol Teratol. 2015 Jan;47:96-101.	Included in NHMCR review
Craig L, Lutz A, Berry KA, Yang W. Recommendations for fluoride limits in drinking water based on estimated daily fluoride intake in the Upper East Region, Ghana. Sci Total Environ. 2015 Nov 1;532:127-37.	No useful outcome data
Crocombe L. Three Years of Water Fluoridation May Lead to a Decrease in Dental Caries Prevalence and Dental Caries Experience in a Community With High Caries Rates. J Evid -Based Dent Pract.	Summary

Citation	Reason for exclusion
2015 Sep;15(3):124-5.	
Crocombe LA, Brennan DS, Slade GD, Stewart JF, Spencer AJ. The effect of lifetime fluoridation exposure on dental caries experience of younger rural adults. Aust Dent J. 2015 Mar;60(1):30-7.	Included in NHMCR review
da Silva JV, Machado FC, Ferreira MA. Social inequalities and the oral health in Brazilian capitals. Cienc Saude Colet [Internet]. 2015 Aug;20(8):2539-48.	Included in NHMCR review
Do LG, Ha DH, Spencer AJ. Factors attributable for the prevalence of dental caries in Queensland children. Community Dent Oral Epidemiol. 2015 Oct;43(5):397-405.	Included in NHMCR review
Do L, Spencer AJ. Contemporary multilevel analysis of the effectiveness of water fluoridation in Australia. Aust N Z J Public Health. 2015 Feb;39(1):44-50.	Included in NHMCR review
Haysom L, Indig D, Byun R, Moore E, van den Dolder P. Oral health and risk factors for dental disease of Australian young people in custody. J Paediatr Child Health. 2015;(51):545-51.	Included in NHMCR review
Fluoridation helps older adults keep their teeth, study finds. Journal of the American Dental Association (JADA). 2015 Aug;146(8):571.	Letter to editor
Jarquín-Yañez L, de Jesus Mejia-Saavedra J, Molina-Frechero N, Gaona E, Rocha-Amador DO, López-Guzmán OD, et al. Association between urine fluoride and dental fluorosis as a toxicity factor in a rural community in the state of San Luis Potosi. ScientificWorldJournal [Internet]. 2015 [cited 2017 Nov 6];2015:647184.	No comparison between F levels in drinking water
John J, Hariharan M, Remy V, Haleem S, Thajuraj PK, Deepak B, et al. Prevalence of skeletal fluorosis in fisherman from Kutch coast, Gujarat, India. Rocz Panstw Zakl Hig. 2015 [cited 2017 Nov 7];66(4):379-82.	No comparison between F levels in drinking water
Joshua AD, NethajiMariappan VE, Anne BM, Vadivel N. Evaluating fluoride contamination in ground water of Dharmapuri district in Tamilnadu. Journal of Chemical and Pharmaceutical Sciences [Internet]. 2015 [cited 2017 Nov 7];8(1):18-24.	No comparison between F levels in drinking water
Keshavarz S, Ebrahimi A, Nikaeen M. Fluoride exposure and its health risk assessment in drinking water and staple food in the population of Dayyer, Iran, in 2013. J Educ Health Promot [Internet]. 2015 [cited 2017 Nov 7];4:72.	No comparison between F levels in drinking water
Kim MJ, Kim HN, Jun EJ, Ha JE, Han DH, Kim JB. Association between estimated fluoride intake and dental caries prevalence among 5-year-old children in Korea. BMC Oral Health [Internet]. 2015 Dec 30 [cited 2017 Nov 6];15:169.	Irrelevant intervention
Klivitsky A, Tasher D, Stein M, Gavron E, Somekh E. Hospitalizations for dental infections: optimally versus nonoptimally fluoridated areas in Israel. J Am Dent Assoc. 2015 Mar;146(3):179-83.	Comparator: not <0.4 ppm
Koh R, Pukallus ML, Newman B, Foley M, Walsh LJ, Seow WK. Effects of water fluoridation on caries experience in the primary dentition in a high caries risk community in Queensland, Australia. Caries Res. 2015;49(2):184-91.	No multivariable analysis
Lalloo R, Jamieson LM, Ha D, Ellershaw A, Luzzi L. Does fluoride in the water close the dental caries gap between Indigenous and non-Indigenous children? Aust Dent J. 2015 Sep;60(3):390-6.	Included in NHMCR review
Lee HJ, Han DH. Exploring the determinants of secular decreases in dental caries among Korean children. Community Dent Oral Epidemiol. 2015 Aug;43(4):357-65.	Included in NHMCR review
Malin AJ, Till C. Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: An ecological association Children's Environmental Health. Environmental Health: A Global Access Science Source [Internet]. 2015 [cited 2017 Nov 7];14(1).	No comparison between F levels in drinking water
Matloob MH. Dental caries in Iraqi 12-year-olds and background fluoride exposure. Community Dent Health. 2015 Sep;32(3):163-9.	No comparison between F levels in drinking water
Molina-Frechero N, Gaona E, Angulo M, Sanchez PL, González González R, Nevárez Rascon M, et al. Fluoride exposure effects and dental fluorosis in children in Mexico City. Med Sci Monit. 2015 Nov 26;21:3664-70.	No comparison between F levels in drinking water
Department of Health and Human Services Federal Panel on Community Water Fluoridation. U.S. Public Health Service recommendation for fluoride concentration in drinking water for the prevention of dental caries. Public Health Rep [Internet]. 2015 Jul;130(4):318-31.	Guidelines
O'Sullivan V, O'Connell BC. Water fluoridation, dentition status and bone health of older people in Ireland [Malden, Massachusetts]. Community Dentistry & Oral Epidemiology. 2015 Feb;43(1):58-67.	No comparison between F levels in drinking water

Citation	Reason for exclusion
Ramezani G, Valaie N, Rakhshan V. The effect of water fluoride concentration on dental caries and fluorosis in five Iran provinces: A multi-center two-phase study. Dent Res J (Isfahan) [Internet]. 2015 Jan [cited 2017 Nov 7];12(1):31-7.	Irrelevant comparator
Warren JJ, Saraiva MC. No evidence supports the claim that water fluoridation causes hypothyroidism. J Evid-Based Dent Pract. 2015 Sep;15(3):137-9.	Summary and commentary
Young N, Newton J, Morris J, Morris J, Langford J, Iloya J, et al. Community water fluoridation and health outcomes in England: a cross-sectional study. Community Dent Oral Epidemiol. 2015 Dec;43(6):550-9.	Duplicate publication of a 2014 paper (Public Health England 2014)
Zhao MX, Zhou GY, Zhu JY, Gong B, Hou JX, Zhou T, et al. Fluoride exposure, follicle stimulating hormone receptor gene polymorphism and hypothalamus-pituitary-ovarian axis hormones in Chinese women. Biomed Environ Sci [Internet]. 2015 Sep [cited 2017 Nov 6];28(9):696-700.	Irrelevant outcomes
2014	
Blakey K, Feltbower RG, Parslow RC, James PW, Gomez PB, Stiller C, et al. Is fluoride a risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005. Int J Epidemiol [Internet]. 2014 Feb [cited 2017 Nov 7];43(1):224-34.	Included in NHMCR review
Chahal A, Bala M, Dahiya RS, Ghalaut VS. Comparative evaluation of serum fluoride levels in patients with and without chronic abdominal pain. Clin Chim Acta. 2014 Feb 15;429:140-2.	Water F only measured in cases
Chestnutt IG. Summary of: an alternative marker for the effectiveness of water fluoridation: hospital extraction rates for dental decay, a two-region study. Br Dent J. 2014 Mar;216(5):248-9.	Commentary
Cho HJ, Lee HS, Paik DI, Bae KH. Association of dental caries with socioeconomic status in relation to different water fluoridation levels. Community Dentistry & Oral Epidemiology. 2014 Dec;42(6):536-42.	No useful outcome data
Cho HJ, Jin BH, Park DY, Jung SH, Lee HS, Paik DI, et al. Systemic effect of water fluoridation on dental caries prevalence. Community Dent Oral Epidemiol. 2014 Aug;42(4):341-8.	Included in McLaren review
Do LG, Miller J, Phelan C, Sivaneswaran S, Spencer AJ, Wright C. Dental caries and fluorosis experience of 8-12-year-old children by early-life exposure to fluoride. Community Dent Oral Epidemiol. 2014 Dec;42(6):553-62.	Included in NHMCR review
Elmer TB, Langford JW, Morris AJ. An alternative marker for the effectiveness of water fluoridation: hospital extraction rates for dental decay, a two-region study. Br Dent J. 2014 Mar;216(5):E10.	Summary
Ha DH, Crocombe LA, Mejia GC. Clinical oral health of Australia's rural children in a sample attending school dental services. Aust J Rural Health. 2014 Dec;22(6):316-22.	Superseded data
Hong CH, Bagramian RA, Hashim Nainar SM, Straffon LH, Shen L, Hsu CY. High caries prevalence and risk factors among young preschool children in an urban community with water fluoridation. Int J Paediatr Dent. 2014 Jan;24(1):32-42.	No comparison between F levels in drinking water
Johnson NW, Lalloo R, Kroon J, Fernando S, Tut O. Effectiveness of water fluoridation in caries reduction in a remote Indigenous community in Far North Queensland. Aust Dent J. 2014 Sep;59(3):366-71.	No multivariable analysis
Jolaoso IA, Kumar J, Moss ME. Does fluoride in drinking water delay tooth eruption? J Public Health Dent. 2014;74(3):241-7.	Included in NHMCR review
Kale SS, Ghole VS, Pawar NJ, Jagtap DV. Inter-annual variability of urolithiasis epidemic from semi-arid part of Deccan Volcanic Province, India: climatic and hydrogeochemical perspectives. International Journal of Environmental Health Research. 2014 Jun;24(3):278-89.	No useful outcome data
Karimzade S, Aghaei M, Mahvi AH. IQ of 9-12-year-old children in high- and low-drinking water fluoride areas in west Azerbaijan Province, Iran: further information on the two villages in the study and the confounding factors considered. Fluoride. 2014;47(3):266-71.	Letter to editor
Karimzade S, Aghaei M, Mahvi AH. Investigation of intelligence quotient in 9-12-year-old children exposed to high- and low-drinking water fluoride in West Azerbaijan Province, Iran. Fluoride. 2014;47(1):9-14.	Included in NHMCR review
Kececi AD, Kaya BU, Guldas E, Saritekin E, Sener E. Evaluation of dental fluorosis in relation to DMFT rates in a fluorotic rural area of Turkey. Fluoride. 2014;47(2):119-32.	No comparison between F levels in drinking water
Levy SM, Warren JJ, Phipps K, Letuchy E, Broffitt B, Eichenberger-Gilmore J, et al. Effects of life-long fluoride intake on bone measures of adolescents: a prospective cohort study. J Dent Res [Internet].	No comparison between F levels in drinking water

Citation	Reason for exclusion
2014 Apr [cited 2017 Nov 7];93(4):353-9.	
Liu H, Gao Y, Sun L, Li M, Li B, Sun D. Assessment of relationship on excess fluoride intake from drinking water and carotid atherosclerosis development in adults in fluoride endemic areas, China. Int J Hyg Environ Health. 2014 Mar;217(2-3):413-20.	Included in NHMCR review
Marya CM, Ashokkumar BR, Dhingra S, Dahiya V, Gupta A. Exposure to high-fluoride drinking water and risk of dental caries and dental fluorosis in Haryana, India. Asia Pac J Public Health. 2014 May;26(3):295-303.	No statistical analysis
McLaren L. The impact of removing fluoridation from municipal water supplies in Canada: a tale of two cities. J Can Dent Assoc [Internet]. 2014 [cited 2017 Nov 15];80:e30.	Questions and answers
Nazemi S, Dehghani M. Drinking water fluoride and child dental caries in Khartooran, Iran. Fluoride. 2014;47(1):85-91.	Comparator: not <0.4 ppm F
Pawar AC, Naik SJK, Kumari SA. Cytogenetic analysis of human lymphocytes of fluorosis-affected men from the endemic fluorosis region in Nalgonda district of Andhra Pradesh, India. Fluoride. 2014;47(1):78-84.	No useful outcome data
Perez-Perez N, Torres-Mendoza N, Borges-Yanez A, Irigoyen-Camacho ME. Dental fluorosis: concentration of fluoride in drinking water and consumption of bottled beverages in school children. J Clin Pediatr Dent. 2014;38(4):338-44.	Received fluoridated salts
Schwartz GG. Eye cancer incidence in U.S. states and access to fluoridated water. Cancer Epidemiol Biomarkers Prev. 2014 Sep;23(9):1707-11.	Included in NHMCR review
Shanthi M, Reddy BV, Venkataramana V, Gowrisankar S, Reddy BV, Chennupati S. Relationship between drinking water fluoride levels, dental fluorosis, dental caries and associated risk factors in 9-12 years old school children of Nelakondapally Mandal of Khammam District, Andhra Pradesh, India: a cross-sectional survey. J Int Oral Health [Internet]. 2014 Jun [cited 2017 Nov 7];6(3):106-10.	Comparator: not <0.4 ppm F
Singh N, Verma KG, Verma P, Sidhu GK, Sachdeva S. A comparative study of fluoride ingestion levels, serum thyroid hormone & TSH level derangements, dental fluorosis status among school children from endemic and non-endemic fluorosis areas. Springerplus [Internet]. 2014 Jan 3 [cited 2017 Nov 7];3:7.	Included in NHMCR review
Skinner J, Johnson G, Blinkhorn A, Byun R. Factors associated with dental caries experience and oral health status among New South Wales adolescents. Aust N Z J Public Health. 2014 Oct;38(5):485-9.	No comparison between F levels in drinking water
Spittle B. Fluoride, IQ, and advice on type I and II errors. Fluoride. 2014;47(3):188-90.	Summary
Torjesen I. Water fluoridation almost halves hospital admissions for dental caries, report finds. BMJ. 2014 Mar 26;348:g2394.	Letter to editor
Vilasrao GS, Kamble KM, Sabat RN. Child fluorosis in Chhattisgarh, India: a community-based survey. Indian Pediatr. 2014 Nov;51(11):903-5.	Included in NHMCR review
Vincent J, Balakumar P. Assessment of fluoride concentrations of groundwater in Tiruchendur, Thoothukudi district, Tamilnadu by SPADNS method. International Journal of ChemTech Research. 2014;6(11):4807-9.	No useful outcome data
White BA, Gordon SM. Preventing dental caries through community water fluoridation. NC Med J. 2014 Nov;75(6):430-1.	Letter to editor
Zhang Y, Cheng R, Cheng G, Zhang X. Prevalence of dentine hypersensitivity in Chinese rural adults with dental fluorosis. J Oral Rehabil. 2014 Apr;41(4):289-95.	No comparison between F levels in drinking water

Appendix 8: Study and Report Characteristics — Review of Dental Caries and Other Health Outcomes

Table 59: Characteristics of the Updated Systematic Reviews

Author, Publication Year, Country, Funding Source	Review Methods and QA Tools Used	Study Types, and Numbers of Relevant Primary Studies Included	Intervention(s) and Comparator(s)	Outcomes Reported by Systematic Reviews	Subgroup Analyses of Interest Conducted
Jack et al. 2016 Australia NHMRC	Overview of SRs and SR of primary studies AMSTAR for SRs; SIGN checklists for cohort and case-control studies and NICE checklists for cross-sectional and ecological studies	3 SRs 66 primary studies (6 cohort studies; 49 ecological studies; 9 cross-sectional studies; and 2 case-control studies	Intervention: • Dental Caries: fluoride level 0.4ppm to 1.5ppm • Other health outcomes: fluoride at a given concentration Comparator: • Dental Caries: fluoride level < 0.4ppm • Other health outcomes: non-fluoridated or fluoridated drinking water at a different concentration	Outcomes for assessment of dental caries: • dmft and DMFT, respectively • dmfs and DMFS, respectively • Caries prevalence and proportion caries-free : deciduous and permanent teeth • Incidence of dental caries : permanent teeth • Combined caries measures Other dental outcomes: • Disparities • Tooth loss • Delayed tooth eruption • Tooth wear • Hospital admissions for caries • Dental fluorosis Other health outcomes: All-cause mortality, atherosclerosis, hypertension, osteosarcoma, Ewing sarcoma, total cancer incidence, skeletal fluorosis, hip fracture, osteoporosis, musculoskeletal pain, low birth weight, Down syndrome, IQ and cognitive function, thyroid function, kidney stones, chronic kidney disease, gastric discomfort, headache, insomnia, age of menarche, Alzheimer disease/impaired mental functioning, anaemia during pregnancy, birth rates, childhood behaviour problems, congenital malformations, coronary heart disease mortality, fetal	Overview of SRs: Presented evidence of subgroup analyses when reported SR of primary studies: NR

Author, Publication Year, Country, Funding Source	Review Methods and QA Tools Used	Study Types, and Numbers of Relevant Primary Studies Included	Intervention(s) and Comparator(s)	Outcomes Reported by Systematic Reviews	Subgroup Analyses of Interest Conducted
				and perinatal mortality, fractures (other than hip fractures), goitre, otosclerosis, primary degenerative dementia, slipped epiphysis, infant mortality, sudden infant death syndrome, thyroid cancer.	
McLaren and Singhal, 2016 Canada CIHR, PHAC, Alberta Innovates – Health Solutions	SR and MA of primary studies Cochrane Risk of Bias Tool	29 articles of 15 instances of fluoride cessation	Intervention: Cessation of CWF with the following reasons: • Aging infrastructure • Significant political/economic events • Lack of clarity about pertinent laws • Increased in dental fluorosis • Anti-fluoridation movements • Public vote Comparator: With or without a comparison community (fluoridated or non-fluoridated)	• DMFT • deft • DMFS • defs	NR

Table 60: Characteristics of Included Primary Studies for Research Question 1

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
PHE 2018[79] England Ecological Acceptable Partial	Children aged 5 years for prevalence of d3mft > 0 N = 111,455 Children and adolescents aged 0 to 19 years for hospital admissions for dental extraction due to dental caries N = 114,530,000 person-years	–	Fluoride level in water supply (regardless of source): < 0.1 ppm, 0.1 to < 0.2 ppm, 0.2 to < 0.4 ppm, 0.4 to < 0.7 ppm, ≥ 0.7 ppm	• Caries prevalence of deciduous teeth (d3mft > 0) • Incidence of hospital admissions due to dental caries	Multivariable regression	Age, gender, ethinicity
Aggeborn and Öhman 2017[69] Sweden Ecological Acceptable Partial	Individuals ≥ 16 years, who were born from 1985 to1992 and were participants in Swedish survey 2013 N = 437,987 to 725,286 Sex: NR	–	Naturally occurring fluoridated water with various CWF levels ≤ 1.5 ppm	• Visit dental clinic • Repair treatment (tooth filled) • Risk evaluation, health improvement measures • Disease prevention • Disease treatment • Root canal treatment	Multivariable regression	Sex, marital status, parent's education, parent's income, father's cognitive and non-cognitive ability, parent immigrant, cohort mean education [at birth, at school start, at 16 years age])
Aguiar et al. 2017[75] Brazil Ecological Low Limited	Children aged 12 years and 15 to 19 years, who were participants in a national representative survey in Brazil	–	• CWF (F level NR) • Non-CWF (F level NR)	Prevalence of DMFT (DT ≥1; MT ≥1; FT ≥1	Multilevel logistic regression	Age, gender, equivalent household income, time since last dental visit (years), interviewee's education (years of schooling), per capita gross domestic product, population size

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
	N = 10,124 Sex: NR					
Do et al. 2017[73] Australia Ecological Acceptable Partial	Individuals aged 15 to 91 years, who participated in the Australian National Survey of Adult Oral Health 2004-2006 N = 4,090 Sex: NR	15 to 34 years 35 to 44 years 45 to 54 years 55+ years	Per cent life time access to the equivalent of 1.0 ppm fluoride in drinking water	Mean DMFS	Multivariable regression	Age, sex, residential location, dental visit pattern, toothbrushing frequency, household income, and oral hygiene
Heima et al. 2017[76] USA Cross-sectional Low Partial	Chart review of children aged 5 months to 5 years N = 388 Sex: 51.5% male	–	• CWF (F level NR) • Non-CWF (F level NR)	Mean dt	Negative binomial regression	Children demographics (age, gender, Medicaid, total number of primary teeth) and social demographic factors (total number of Medicaid dentists, population/1000)
Kim et al. 2017[71] South Korea Cross-sectional Low Partial	School children aged 6, 8, 11 years from two biggest primary schools in CWF area and three biggest primary schools in non-CWF area N = 1,411 Sex: NR	6 years 8 years 11 years	• CWF (F level NR) • Non-CWF (F level NR)	• Mean DMFT • Mean DMFS • Mean pit and fissure DMFS • Mean smooth surface DMFS	Multilevel logistic regression	Sex, monthly family income, householder educational level, Family Affluence Scale score, and number of sealed teeth
Spencer et al. 2017[74] Australia Cross-sectional	Adults aged 20 to 35 years were traced from the previous sample recruited	Access to CWF: • Early in life • Across maturation to	Percent life time access to fluoridated water: • 0 to 74%	• Mean DMFS • Caries prevalence (% DMFS>0)	Negative binomial regression	Age, sex, parents' education, education of self as a young adult, toothbrushing as a child and as a young adult

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Low Partial	into previous studies in 1991/92, when children had been 5 to 17 years old N = 1,220 Sex: 50.5% male	young adulthood • Life time	• 75 to 99% • 100%			
Arrow 2016[74] Australia Cross-sectional Acceptable Partial	Schoolchildren aged 5 to 15 years old, who presented for a dental examination in 2014 at the Western Australia School Dental Service N = 10,108 Sex: 48.5% male	5 to 10 years 6 to 15 years	• CWF (F level NR) • Non-CWF (F level NR)	• Mean dmft • Mean DMFT •	Negative binomial regression	Age, gender, sealants, Aboriginality, SES, interval between dental checkup, region, inflammation
Chalub et al. 2016[80] Brazil Cross-sectional Low Limited	Adults aged 35 to 44 years who participated in the 2010 National Oral Health Survey 2010 N = 9,564 Sex: 36.6% male	–	• CWF (F level NR) • Non-CWF (F level NR)	Functional dentition	Multi-level mixed-effect Poisson regression	Gender, self-declared skin colour, schooling, monthly household income, age group, self-rated treatment need, dental appointment in the previous 12 months, dental services and 2010 Municipal Human Development Index
Cho et al. 2016[82] South Korea Ecological Low Partial	National Health Insurance Service National Sample Cohort 2003 to 2013 of individuals aged <19 to >70 years	<19 years 20 to 29 years 30 to 39 years 40 to 49 years 50 to 59 years 60 to 69 years >70 years	• CWF (F level NR) • Non-CWF (F level NR)	• Percentage of patients experienced an outpatient dental visit • Number of dental care visits • Dental care costs	Cox proportional hazard model, and negative binomial regression	Regional variables (period from introduction of water fluoridation, number of dentists, financial independence rate of local government), and Individual variables (sex, age, income, type of insurance, year of baseline,

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
	N = 472,250 Sex: 50.7% male					dental facial anomalies, disorders of tooth development, and eruption)
Crocombe et al. 2016[70] Australia Ecological Low Partial	Individuals ≥ 15 years, who were participants in the Australian National Survey of Adult Oral Health 2004 to 2006 N = 3,770 Sex: 48.5% male	–	Mean lifetime exposure: • 59.1% (capital cities) • 42.3% (non-capital cities)	Mean DMFT	Multivariable regression	Age, income, education, time brushed, and access to dental care
Crouchley and Trevithick 2016[68] Australia Ecological Low Partial	Children 5 to 12 years old who presented at selected at Dental Treatment Centres in the non-fluoridated areas of the southwest of Western Australia and the fluoridated Perth metropolitan region from January 2011 to December 2012 N = 10,825 Sex: NR	5 to 9 years 6 to 12 years	• CWF (F level NR) • Non-CWF (F level NR)	• Mean dmft • Mean DMFT • Caries prevalence (% dmft > 0) • Caries prevalence (% DMFT > 0) • SiC[10] scores for deciduous teeth • SiC[10] scores for permanent teeth	Multivariable regression	Age, sex, aboriginal status, and having a record of an initial examination at a Dental Treatment Centre
Ha et al. 2016[77] Australia Ecological Low Partial	Indigenous children aged 5 to 15 years, who enrolled in School Dental Services, South	5 to 10 years 6 to 15 years	• CWF (> 0.5 ppm) • Non-CWF (≤ 0.5 ppm)	• Mean dmft • Mean DMFT	Multivariable regression	Time trend, SES, and remoteness

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
	Australia N = 18,067 Sex: NR					
Peres et al. 2016[72] Brazil Cross-sectional Low Limited	Adults aged 20 to 59 years from a population-based cohort study 2009 in a city of southern of Brazil N = 209 Sex: 44% male	–	Life time access to fluoridated water: • > 75% • 50% to 75% • < 50%	Mean DMFT	Multiple negative binomial regression	Sex, age, education, income, SES, pattern of dental attendance, and smoking
Schluter and Lee 2016[78] New Zealand Ecological Low Partial	Children aged 5 years and 12 to 13 years who received dental treatment in New Zealand's child oral health services between 2004 and 2013 N = 417,318 (5 years) N = 417,333 (12 to 13 years) Sex: NR	5 years (Maori, non-Māori) 12 to13 years (Maori, non-Maori)	• CWF 0.7 to 1.0 ppm) • Non-CWF (< 0.2 ppm)	• Mean dmft • Mean DMFT • Caries-free prevalence (% dmft = 0) • Caries-free prevalence (% DMFT = 0)	Unweighted linear regression	Age, ethnicity, and year of data collection
Babarto et al. 2015[81] Brazil Cross-sectional Low Limited	Adults aged 20 to 59 years residing in the city of Florianopolis, Southern Brazil N = 1,720 Sex: 44.2% male	–	CWF availability: • 27 years • 13 years	Tooth loss	Multilevel logistic regression	SES, gender, age, years of education, household income per capita, and length of residence in the same location

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Blinkborn et al. 2015[67] Australia Cross-sectional Low Partial	Children aged 5 to 7 years in the first year of Public and Catholic Schools in three areas of New South Wales, Australia N = 2,129 Sex: 49.9% male	–	• CWF (F level NR) • Pre-CWF (F level NR) • Non-CWF (F level NR)	• Mean dmft • Caries-free prevalence • SiC[30] scores for deciduous teeth	Multivariable regression	Age, gender, Indigenous status, cardholder status, and mother’s country of birth

CWF = community water fluoridation; dmfs/DMFS = decayed, missing, or filled deciduous/permanent tooth surface; dmft/DMFT = decayed, missing, or filled deciduous/permanent teeth; F = fluoride; NR = not reported; SiC = significant caries index; SES = social-economic status.

[a] Applicability to Canadian context (based on conditions such as water fluoride level, health and dental care system, and socio-economic factors [e.g., income and education levels]).

Table 61: Characteristics of Included Primary Studies for Research Question 2

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
McLaren et al. 2017[83] Canada Pre-post cross-sectional Acceptable High	Grade 2 children (~7 years old) from public or catholic school systems in Calgary and Edmonton, Alberta N = 11,689 Sex: NR	–	Calgary, fluoridated (ranged 0.59 ppm to 0.89 ppm) until 2011 (ranged 0.07 ppm to 0.30 ppm) Edmonton, continued fluoridation (average 0.7 ppm)	• Mean dmft • Caries prevalence (% dmft>0) • Mean DMFT • Caries prevalence (% DMFS>0)	Multivariable regression	General health of child's mouth, brush twice daily, visit dentist only for emergency or never, last visit dentist within the last year, fruit and vegetable at least once a day, sugar drink at least once a day, fluoride treatment at dentist office, household education of bachelor's degree or higher, home ownership, ethno-cultural background, and age
McLaren et al. 2016a[85] Canada Pre-post cross-sectional Acceptable High	Grade 2 children (~7 years old) from public or catholic school systems in Calgary and Edmonton, Alberta N = 12,581 Sex: NR	–	Calgary, fluoridated (ranged 0.59 ppm to 0.89 ppm) until 2011 (ranged 0.07 ppm to 0.30 ppm) Edmonton, continued fluoridation (average 0.7 ppm)	• Mean defs • Mean DMFS	Weighted analyses	–
McLaren et al. 2016b[86] Canada Pre-post cross-sectional Acceptable High	Grade 2 children (~7 years old) from public or catholic school systems in Calgary and Edmonton, Alberta N = 3,787 Sex: NR	–	Calgary, fluoridated (ranged 0.59 ppm to 0.89 ppm) until 2011 (ranged 0.07 ppm to 0.30 ppm) Edmonton, continued fluoridation (average 0.7 ppm)	• Mean defs • Mean DMFS	Zero-inflated Poisson regression or logistic regression	SES: dental insurance and material deprivation (Pampalon index based on income, employment, and education)
PHE 2015[84] UK Pre-post cross-sectional Low Partial	Data from dental survey of children aged 5 years living in Bedford Borough in 2008 (water fluoridation) and in 2015 (water fluoridation cessation), conducted by the National Dental Public	Index of Multiple Deprivation (IMD): 1 (most deprived, 2, 3, 4, 5 (most affluent)	Pre-cessation: 0.51 to 0.83 ppm Cessation: 0.24 to 0.26 ppm	• Mean dmft • Caries prevalence (% dmft>0) • Perception of fluorosis (12 years old children)	Chi-square test	–

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
	Health Epidemiology Programme in England N = 1,873 Sex: NR					

defs = decayed, missing, extracted, filled deciduous tooth surface; dmfs/DMFS = decayed, missing or filled deciduous/permanent tooth surface; IMD = Index of Multiple Deprivation; NR = not reported; ppm = parts per million; SES = socio-economic status.

[a] Applicability to Canadian context (based on conditions such as water fluoride level, health and dental care system, and socio-economic factors [e.g., income and education levels]).

Table 62: Characteristics of Included Primary Studies for Research Question 3

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Chafe et al. 2018[129] Canada Case-control Low High	Children aged 0 to 14 years Communities with at least one case of type 1 diabetes and communities had no cases in Newfoundland and Labrador, Canada Cases: 499 Controls: NR Sex: NR	–	Components in public water supply including fluoride ion	– Type 1 diabetes	One-way ANOVA; linear regression analysis	–
Khandare et al. 2018[112] India Cross-sectional Low Limited	Children aged 8 to 14 years living in areas having different fluoride levels N = 1,934 Sex: 46.7% boys	–	NOF • 3.77 ppm • 2.53 ppm • < 1 ppm (initial was 4.515 ppm followed by intervention with safe drinking water for 5 years) • 0.877 ppm	• Dental fluorosis prevalence • Biomarkers measured from blood tests	Chi-square test	–
Kheradpisheh et al. 2018[123] Iran Case-control Low Limited	Participants aged 20 to 70 years from the Yazd Healthy Study project N = 411 Sex: • Cases: 19.2% male • Controls: 41.3% male	–		Thyroid function (T3, T4, and TSH)	Multivariable logistic regression analysis	Gender, family history of thyroid disease, amount of water consumption, exercise, diabetes, and hypertension
Moghaddam et al. 2018[126] Iran	Pregnant women living in areas having different fluoride levels	–	NOF • ≥ 3 ppm (n = 70) • 1.5 ppm to	Abortion	Multilevel Poisson regression analysis	–

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Cross-sectional Low Limited	N = 2,601 Sex: 100% female		3.00 ppm (n = 43) • ≤ 1.5 ppm (n = 2,488)			
PHE 2018[79] England Ecological Acceptable Partial	Hip fracture: Age 0 to 80+ years (2007 to 2015) N = 477,610,000 person-years Kidney stone: Age NR (2007 to 2015) N = 477,610,000 person-years Down's syndrome: Live births (2012 to 2014) N = 2,020,259 Bladder cancer: Age NR (2007 to2015) N = 827,660,000 person-years Osteosarcoma: Age 0 to 49 years (1995 to 2015) N = 710,260,000 person-years	By age for hip fracture	Fluoride level in water supply (regardless of source): <0.1 ppm, 0.1 to <0.2 ppm, 0.2 to <0.4 ppm, 0.4 to <0.7 ppm, ≥0.7 ppm	• Hip fracture • Kidney stone • Down's syndrome • Bladder cancer • Osteosarcoma	Multivariable regression	Age, gender, ethnicity, and deprivation status
Yousefi et al. 2018[113] Iran Cross-sectional Low Limited	Residents aged 27 to 43 years living in two villages in the Northwest part of Iran N = 360 Sex: 45.7% male	–	NOF • 10.15 ppm • 0.75 ppm	Hypertension	Chi-square test, multivariable logistic regression	Age, sex, BMI, and waist circumference
Aggeborn and Öhman 2017[69] Sweden Ecological Acceptable	Individuals ≥ 16 years, who were born from 1985 to1992 and were participants in Swedish survey 2013	–	NOF with fluoride levels in the community water ≤1.5 ppm. De-fluoridation is	• Cognitive ability (up to age 18) • Non-cognitive ability (up to age 18) • Math test (ninth grade)	Multivariable regression	Covariate group 1 = sex, marital status Covariate group 2 = parent's education, parent's income,

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Partial	N = 17,864 to 728,074 Sex: NR		conducted when fluoride level exceeds 1.5 ppm	• Log annual labour income • Log employment status		father's cognitive and non-cognitive ability, parent immigrant, cohort mean education [at birth, at school start, at 16 years age])
Arora et al. 2017[91] USA Ecological Acceptable Partial	Children aged 7 to 11 years and 12 to 17 years, who were participants in the National Survey of Oral Health of US School Children 1986 to 1987 N = 16,060 Sex: 51.8%	• White, Non-Hispanic • Black, Non-Hispanic • Hispanic • Others	Water fluoridation • < 0.3 ppm • 0.3 ppm to <0.7 ppm • 0.7 ppm to 1.2 ppm	Dental fluorosis prevalence	Logistic regression	Age, gender, race/ethnicity, other sources of fluoride, region
Barberio et al. 2017a[120] Canada Ecological Low High	Children aged 3 to 12 years living in private households in the 10 provinces, who were participants of the Statistics Canada's Canadian Health Measures Survey – Cycle 2 (2009 to 2011) and Cycle 3 (2012 to 2013) N = 1,844 from Cycle 2 Gender: 52% male N = 1,726 from Cycle 3 Sex: 51% male	–	Determined from urine fluoride levels (Cycle 2 [2009 to 2011]) and tap water fluoride levels (Cycle 3 [2012 to 2013])	• Parental- or self-reported learning disability • Parental- or self-reported diagnosis of ADHD • Parental- or self-reported diagnosis of ADD	Logistic regression	Age, sex, household income adequacy, and highest attained education in the household
Barberio et al. 2017b[124] Canada	Canadians aged 3 to 79 years living in private households in the 10	–	Determined from urine fluoride levels (Cycle 2 [2009 to	• Self-reported diagnosis of thyroid condition • TSH level	Logistic regression	Age, sex, household income adequacy, and highest attained

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Ecological Acceptable High	provinces, who were participants of the Statistics Canada's Canadian Health Measures Survey – Cycle 2 (2009 to 2011) and Cycle 3 (2012 to 2013) N = 1,844 from Cycle 2 Gender: 49.9% male N = 1,726 from Cycle 3 Sex: 49.9% male		2011]) and tap water fluoride levels (Cycle 3 [2012 to 2013])	• Blood test for primary hypothyroidism (TSH, free T4, antithyroid peroxidase, antithyroglobulin)		education in the household
Bonola-Gallardo et al. 2017[103] Mexico Cross-sectional Low Limited	Schoolchildren aged 9 to 12 years from public elementary schools located in the state of Morelos in South-Central Mexico N = 141 Sex: 39.8% male	–	NOF • 1.8 ppm • 0.4 ppm	Dental fluorosis prevalence	Chi-square test	–
Garcia-Perez et al. 2017[104] Mexico Cross-sectional Low Limited	Schoolchildren aged 8 to 12 years from public elementary schools located in a rural region in the southeast of the state of Morelos, Central Mexico N = 524 Sex: NR	–	NOF • 1.6 ppm • 0.7 ppm	Dental fluorosis prevalence	Chi-square test	–
Ibiyemi et al. 2017[109] Nigeria Cross-sectional	Schoolchildren aged 8 years living in lower and higher water fluoridation	–	NOF • Urban, higher F: 0.85 (0.19) ppm;	Dental fluorosis prevalence	Multiple multilevel logistic regression	Age, gender, exclusive breastfeeding, age breastfeeding ceased,

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Low Limited	areas of rural and urban parts of Oyo state on south-west Nigeria N = 322 Sex: 48.1% male		Rural, higher F: 2.13 (0.64) ppm • Urban, lower F: 0.07 (0.02) ppm; Rural, lower F: 0.09 (0.02) ppm			infant/childhood disease, age of toothbrushing, frequency of toothbrushing, amount of toothpaste used per brushing, fluoride toothpaste ingestion, normal birth, family history of tooth discoloration
Khandare et al. 2017[96] India Cross-sectional Low Limited	School children aged 8 to 15 years from 8 rural areas of the Doda district, India N = 824 Sex: 60.0% male	–	NOF • 1.43 ppm to 3.84 ppm • 0.32 ppm to 1.18 ppm	• Dental fluorosis prevalence • Kidney function (creatinine) • Thyroid function (PTH, T3, T4, TSH, vitamin D) • Bone metabolic indicators (osteocalcin)	Chi-square test	–
Mohammadi et al. 2017[117] Iran Cross-sectional Low Limited	Adults aged ≤ 40 years old and 41 to ≥ 70 years old from five villages of Poldasht, Iran N = 915 Sex: NR	• Male • Female	NOF • High: 4.02 ppm, 7.63 ppm, 10.15 ppm • Low: 0.68 ppm, 0,79 ppm	Skeletal fluorosis prevalence	Multiple multilevel logistic regression	Age, sex, fast food, and dairy consumption
Rango et al. 2017[107] Ethiopia Cross-sectional Low Limited	Participants aged 10 to 59 years from 27 rural communities in the Ethiopian rift valley N = 386 Sex: NR	Four age groups: • 10 to 15 years • > 15 to 25 years • > 25 to 35 years • > 35 to 50 years	Well water fluoride concentrations varied from 0.6 ppm to 1.5 ppm	Dental fluorosis prevalence	Multivariable regression	Age, sex, and BMI

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Razdan et al. 2017[97] India Cross-sectional Low Limited	Children aged 12 to 14 years in three villages of India N = 219 Sex: NR	–	NOF • 4.99 ppm • 1.70 ppm • 0.6 ppm	• Dental fluorosis prevalence • IQ	Chi-square test	–
Yousefi et al. 2017[127] Iran Cross-sectional Low Limited	Women aged 10 to 49 years living in five villages of Poldasht county, Iran N = 3,392 Sex: NR	–	NOF • 8.10 ppm • 1.90 ppm	Fertility, infertility, and abortion prevalence	Chi-square test	–
Aravind et al. 2016[121] India Cross-sectional Low Limited	Children aged 10 to 12 years from three villages in India N = 288 Sex: 49.0% male	• Male • Female	NOF • > 2 ppm • 1.2 ppm to 2 ppm • < 1.2 ppm	• Mean IQ scores • Prevalence of different intellectual levels	ANOVA, Student’s *t*-test, Spearman’s rank correlation coefficient	–
Archer et al. 2016[115] USA Population-based case-control Acceptable Partial	Cases: Children and adolescents aged 0 to 19 years who reported to the Texas Cancer Registry and were diagnosed with primary malignant osteosarcoma between January 1, 1996 and December 31, 2006. Controls: Children and adolescents (0 to 19 years) with either central nervous system tumours or leukemia during the same time period. N = 1,510	• Male • Female	Public water system fluoride levels • > 1.3 ppm • 0.7 ppm to 1.22 ppm • 0 ppm to 0.6 ppm	Osteosarcoma	Logistic regression	Age, sex, race/ethnicity, and percent of census tract below poverty index

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
	Sex: 56.4% male					
Bin et al. 2016[128] China Cross-sectional Low Limited	Residents aged ≥ 40 years from four counties in Northern China N = 1,415 Sex: 72.0% male	–	NOF • 1.47 ppm • 0.2 ppm	Prevalence of myopia, hyperopia, astigmatism	Multiple linear regression	Age
Fluegge 2016[130] USA Ecological Low Partial	Participant data were obtained from the County Data Indicators profile of the Diabetes Data and statistics portal through the CDC N = NR Sex: NR	–	CWF • 0.71 ppm ± 0.31 ppm (added fluoride) • 0.23 ppm ± 0.27 ppm (natural fluoride)	Diabetes incidence and prevalence	Regression analysis using generalized estimating equations (GEE)	Physical inactivity, obesity, poverty, log population per square mile, mean of years fluoridated and year
Irigoyen-Camacho et al. 2016[105] Mexico Cross-sectional Low Limited	Children aged between 8 and 12 years living in three communities with different well water fluoride concentrations in Mexico N = 734 Sex: 49.2% male	–	NOF • 1.60 ppm • 0.70 ppm • 0.56 ppm	Dental fluorosis prevalence	Multiple logistic regression	Sex, number of teeth, source of drinking water, use of fluoridated toothpaste and weight-for-age (or height-for-age)
Mahantesha et al. 2016[98] India Cross-sectional Low Limited	Children aged 9 to 15 years in three villages in India N = 289 Sex: NR	–	NOF • 1.36 ppm • 0.381 ppm • 0.136 ppm	Prevalence and severity of dental fluorosis	Multiple logistic regression	Tea consumption, nutritional status and water consumption
Nasman et al. 2016[131] Sweden	Individuals aged 44 to 87 years from several nationwide registers, alive	Gender: • Male • Female	NOF • ≥ 1.5 ppm • 0.7 ppm to	Myocardial infarction	Cox proportional hazard regression model	Sex, age, calendar period for study entry, geographical area of

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Ecological Low Partial	and living in municipalities of birth at the time of start of follow-up N = 455,619 Sex: 54.1% male	Age: • < 65 years • ≥ 65 years	< 1.5 ppm • 0.3 ppm to <0.7 ppm • < 0.3 ppm			residence and water hardness
Pretty et al. 2016[93] UK Cross-sectional Low Partial	Schoolchildren aged 11 to 14 years from four English cities, who were participants in a survey N = 1,904 Sex NR	–	• CWF (1.0 ppm) • Non-CWF (F level NR)	• Dental fluorosis prevalence • Response rate to self-perceived aesthetic score	Chi-square test	–
Ramadan and Ghandour 2016[110] Sudan Cross-sectional Low Limited	Residents in two communities, mean age 17.43 years and 16.9 years, range 6 to 63 years N = 800 Sex: NR	6 to 8 years 10 to 12 years 15 to 20 years ≥ 25 years	NOF • 1.36 ppm • 0.45 ppm	Dental fluorosis prevalence	Chi-square test	–
Sebastian et al. 2016[99] India Cross-sectional Low Limited	School children aged 10 to 12 years, born and raised in three villages of Mysore district N = 405 Sex: 50.4% male	–	NOF • 2.0 ppm • 1.2 ppm • 0.4 ppm	Dental fluorosis prevalence	Chi-square test Spearman's rank correlation coefficient	–
Shruthi et al. 2016[118] India Cross-sectional Low Limited	Adults aged 20 to 90 years living in three villages with fluoride concentrations of 4.13 ppm, 2.59 ppm and 0.61 ppm were divided into two groups	–	NOF • > 1.5 ppm • < 1.0 ppm	Skeletal fluorosis prevalence	Chi-square test	–

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
	N = 680 Sex: NR					
Aghaei et al. 2015a[119] Iran Cross-sectional Low Limited	Babies born during 2013 from 35 villages and towns in Zarand county, Iran N = 492 Sex: NR	–	NOF • > 1.5 ppm • 0.7 ppm to 1.5 ppm • < 0.7 ppm	• Babies' height • Birthweight	Chi-square test, Pearson's correlation	–
Aghaei et al. 2015b[114] Iran Cross-sectional Low Limited	Adults aged 20 to 65 years living in high and low fluoride areas in West Azerbaijan, Iran N = 2,878 Sex: 48.6% male	• Male • Female	NOF • 3.94 ppm • 0.25 ppm	Hypertension	Logistic regression	Age, sex
Bal et al. 2015[92] Australia Cross-sectional Low Partial	School children aged 7 to 11 years in the Blue Mountains and Hawkesbury local government area of New South Wales, Australia N = 1,326 Sex: NR	–	Lifetime fluoride exposure: • 100% • 1% to 99% • 0%	Dental fluorosis prevalence	Logistic regression	Frequency of toothbrushing, rinsing habit after toothbrushing, licked or ate toothpaste
Balmer et al. 2015[94] UK Cross-sectional Low Partial	Children of 12 years participating in the 2008-2009 National Dental Epidemiological Programme in five regions in Northern England N = 3,233	–	• CWF (F level NR) • Non-CWF (F level NR)	Prevalence of molar incisor hypomineralization	Binary logistic regression	Gender and index of multiple deprivation

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
	Sex: NR					
Khan et al. 2015[122] India Cross-sectional Low Limited	Children aged 6 to 11 years from areas in and around Lucknow district, India N = 429 Sex: 52.9% male	–	NOF • 2.41 ppm • 0.19 ppm	Prevalence of different IQ grades	Chi-square test	–
Moimaz et al. 2015[106] Brazil Cross-sectional Low Limited	All children aged 12 years registered in public schools of Birigui, Sao Paulo, Brazil N = 496 Sex: 47.8% male	–	NOF • 1.2 ppm • 0.7 ppm	Dental fluorosis prevalence	Fisher's test	–
Peckham et al. 2015[125] UK Cross-sectional Low Partial	Individuals aged 40 years and over from two areas in England (Secondary data from the National General Practice Profiles in England) N = 7,935 Sex: 50.1% male	–	Fluoridated water • > 0.7 ppm • > 0.3 ppm to ≤ 0.7 ppm • ≤ 0.3 ppm	Hypothyroidism prevalence	Binary logistic regression	Proportion of women registered with the practice, proportion of patients over 40 years old registered with the practice, and Index of Multiple Deprivation
Sebastian and Sunitha 2015[100] India Cross-sectional Low Limited	Children aged 10 to 12 years in three villages of Mysore district, India N = 405 Sex: NR	–	NOF • 2.0 ppm • 1.2 ppm • 0.4 ppm	• Dental fluorosis prevalence • Mean IQ score • IQ prevalence	Binary logistic regression	Age, gender, parental education and family income
Punitha et al. 2014[101] India Cross-sectional	Children aged 7 to 15 years attended schools in five villages in India	–	NOF • 2.05 ppm • 0.47 ppm	Dental fluorosis prevalence	Chi-square test	–

Study Country Design Quality Applicability[a]	Population	Subgroups	Exposures	Outcomes	Statistical analysis	Adjustment for confounders
Low Limited	N = 348 Sex: 52.9% male					
Rango et al. 2014[108] Ethiopia Cross-sectional Low Limited	Children aged 10 to 15 years from 33 rural communities (out of 94) where ground water was the main source of drinking water N = 491 Sex: 47.7% male	–	Fluoride levels varies from 1.06 ppm to 18.0 ppm	Dental fluorosis prevalence	Multivariable regression	Age, sex, BMI, and breast feeding duration
Sukhabogi et al. 2014[102] India Cross-sectional Low Limited	Schoolchildren aged 12 and 15 years in Nalgonda district, Andhra Pradesh, India N = 1,875 Sex: 47.9% male	• 12 years • 15 years	NOF • 4.0 ppm to 6.28 ppm • 1.2 ppm to < 4.0 ppm • 0.7 ppm to < 1.2 ppm • < 0.7 ppm	Dental fluorosis prevalence	Chi-square test; Spearman's correlation	--
Wong et al. 2014[111] Hong Kong Cross-sectional Low Limited	Data from the photographic slides of children aged 12 years were taken from the four previous epidemiological surveys in Hong Kong (1983, 1991, 2002 and 2010) N = 2,658 Sex: NR	–	CWF • 1.0 ppm (1983) • 0.7 ppm (1991) • 0.5 ppm (2001) • 0.5 ppm (2010)	Prevalence of diffuse opacities	Chi-square test	–

ADD = attention deficit disorder; ADHD = attention deficit hyperactive disorder; CWF = community water fluoridation; IMD = Index of Multiple Deprivation; IQ = intelligence quotient; NOF = naturally occurring fluoride; ppm = parts per million; PTH = parathyroid hormone; SES = socio-economic status; T3 = total triiodothyronine; T4 = total thyroxine; FT4 = free thyroxine; TSH = thyroid-stimulating hormone.

[a] Applicability to Canadian context based on conditions such as water fluoride level, health and dental care system, and socio-economic factors (e.g., income and education levels).

Appendix 9: Completed Quality Assessment and Data Extraction for Included Primary Studies

Table 63: Research Question 1 Quality Assessment and Data Extraction

PHE 2018[79]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Study set in England
1.2	Is the eligible population or area representative of the source population or area?	++	Study includes all of England, multiple registers used for all the outcomes
1.3	Do the selected participants or areas represent the eligible population or area?	++	Area level analysis including all of England
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Fluoridation levels grouped in to 5 categories
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Most important confounders adjusted for
2.5	Is the setting applicable to Canada?	+	May be applicable to Canada due to similar health care context
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Trained dental examiner for dental outcomes, registers for other outcomes may be potential bias
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	++	Benefits and harms assessed
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	+	No sample size calculation , country wide study
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	++	Multivariate analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	P-values and CIs provided
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	++	Most confounders adjusted for, representative of the general population, appropriate statistical methods
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	May be applicable to the Canadian population
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	Water fluoridation: Health monitoring report for England 2018
Author(s)	Public Health England
Publication year	2018
Country (where the study was conducted):	England
Funding sources	Government of UK
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To determine the association between concentration of fluoride in public water supply in England and selected dental outcomes
Study design	Ecological
Study location	England
Study duration	NA
Exposure duration	Lifetime since birth
Fluoride levels or Exposures:	
• Intervention and comparator	Fluoride level in water supply (regardless of source): < 0.1 ppm, 0.1 to < 0.2 ppm, 0.2 to < 0.4 ppm, 0.4 to < 0.7 ppm, ≥ 0.7 ppm
Setting	National
Source of population	Children aged 5 years for d3mft, prevalence of d3mft>0, and participants aged 0 to 19 years for hospital admissions for dental extraction due to dental caries
Inclusion/exclusion criteria	Populations in receipt of public water supplies
Recruitment or sampling procedure	Population data obtained from the Census and related mid-year estimates computed by the Office of National Statistics
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited
PARTICIPANT CHARACTERISTICS	
Number of participants	N = 111,500 five-year-old children for d3mft and prevalence of d3mft > 0 N = 114,530,000 person-years for hospital admissions for dental extraction due to dental caries
Gender	NR
Subgroups	By deprivation (quintile of index of multiple deprivation)

REPORTED OUTCOMES	
Definition (with units) and method of measurement	- Mean d3mft - Prevalence of caries experience (d3mft > 0) - Hospital admissions for dental extraction due to dental caries
Number of participants analysed	N = 111,500 five-year-old children for d3mft and prevalence of d3mft > 0 N = 114,530,000 person-years for hospital admissions for dental extraction due to dental caries
Number of participants excluded or missing (with reasons)	45 (did not have a fluoride concentration or fluoridation status allocated)
Imputing of missing data	NR
Statistical method of data analysis	Multivariable analysis adjusting for confounders (age, gender, deprivation and ethnicity)
Results	

Mean d3mft in children aged 5 years (2009 to 2015)

Fluoride levels (ppm)	Weighted* mean d3mft (95% CI)
< 0.1	0.92 (0.90 to 0.93)
0.1 to < 0.2	0.89 (0.88 to 0.90)
0.2 to < 0.4	0.71 (0.69 to 0.72)
0.4 to < 0.7	0.81 (0.79 to 0.84)
≥ 0.7	0.59 (0.57 to 0.60)

*By sample size.

- Mean d3mft decreased by 36% between areas with fluoride level of <0.1 ppm (0.92 d3mft) and areas with fluoride level of ≥0.7 ppm (0.59 d3mft).

Dental caries prevalence in children aged 5 years (2014 to 2015)

Fluoride levels (ppm)	dmft prevalence (%) (95% CI)	Crude OR (95% CI)	*P* value
< 0.1	26.3 (25.8 to 26.8)	Ref (1)	--
0.1 to < 0.2	25.5 (25.1 to 25.9)	0.96 (0.92 to 1.00)	0.03
0.2 to < 0.4	21.8 (21.2 to 22.4)	0.78 (0.74 to 0.82)	< 0.001
0.4 to < 0.7	24.3 (23.2 to 25.4)	0.90 (0.83 to 0.97)	0.007
≥ 0.7	20.7 (20.0 to 21.4)	0.73 (0.69 to 0.77)	< 0.001

- Dental caries prevalence (d3mft > 0) decreased by 5.6% (20.7% minus 26.3%) between areas with fluoride level of ≥ 0.7 ppm and areas with fluoride level of <0.1 ppm.
- Adjustment for ethnicity in the model significantly improved model fit (*P* < 0.001 indicating an independent association between ethnicity and d3mft).

Disparity in caries prevalence in children aged 5 years (2014 to 2015), by fluoride level and stratified by index of multiple deprivation (IMD)

Quintile of IMD	Fluoride level (ppm)	Adjusted OR (95% CI)[a]	*P* value
1 (least deprived)	< 0.1	Ref (1)	–
	0.1 to < 0.2	0.96 (0.87 to 1.06)	0.451
	0.2 to < 0.4	0.92 (0.81 to 1.04)	0.163
	0.4 to < 0.7	0.99 (0.78 to 1.26)	0.957
	≥ 0.7	0.77 (0.61 to 0.91)	0.002
2	< 0.1	Ref (1)	–
	0.1 to < 0.2	1.01 (0.92 to 1.10)	0.865
	0.2 to < 0.4	0.92 (0.82 to 1.03)	0.132
	0.4 to < 0.7	0.77 (0.64 to 0.94)	0.009
	≥ 0.7	0.72 (0.63 to 0.84)	< 0.001
3	< 0.1	Ref (1)	–

Quintile of IMD	Fluoride level (ppm)	Adjusted OR (95% CI)[a]	*P* value
	0.1 to < 0.2	0.99 (0.91 to 1.08)	0.893
	0.2 to < 0.4	0.94 (0.84 to 1.05)	0.277
	0.4 to < 0.7	0.89 (0.75 to 1.06)	0.173
	≥ 0.7	0.73 (0.64 to 0.83)	< 0.001
4	< 0.1	Ref (1)	–
	0.1 to < 0.2	0.86 (0.79 to 0.92)	< 0.001
	0.2 to < 0.4	0.81 (0.73 to 0.90)	< 0.001
	0.4 to < 0.7	0.93 (0.80 to 1.09)	0.362
	≥ 0.7	0.71 (0.63 to 0.80)	< 0.001
5	< 0.1	Ref (1)	–
	0.1 to < 0.2	0.62 (0.58 to 0.67)	< 0.001
	0.2 to < 0.4	0.73 (0.66 to 0.80)	< 0.001
	0.4 to < 0.7	0.64 (0.57 to 0.73)	< 0.001
	≥ 0.7	0.48 (0.44 to 0.53)	< 0.001

[a] Adjusted for ethnicity.

- The odds of caries prevalence were lower in children living in area with highest fluoride level compared with lowest fluoride levels at all levels of deprivation.
- The magnitude of decreasing in odds of caries prevalence between highest and lowest fluoride levels was larger in the most deprived children (quintile 5) compared to the least deprived children (quintile 1), suggesting that fluoride exposure had largest impact on the most deprived children.

Disparity in caries prevalence in children aged 5 years (2014 to 2015), by fluoridation status and stratified by index of multiple deprivation (IMD)

Quintile of IMD	Fluoridation status[a]	Adjusted OR (95% CI)[b]	*P* value
1 (least deprived)	No	Ref (1)	
	Yes	0.81 (0.70 to 0.94)	0.007
2	No	Ref (1)	
	Yes	0.73 (0.63 to 0.84)	< 0.001
3	No	Ref (1)	
	Yes	0.73 (0.64 to 0.83)	< 0.001
4	No	Ref (1)	
	Yes	0.76 (0.68 to 0.85)	< 0.001
5 (most deprived)	No	Ref (1)	
	Yes	0.61 (0.56 to 0.66)	< 0.001

[a] Yes = fluoride level ≥ 0.7 ppm; No = fluoride level < 0.2 ppm.
[b] Adjusted for ethnicity.

- When comparing areas with no fluoridation (fluoride level < 0.2 ppm), the odds of caries prevalence in the most deprived children was 39% lower (OR = 0.61; 95% CI 0.56 to 0.66) in areas with fluoridation (fluoride level ≥ 0.7 ppm).
- In least deprived children, the difference was 19% lower in areas with fluoridation compared to areas without fluoridation.

Adjusted incidence rate ratios of hospital admissions for dental extraction due to dental caries in children aged 0 to 19 years (2007 to 2015), by fluoride level

Fluoride level (ppm)	Adjusted IRR (95% CI)[a]	*P* value
< 0.1	Ref (1)	–
0.1 to < 0.2	0.74 (0.62 to 0.88)	0.001
0.2 to < 0.4	0.55 (0.44 to 0.68)	0.000
0.4 to < 0.7	0.61 (0.46 to 0.80)	0.000
≥ 0.7	0.41 (0.24 to 0.67)	0.000

[a] Adjusted for age, gender, ethnicity and deprivation.

- The incidence hospital admissions for caries-related dental extraction was 59% lower (OR [95% CI] = 0.61 [0.56 to 0.66]) in areas with fluoride level of ≥0.7 ppm compared to areas with fluoride levels <0.1 ppm.
- There was no significant difference in incidence rate of hospital admissions between areas of 0.4 to <0.7 ppm and 0.2 to <0.4 ppm, judging from the overlap of confidence intervals.

Disparity in incidence of hospital admissions for caries-related dental extraction in children aged 0 to 19 years (2007 to 2015), by fluoridation status and stratified by index of multiple deprivation (IMD)

Quintile of IMD	Fluoridation status[a]	Adjusted IRR (95% CI)[b]	*P* value
1 (least deprived)	No	Ref (1)	
	Yes	0.52 (0.32 to 0.83)	0.007
2	No	Ref (1)	
	Yes	0.53 (0.35 to 0.81)	0.003
3	No	Ref (1)	
	Yes	0.55 (0.33 to 0.90)	0.016
4	No	Ref (1)	
	Yes	0.46 (0.26 to 0.80)	0.005
5 (most deprived)	No	Ref (1)	
	Yes	0.32 (0.17 to 0.60)	0.000

[a] Yes = fluoride level ≥ 0.7 ppm; No = fluoride concentration < 0.2 ppm.
[b] Adjusted for age and gender.

- After adjustment for age and gender, the risk of hospital admissions for caries-related dental extraction was significantly lower in all level of deprivation in fluoridation areas compared to non-fluoridation areas.
- The magnitude of decreasing in odds of hospital admissions between non-fluoridation and non-fluoridation was larger in the most deprived children (quintile 5) compared to the least deprived children (quintile 1), suggesting that fluoride exposure had largest impact on the most deprived children.

CONCLUSION

Authors’ conclusion	*“The nature of water fluoridation is such that the whole population receiving the water supply is able to benefit without the need for individuals to change their behaviour or comply with advice of healthcare professionals, thereby contributing to the narrowing of dental health inequalities.”*(p.116)[79]
Reviewer’s note	

Aggeborn 2017[69]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data from Swedish registers for cohort born 1985-1992 and information on fluoride levels in CWF.
1.2	Is the eligible population or area representative of the source population or area?	++	Yes
1.3	Do the selected participants or areas represent the eligible population or area?	++	Method of selection of participants (aged 16 and older) was well described. Inclusion/exclusion criteria were explicit.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on fluoride levels in drinking water (from the Swedish Geological Survey data and drinking water data from municipalities), and fluoride exposure since birth.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Evidence for hypothesis derived from previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Sex, marital status, parent’s education, parent’s income, father’s cognitive and non-cognitive ability, parent immigrant, cohort mean education (at birth, at school start, at 16 years age). No dental habit or diet.
2.5	Is the setting applicable to Canada?	+	Set in Sweden. May be applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Dental health data were from The National Board of Health and Welfare. Cognitive and non-cognitive ability measures were assessed according to the Stanine scale. Labour market outcome data were from the Swedish tax agency.
3.2	Were all outcome measurements complete?	+	All participant born between 1985 and 1992 eligible.
3.3	Were all important outcomes assessed?	++	Dental outcomes, cognitive ability, non-cognitive ability, math test scores, and labour market outcomes
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	++	Weightened regression analysis.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs and p values reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	++	Good in population recruitment, method of selection of exposure, outcome measure and data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study conducted in Sweden. May be generalizable to the Canadian Context due to comparable fluoride levels.
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	The effect of fluoride in the drinking water
Author(s)	Aggeborn and Öhman
Publication year	2017
Country (where the study was conducted):	Sweden
Funding sources	U-CARE
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To study the effect of fluoride exposure through the drinking water throughout life on dental health
Study design	Ecological
Study location	Sweden
Study duration	NA
Exposure duration	Lifetime since birth
Fluoride levels or Exposures:	
• Intervention and comparator	Naturally occurring fluoridated water with fluoride levels in the community water ≤ 1.5 ppm.
Setting	National
Source of population	Individuals of age 16 and older
Inclusion/exclusion criteria	Cohorts born between 1985 and 1992. Individuals immigrated to Sweden during childhood were excluded.
Recruitment or sampling procedure	Dental health data were from The National Board of Health and Welfare.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited
PARTICIPANT CHARACTERISTICS	
Number of observations	
Dental outcomes	437,987 to 725,286

REPORTED OUTCOMES	
Definition (with units) and method of measurement	**Dental outcomes:** Visits to a dental clinic Repair treatment (tooth filled) Risk evaluation, health improvement measures Disease prevention Disease treatment Root canal treatment
Number of participants analysed	NR
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Regression analysis.
Results	

Dental outcomes of 2013 full data set	β-coefficient (SE); expressed in 0.1 ppm F	
	Unadjusted[a]	Adjusted[b]
Visit dental clinic	-0.2903 (0.0386)***	-0.0044 (0.0212)
Repair treatment (tooth filled)	-0.0777 (0.0134)***	-0.0583 (0.0155)***
Risk evaluation, health improvement measures	-0.3032 (0.0400)***	-0.0026 (0.0214)
Disease prevention	-0.5169 (0.0462)***	-0.0617 (0.0190)***
Disease treatment	-0.0656 (0.0280)**	-0.0324 (0.0199)
Root canal treatment	-0.0051 (0.0042)	-0.0122 (0.0060)**
Covariate group 1	No	Yes
Covariate group 2	No	Yes
Birth municipal FE	No	Yes
Cohort FE	No	Yes
Municipal 2014 FE	No	Yes
Sample	All	All

FE = fixed effect; SE = standard error
[a] Without FE and covariates
[b] With FE and covariates of group 1 and group 2
Covariate group 1 = sex, marital status
Covariate group 2 = parent's education, parent's income, father's cognitive and non-cognitive ability, parent immigrant, cohort mean education (at birth, at school start, at 16 years age)
*** $P < 0.01$, ** $P < 0.05$

CONCLUSION	
Authors' conclusion	*"We investigate and confirm the positive relationship between fluoride and dental health."* (p.1)[69]
Reviewer's note	The results were negative and often statistically significant for fluoride, especially for the 2013 sample. For dental repair, a tooth filled would decrease by approximately 0.6 percentage points if fluoride increased by 1 ppm.

Aguiar 2017[75]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	**Is the source population or source area well described?**	++	A national representative survey in Brazil for the young population of 12 years old and 15 to 19 years old.
1.2	Is the eligible population or area representative of the source population or area?	++	Yes
1.3	Do the selected participants or areas represent the eligible population or area?	++	Complex sampling was used. The response rate was 90.6 % among 12-year-old individuals and 77.9% among the 15- to 19-year-old individuals.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on the presence or absence of water fluoridation
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis derived from previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, gender, equivalent household income, time since last dental visit (years), education, per capita municipal domestic gross product, population size.
2.5	Is the setting applicable to Canada?	-	Set in Brazil. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	DMFT assessed by trained and calibrated examiners according to WHO criteria.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	DMFT
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multilevel logistic regression models.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported.

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good in population recruitment, method of selection of exposure, outcome measure and data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study conducted in Brazil with difference in healthcare system, sociodemographic characteristics to Canada. Could not be generalizable to the Canadian Context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION			
Title	The role of municipal public policies in oral health socio-economic inequalities in Brazil: A multilevel study		
Author(s)	Aguiar et al.		
Publication year	2017		
Country (where the study was conducted):	Brazil		
Funding sources	NR		
Reported conflict of interest	☑ Yes ☐ No		
STUDY CHARACTERISTICS			
Objectives	To assess the effect of public policies on different components of caries experience (decayed, missing and filled teeth) across different social strata.		
Study design	Ecological		
Study location	Brazil		
Study duration	NA		
Exposure duration	Lifetime		
Fluoride levels or Exposures:			
• Intervention	CWF (fluoride level NR)		
• Comparator	Non-CWF (fluoride level NR)		
Setting	School-based		
Source of population	Nationally representative sample		
Inclusion/exclusion criteria	Children aged 12 years and 15 to 19 years.		
Recruitment or sampling procedure	Individuals were recruited for both oral examination and questionnaire survey.		
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited		
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	12,773	9,901	2,872
Age	12 years and 15 to 19 years	12 years and 15 to 19 years	12 years and 15 to 19 years
Gender	NR	NR	NR
Subgroups reported	NR	NR	NR

<table>
<tr><th colspan="2">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td>Prevalence of DMFT (decayed, missing or filled permanent teeth)
DT ≥1; MT ≥1; FT ≥1</td></tr>
<tr><td>Number of participants analysed</td><td>10,124 (79.3%) analyzed in the fully adjusted model.</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>2,649 (due to missing data in at least one covariate)</td></tr>
<tr><td>Imputing of missing data</td><td>NR</td></tr>
<tr><td>Statistical method of data analysis</td><td>Multilevel logistic models adjusted by age, gender, equivalent household income, time since last dental visit (years), interviewee's education (years of schooling), per capita gross domestic product, population size.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th colspan="2">DT ≥ 1</th><th colspan="2">MT ≥ 1</th><th colspan="2">FT ≥ 1</th></tr>
<tr><td colspan="7">Prevalence of decay, missing and filled teeth</td></tr>
<tr><td>Water fluoridation</td><td>%</td><td><i>P</i> value</td><td>%</td><td><i>P</i> value</td><td>%</td><td><i>P</i> value</td></tr>
<tr><td>Yes</td><td>43.9</td><td>< 0.01</td><td>13.3</td><td>< 0.01</td><td>48.7</td><td>< 0.01</td></tr>
<tr><td>No</td><td>66.5</td><td></td><td>25.8</td><td></td><td>40.1</td><td></td></tr>
<tr><td colspan="7">Adjusted[a] odds ratio of having at least one decay (DT), missing (MT) or filled (FT) tooth</td></tr>
<tr><td>Water fluoridation</td><td colspan="2">OR (95% CI)</td><td colspan="2">OR (95% CI)</td><td colspan="2">OR (95% CI)</td></tr>
<tr><td>Yes (Ref)</td><td colspan="2">1</td><td colspan="2">1</td><td colspan="2">1</td></tr>
<tr><td>No</td><td colspan="2">1.42 (1.08 to 1.86)</td><td colspan="2">1.57 (1.16 to 2.14)</td><td colspan="2">0.85 (0.64 to 1.13)</td></tr>
</table>
[a] Adjusted by age, gender, equivalent household income, time since last dental visit (years), interviewee's education (years of schooling), per capita gross domestic product, population size.
</td></tr>
<tr><th colspan="2">CONCLUSION</th></tr>
<tr><td>Authors' conclusion</td><td><i>"The lack of fluoridated water in Brazilian municipalities was associated with higher odds of untreated caries, missing teeth, and lower odds of filled teeth"</i>(p.3)[75]</td></tr>
<tr><td>Reviewer's note</td><td>Residential mobility was not considered in the analysis. However, this age group may stay in the same community until finishing school.
Preventive effects of fluoridation on dental caries (decay, missing)
Filled teeth may be a result of more access to dental care.</td></tr>
</table>

Do 2017[73]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	**Is the source population or source area well described?**	++	Australian National Survey of Adult Oral Health 2004-2006 data on individuals aged 15 to 91 years randomly sample by stratified, multistage probability method. Population demographics adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Selection was done based on postal codes, households and one person per household.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Computer-assisted telephone interview (CATI) was conducted to collected socio demographics and dental care information, followed by oral epidemiological examination to complete a mailed questionnaire. Of 14,123 persons underwent CATI, 5505 were examined, and 4090 completed three rounds of data collection, whose data were used in the analysis.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Cohort stratified and categorized by percent lifetime access to fluoridated water (LAFW). Residential history was used to calculate the % LAFW. Unclear how selection bias was controlled.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	++	Age, sex, residential location, dental visit pattern, tooth brushing frequency, household income, and oral hygiene were included in the analysis. Risk of recall bias.
2.5	Is the setting applicable to Canada?	+	Set in Australia, which has similar socio-economic factors and healthcare to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Oral examination was performed by trained and standardized dentist to determine DMFS.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	DMFS = decayed, missing or filled permanent tooth surface
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multivariable analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CI reported

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	++	Adjusted for most important confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Set in Australia, which has similar level of fluoride fluoridated water as in Canada. Also similar in socio economic factors and healthcare.
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	Effectiveness of water fluoridation in the prevention of dental caries across adult age groups
Author(s)	Do et al.
Publication year	2017
Country (where the study was conducted):	Australia
Funding sources	NSW Health; Australian National Health and Medical Research Council; Australian Government Department of Health and Aging; Australian Institute of Health and Welfare; Australian Dental Association, Colgate Oral care; US Centers for Disease Control and Prevention and state and territory health departments and dental services.
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To examine the age group variation in percent lifetime access to fluoridated water (LAFW) and caries experience; and the association of % LAFW with caries within and across age groups of adults.
Study design	Ecological
Study location	Eight Australian states and territories
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures	Expressed as % life time access to the equivalent of 1.0 ppm fluoride in drinking water

Fluoride exposure			
Age group	Quartile	n	% lifetime access
15 to 34 years	Q1	181	0 to 20
	Q2	174	> 20 to < 84
	Q3	190	84 to < 100
	Q4	189	100
35 to 44 years	Q1	208	0 to < 26
	Q2	206	26 to < 78
	Q3	191	78 to < 100
	Q4	223	100
45 to 54 years	Q1	209	0 to < 34
	Q2	212	34 to < 67
	Q3	204	67 to < 78
	Q4	202	78 to 89[a]
55+ years	Q1	424	0 to < 23
	Q2	418	23 to < 52
	Q3	408	52 to < 61
	Q4	430	61 to 73[a]

[a] Maximum levels of exposure to the age group.

Setting	Nationally representative sample
Source of population	Australian National Survey of Adult Oral Health 2004-2006 data on individuals aged 15 to 91 years
Inclusion/exclusion criteria	Selection based on postcodes, household and one person per household
Recruitment or sampling procedure	Computer-assisted telephone interview.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS

	Total	**15 to 34 years**	**34 to 44 years**	**45 to 54 years**	**55+ years**
Number of participants enrolled	4,090	743	832	830	1,685

REPORTED OUTCOMES

Definition (with units) and method of measurement	Mean DMFS (decayed, missing or filled permanent tooth surface)
Number of participants analysed	4,090
Number of participants excluded or missing (with reasons)	1,415 (not completed Computer-assisted telephone interview and postal questionnaire
Imputing of missing data	NA
Statistical method of data analysis	Multivariable regression analysis
Results	

Age group	Quartile	Unadjusted mean DMFS (95% CI)	Effect size[a] Mean ratio (95% CI)
15 to 34 years	Q1	9.41 (7.50 to 11.32)	Ref
	Q2	11.91 (8.45 to 15.37)	0.98 (0.72 to 1.32)
	Q3	8.51 (5.54 to 11.48)	0.70 (0.47 to 1.05)
	Q4	6.14 (4.80 to 7.79)	0.67 (0.48 to 0.92)
35 to 44 years	Q1	26.23 (23.55 to 28.91)	Ref
	Q2	25.45 (22.70 to 28.19)	1.04 (0.85 to 1.26)
	Q3	24.06 (21.35 to 26.76)	0.87 (0.73 to 1.04)
	Q4	19.48 (17.47 to 21.48)	0.78 (0.66 to 0.93)
45 to 54 years	Q1	52.92 49.65 to 56.19)	Ref
	Q2	54.09 (51.12 to 57.06)	0.93 (0.83 to 1.05)
	Q3	53.69 (50.58 to 56.81)	0.92 (0.82 to 1.03)
	Q4	46.82 (44.40 to 49.23)	0.93 (0.82 to 1.04)
55+ years	Q1	60.53 (58.12 to 62.95)	Ref
	Q2	59.55 (57.22 to 61.88)	0.98 (0.90 to 1.07)
	Q3	61.20 (58.71 to 63.69)	1.03 (0.96 to 1.12)
	Q4	61.58 (59.45 to 63.70)	1.00 (0.93 to 1.08)

[a] Adjusted for age, sex, residential location, dental visit pattern, tooth brushing frequency, household income, and oral hygiene

Summary of findings:

- Age groups of 15 to 54 years old with highest % LAFW (Q4) had lower mean DMFS score compared to those with lowest % LAFW (Q1).
- After controlling for covariates, % LAFW was associated with caries experience in the two younger age groups (15 to 34 years and 35 to 44 years).
- Age group of 15 to 34 years in Q4 had 0.67 times lower in the mean DMFS score than those in Q1. This age group showed strongest association.

	- Age group of 35 to 44 years in Q4 had 0.78 times lower in the mean DMFS score than those in Q1. - No significant association between % LAFW and caries experience in older age groups (i.e., 45 to 54 years and 55+ years).
CONCLUSION	
Authors' conclusion	*"The association of water fluoridation with lower caries experience observed in the young and middle-aged adults points to longer term benefits from this preventive measure"*(p.231)[73]
Reviewer's note	Residential history was used to calculate % LAFW. Risk of recalling bias. Not possible to collect data on individual public water consumption due to long potential recall periods. Only % LAFW was estimated but not % lifetime exposure to water. Relatively low response rate (34% of the dentate sample). **Calculation of the % LAFW:** The number of years at each concentration was multiplied by the concentration; the products were then summed and divided by the person's age and multiplied by 100 to express the percent life time access to the equivalent of 1.0 ppm fluoride in drinking water.

Heima 2017[76]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	**Is the source population or source area well described?**	+	A cross-sectional review chart study of 388 charts. Population demographics were not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	5696 charts enrolled in the Head Start program, generated between Jan 2011 to Dec 2014 in Northeast Ohio
1.3	Do the selected participants or areas represent the eligible population or area?	+	400 charts from 5696 charts were randomly selected for review. Inclusion/exclusion criteria were not explicit.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on the presence or absence of water fluoridation
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis derived from previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Children demographics (age, gender, Medicaid, total number of primary teeth); social demographic factors (total number of Medicaid dentists, population/1000). Oher confounders likely not considered.
2.5	Is the setting applicable to Canada?	+	Set in US. May be applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Standardized dental caries assessment. Unclear about measurement reliability and validity.
3.2	Were all outcome measurements complete?	NR	

Item	Question	Rating	Comment
3.3	Were all important outcomes assessed?	+	dt
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	Yes
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Negative binomial regression model.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	P values and SE reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Limitations in population recruitment, method of selection of exposure, and outcome measure.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study conducted in USA for a specific population. May not be generalizable to the Canadian Context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	The effect of social geographic factors on the untreated tooth decay among head start children
Author(s)	Heima et al.
Publication year	2017
Country (where the study was conducted):	USA
Funding sources	Summer Research Program at Case Western Reserve University School of Dental Medicine and the Clinical Translational Award
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To explore the effect of sociogeographic factors on the number of primary teeth with untreated dental caries among children from low-income families who are enrolled in Head Start programs throughout Northeast Ohio in the United States.
Study design	Cross-sectional
Study location	Ohio, USA
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	CWF (fluoride level NR)

<table>
<tr><td>• Comparator</td><td colspan="3">Non-CWF (fluoride level NR)</td></tr>
<tr><td>Setting</td><td colspan="3">School-based</td></tr>
<tr><td>Source of population</td><td colspan="3">Children aged 5 months to 5 years.</td></tr>
<tr><td>Inclusion/exclusion criteria</td><td colspan="3">NR</td></tr>
<tr><td>Recruitment or sampling procedure</td><td colspan="3">Chart review.</td></tr>
<tr><td>Applicability to Canadian context (based on conditions such as fluoridation level, health and dental care system, and socio-economic factors [e.g., income and education levels])</td><td colspan="3">☐ High ☑ Partial ☐ Limited</td></tr>
<tr><td colspan="4">PARTICIPANT CHARACTERISTICS</td></tr>
<tr><td></td><td>Total</td><td>Intervention</td><td>Comparator</td></tr>
<tr><td>Number of participants enrolled</td><td>388</td><td>311</td><td>77</td></tr>
<tr><td>Age, mean (SD)</td><td>3.51 (1.14) years</td><td>NR</td><td>NR</td></tr>
<tr><td>Gender</td><td>200 boys; 188 girls</td><td>NR</td><td>NR</td></tr>
<tr><td>Subgroups reported</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td>Definition (with units) and method of measurement</td><td colspan="3">Mean dt (untreated dental caries)</td></tr>
<tr><td>Number of participants analysed</td><td colspan="3">388</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td colspan="3">12 (lack of critical information)</td></tr>
<tr><td>Imputing of missing data</td><td colspan="3">NA</td></tr>
<tr><td>Statistical method of data analysis</td><td colspan="3">Bivariate analysis and negative binomial regression model analysis</td></tr>
<tr><td>Results</td><td colspan="3">
<table>
<tr><th>Fluoridation</th><th>dt, mean (SD)</th><th>β-coefficient (SE)[a]</th></tr>
<tr><td>Yes</td><td>0.76 (2.09)</td><td>0.177 (0.304)</td></tr>
<tr><td>No</td><td>2.39 (11.24)</td><td></td></tr>
<tr><td><i>P</i> value</td><td>0.015</td><td>0.561</td></tr>
</table>
[a] Adjusted for children demographics (age, gender, Medicaid, total number of primary teeth) and social demographic factors (total number of Medicaid dentists, population/1000)
</td></tr>
<tr><td colspan="4">CONCLUSION</td></tr>
<tr><td>Authors’ conclusion</td><td colspan="3"><i>“Children (n = 311) who had available fluoridated water indicated significantly less dt than children (n = 77) who did not have it available.”</i>[76] p.e1226
<i>“After controlling other variables by the negative binomial regression model analysis, this significant association has disappeared.”</i>(p.e1228)[76]</td></tr>
<tr><td>Reviewer’s note</td><td colspan="3">Sample size of children in the non-fluoridated areas (n = 77) was lower than that in the fluoridated areas (n = 311).
The study only measured the number of untreated dental caries (dt), but not the number of dental caries experience teeth, i.e., decayed, missing and filled deciduous teeth (dmft).</td></tr>
</table>

Kim 2017[71]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	School children aged 6, 8, 11 years from two biggest primary schools in CWF area and three biggest primary schools in non-CWF area. Population demographics adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Recruitment through the permission of the directors of public health centers and principles of selected schools. Both areas were the most populous one.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Using a convenient cluster sampling method. Response rate was 93%. School children aged 6, 8, 11 years. Inclusion/exclusion criteria not reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	CWF versus non-CWF
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, sex, living area, educational level, monthly family income, Family Affluence Scale (FAS) scores. Other relevant confounders not included, such as tooth brushing frequency, habit of sugary food consumption, dentist visit, etc.
2.5	Is the setting applicable to Canada?	+	Moderate applicability
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Blue-white portable examination light used for oral examinations performed by three dentists trained and calibrated for inter-examiner reliability, in accordance with the WHO criteria for oral health surveys.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	DMFT, DMFS
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	++	Logistic regression analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good in method of selection and outcome assessments. May miss some important confounding variables.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Set in Korea, may be partially applicable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Associations of community water fluoridation with caries prevalence and oral health inequity in children
Author(s)	Kim et al.
Publication year	2017
Country (where the study was conducted):	South Korea
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To confirm the association between the community water fluoridation (CWF) programme and dental caries prevention on permanent teeth, comparing to a control area, neighbouring population without the programme, and verifying whether the programme can reduce the socio-economic inequality related to oral health in children in Korea.
Study design	Cross-sectional
Study location	South Korea
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	CWF (fluoride level NR)
• Comparator	Non-CWF (fluoride level NR)
Setting	School-based
Source of population	Elementary schoolchildren aged 6, 8 and 11 years old.
Inclusion/exclusion criteria	Participants who did not answer the questionnaire on either Family Affluence Scale (FAS) level, monthly family income, or parental education level were excluded.
Recruitment or sampling procedure	Elementary schoolchildren were recruited for both oral examination and questionnaire survey.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

<table>
<tr><th colspan="4">PARTICIPANT CHARACTERISTICS</th></tr>
<tr><td></td><td>Total</td><td>Intervention</td><td>Comparator</td></tr>
<tr><td>Number of participants enrolled</td><td>1,411</td><td>751</td><td>660</td></tr>
<tr><td>Age</td><td>6, 8, 11 years</td><td>6, 8, 11 years</td><td>6, 8, 11 years</td></tr>
<tr><td>Gender</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Subgroups reported</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><th colspan="4">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td colspan="3">DMFT = decayed, missing or filled permanent teeth
DMFS = decayed, missing or filled permanent tooth surface
Pit and fissure DMFS
Smooth surface DMFS</td></tr>
<tr><td>Number of participants analysed</td><td colspan="3">Varied depending on outcome measures</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td colspan="3">98 (did not answer the questionnaire on either Family Affluence Scale (FAS) level, monthly family income, or parental education level)</td></tr>
<tr><td>Imputing of missing data</td><td colspan="3">NR</td></tr>
<tr><td>Statistical method of data analysis</td><td colspan="3">Analysis of covariance (ANCOVA) after adjusting for sex, monthly family income, householder educational level, FAS score, and number of fissure-sealed teeth. Statistically significant at <i>P</i> < 0.05. Regression analysis was used to confirm the β coefficients of the relationship between variables and DMFT indices.</td></tr>
<tr><td>Results</td><td colspan="3">Analysis of covariance:
<table>
<tr><th rowspan="2">Caries experience</th><th>Age</th><th>Non-CWF</th><th>CWF</th><th><i>P</i> value*</th></tr>
<tr><td></td><td colspan="2"><i>Mean (SE)</i></td><td></td></tr>
<tr><td>DMFT</td><td>6</td><td>0.13 (0.04)</td><td>0.13 (0.03)</td><td>0.940</td></tr>
<tr><td></td><td>8</td><td>0.56 (0.06)</td><td>0.15 (0.06)</td><td>< 0.001</td></tr>
<tr><td></td><td>11</td><td>1.43 (0.10)</td><td>0.86 (0.10)</td><td>< 0.001</td></tr>
<tr><td>DMFS</td><td>6</td><td>0.16 (0.06)</td><td>0.19 (0.05)</td><td>0.769</td></tr>
<tr><td></td><td>8</td><td>0.79 (0.09)</td><td>0.22 (0.08)</td><td>< 0.001</td></tr>
<tr><td></td><td>11</td><td>2.20 (0.17)</td><td>1.31 (0.17)</td><td>< 0.001</td></tr>
<tr><td>Pit-and-fissure DMFS</td><td>6</td><td>0.08 (0.04)</td><td>0.11 (0.03)</td><td>0.536</td></tr>
<tr><td></td><td>8</td><td>0.52 (0.05)</td><td>0.13 (0.05)</td><td>< 0.001</td></tr>
<tr><td></td><td>11</td><td>1.27 (0.09)</td><td>0.75 (0.09)</td><td>< 0.001</td></tr>
<tr><td>Smooth surface DMFS</td><td>6</td><td>0.09 (0.03)</td><td>0.08 (0.03)</td><td>0.890</td></tr>
<tr><td></td><td>8</td><td>0.28 (0.04)</td><td>0.09 (0.04)</td><td>0.004</td></tr>
<tr><td></td><td>11</td><td>0.93 (0.09)</td><td>0.57 (0.09)</td><td>0.008</td></tr>
</table>
*Calculated using independent sample t-test between the non-CWF area and CWF area after adjusting for sex, monthly family income, householder educational level, FAS score, and number of sealed teeth

Children aged 8 and 11 years in the CWF area had significantly lower mean DMFT, DMFS, pit-and-fissure DMFS, and smooth surface DMFS compared to those in the non-CWF area, after adjustment for sex, monthly family income, householder educational level, FAS score, and number of sealed teeth.

Logistic regression analysis results:
Age, sex, householder educational level, and number of fissure-sealed tooth surface were associated with caries experience in non-CWF area. In the CWF area, age was the variable related to caries experience.</td></tr>
</table>

	Univariate analysis of variance for DMFT scores: In the non-CWF area, children of families with lower householder educational levels (i.e., primary school or lower) tended to have more dental caries than those of families with householders who were college or university graduates or higher (β [SE] = 1.03 [0.25]; *P* < 0.001). Such effect was not observed in CWF area (β [SE] = 0.12 [0.17]; *P* = 0.46). "*Oral health inequality was not observed among children in the CWF area*." (p.10)[71]
CONCLUSION	
Authors' conclusion	*"CWF programmes are effective in the prevention of caries on permanent teeth and can reduce health inequalities among children"*(p.1)[71]
Reviewer's note	Children in both areas widely used fluoridated toothpaste.

Spencer 2017[74]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	South Australian participants aged 20 to 35 years were traced from the previous sample recruited into previous studies in 1991/92, when children had been 5 to 17 years old. Population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Yes
1.3	Do the selected participants or areas represent the eligible population or area?	+	An invitation letter and a questionnaire were sent to the traced participants. Half of the participants traced could be recruited. Unclear how explicit was the inclusion and exclusion criteria.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Percent lifetime exposure to fluoridated water
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	++	Age, sex, parents' educational level, parents' household income, tooth brushing frequency, geographical location.
2.5	Is the setting applicable to Canada?	+	Set in Australia, which has similar socio-economic factors and healthcare to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Oral epidemiological examinations were conducted by specially trained and calibrated examination teams comprising of a dentist and a recorder.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	DMFS

Item	Question	Rating	Comment
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Negative binomial models
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Some aspects not reported. Unclear about the inclusion and exclusion criteria and potential presence of risk of selection bias.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Set in Australia, which has similar level of fluoride fluoridated water as in Canada. Also similar in socio economic factors and healthcare.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Preventive benefit of access to fluoridated water for young adults
Author(s)	Spencer et al.
Publication year	2017
Country (where the study was conducted):	Australia
Funding sources	NHMRC grants
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To analyze the preventive effect of access to fluoridated water on dental caries among young adults.
Study design	Cross-sectional
Study location	South Australian
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures	Expressed as % lifetime access to fluoridated water (% LAFW) 0 to 74%, 75 to 99% and 100% Spans of the life course to fluoridated water: • Early life access: birth to 1991 • Across maturation to young adult access: 1991 to 2006 • Full life time access: birth to 2006
Setting	South Australian School Dental Service clinics
Source of population	Follow-up sub-studies of a cohort of South Australian school children

Inclusion/exclusion criteria	NR		
Recruitment or sampling procedure	An invitation letter and a questionnaire were sent to the traced participants.		
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited		
PARTICIPANT CHARACTERISTICS			
Number of children previously enrolled	9,868	Retained at follow-up as young adults	1,220
Age, years			
5 to 7	3,069	20 to 23	380
8 to 11	3,964	24 to 27	490
12 to 17	2,835	28 to 35	350
Gender		Gender	
Male	4,982	Male	513
Female	4,732	Female	707
REPORTED OUTCOMES			
Definition (with units) and method of measurement	DMFS = decayed, missing or filled permanent tooth surface		
Number of participants analysed	1,220		
Number of participants excluded or missing (with reasons)	NR		
Imputing of missing data	NR		
Statistical method of data analysis	Negative binomial regression		
Results	**Distribution of access to fluoridated water early in life (birth to 1991), across maturation to young adulthood (1991 to 2006) and full life time (birth to 2006) among follow-up participants**		

	n	Mean DMFS (95% CI)[a]	% DMFS > 0 (95% CI)[a]
All	1,220	5.57 (5.04 to 6.10)	72.4 (69.9 to 74.9)
% LAFW (Birth to 1991)			
0 to 74%	427	6.35 (5.47 to 7.23)	77.5 (73.6 to 81.4)
75 to 99%	89	5.01 (3.09 to 6.93)	73.0 (63.8 to 82.2)
100%	704	5.17 (4.48 to 5.85)	69.2 (65.9 to 72.5)
% LAFW (1991 to 2006)			
0 to 74%	167	7.56 (6.16 to 8.96)	77.8 (71.5 to 84.1)
75 to 99%	120	6.40 (4.75 to 8.05)	71.7 (63.7 to 79.7)
100%	933	5.11 (4.52 to 5.70)	71.5 (68.6 to 74.4)
% LAFW (Birth to 2006)			
0 to 74%	287	7.00 (5.93 to 8.07)	77.0 (72.1 to 81.9)
75 to 99%	292	5.87 (4.81 to 6.93)	75.0 (70.1 to 79.9)
100%	641	4.79 (4.08 to 5.51)	69.1 (65.6 to 72.6)

[a] Unadjusted

CI = confidence interval; DMFS = decayed, missing and filled permanent tooth surface

- Compared to lowest access to water fluoridation (0 to 74% LAFW) in the last two periods of access to fluoridated water, highest access (100% LAFW) had significantly lowered caries prevalence and mean DMFS judging from the non-overlapping 95% CIs

Point estimates of caries outcome (DMFS) of young adults by three measures of access to fluoridated water

	Unadjusted		Adjusted[a]	
	RR	(95% CI)	RR	(95% CI)
% LAFW (Birth to 1991)				
0 to 74%	1.23	(1.03 to 1.48)	1.20	(0.99 to 1.45)
75 to 99%	0.97	(0.96 to 1.36)	0.96	(0.67 to 1.32)
100% (Ref)				
% LAFW (1991 to 2006)				
0 to 74%	1.48	(1.15 to 1.90)	1.22	(0.93 to 1.54)
75 to 99%	1.31	(0.94 to 1.82)	0.85	(0.60 to 1.19)
100% (Ref)				
% LAFW (Birth to 2006)				
0 to 74%	1.49	(1.21 to 1.88)	1.26	(1.01 to 1.57)
75 to 99%	1.21	(0.98to 1.57)	1.06	(0.85 to 1.32)
100% (Ref)				

CI = confidence interval; RR = risk ratio
[a] Adjusted for age, sex, parents' education, education of self as a young adult, tooth brushing as a child and as a young adult.

- In an unadjusted model, lowest access to water fluoridation (0 to 74% LAFW) in all three periods of access to fluoridated water had significant higher risk of caries experience (higher count of DMFS) compared to highest access (100% LAFW).
- In adjusted model, only the lowest access to water fluoridation (0 to 74% LAFW) in full life time access to fluoridated water (birth to 2006) showed significantly higher count of DMFS than 100% LAFW.

CONCLUSION

Authors' conclusion	*"Early life access to fluoridated water was not as strongly associated with caries outcome than either full lifetime access or access across the more proximal years with the caries outcome of young adults, especially after adjustment for covariates which may become increasingly important across longer spans of the fife course."* (p.263)[74]
Reviewer's note	Loss of follow-up was high. There was some shift in the characteristics of those retained.

Arrow 2016[66]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data were from the Western Australia School Dental Service, which provides free, statewide, primary dental care to schoolchildren aged 5 to 17 years old.
1.2	Is the eligible population or area representative of the source population or area?	++	The children were sampled based on their date of birth, and from those who presented for a dental examination in 2014. Large sample size that may be representative for the entire population of children in Western Australia.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Data were recorded on optical scanner readable forms, which were scanned and exported into a databased programme. Data included clinical data, location of clinic, gender, date of birth, month and year of the last examination, and aboriginal status. The sample consisted of 11.3% of children examined by school Dental service. Inclusion: Children aged 5 to 15 years whose birth date fell on the 28th, 29th, 30th and 31st of any month and those were examined for the first time in 2014.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Fewer participants in the non-fluoridated areas and may not represent eligible population.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis based on previous studies
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Confounders: Age, gender, sealants, Aboriginality, SES, interval between dental checkup, region, inflammation. No adjustment for fluoride products, dental habits, or diet.
2.5	Is the setting applicable to Canada?	+	The setting was in Australia that may be applicable to Canada due to similar healthcare and socio-economic factors.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Clinical assessment of tooth conditions was conducted by clinicians based on WHO criteria. Individual calibration of the examiners and formal evaluation of the examiner reliability were not undertaken.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	dmft and DMFT.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	

Item	Question	Rating	Comment
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Negative binomial regression modelling
4.4	Was the precision of association given or calculable? Is association meaningful?	++	The differences were considered to be statistically significant where the 95% CIs do not overlapped.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	++	Good in population recruitment and data analysis. Multivariable analysis controlled for appropriate confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study conducted in Australia with similar fluoride level to Canada. May be generalizable to the Canadian context.
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	Oral health of schoolchildren in Western Australia
Author(s)	Arrow
Publication year	2016
Country (where the study was conducted):	Australia
Funding sources	NR
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To present the oral health findings of children examined within the Western Australia School Dental Service during the 2014 calendar year, and to assess factors associated with caries experience to assist in the development of strategies for the management of dental caries among this population.
Study design	Cross-sectional
Study location	Western Australian
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	CWF (fluoride level NR)
• Comparator	Non-CWF (fluoride level NR)
Setting	School-based
Source of population	Service evaluation data were from the Western Australia School Dental Service, which provides free, statewide, primary dental care to schoolchildren aged 5 to 17 years old.
Inclusion/exclusion criteria	Inclusion: Children aged 5 to 15 years whose birth date fell on the 28th, 29th, 30th and 31st of any month and those were examined for the first time in 2014.
Recruitment or sampling procedure	The children were sampled based on their date of birth, and from those who presented for a dental examination in 2014. Details of sample strategy not reported; designed to capture 11.3% of all children examined in 2104.

Applicability to Canadian context	☐ High	☑ Partial	☐ Limited
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of children available for analysis	9,516	NR	NR
Age, years	5 to 15	NR	NR
Gender			
Male	4,900	NR	NR
Female	4,616	NR	NR
REPORTED OUTCOMES			
Definition (with units) and method of measurement	Mean dmft (decayed, missing or filled deciduous teeth) Mean DMFT (decayed, missing or filled permanent teeth)		
Number of participants analysed	5 to 10 years (n = 6,318) 6 to 15 years (n = 8,377)		
Number of participants excluded or missing (with reasons)	NA		
Imputing of missing data	NA		
Statistical method of data analysis	Negative binomial regression models		
Results	See below		

Results:

Dental caries experience of children aged 5 to 10 years (dmft for deciduous teeth) and of children 6 to 15 years (DMFT for permanent teeth) by CWF status

	dmft; mean (95% CI)	DMFT; mean (95% CI)
5 to 10 years		
Fluoridation (n = 5,906)	1.39 (1.33 to 1.45)	--
No fluoridation (n = 412)	1.86 (1.59 to 2.12)	--
6 to 15 years		
Fluoridation (n = 7,834)	--	0.49 (0.46 to 0.52)
No fluoridation (n = 543)	--	0.82 (0.67 to 0.96)

- Mean dmft and DMFT were significantly lower in the fluoridated areas in comparison to non-fluoridated areas, judging from the non-overlapping 95% CI.

Negative binomial regression models for carious deciduous teeth (dt) and for carious permanent teeth (DT) by CWF status

	dt RR[a] (95% CI); *P* value	DT RR[a] (95% CI); *P* value
5 to 10 years		
Fluoridation	Ref (1)	--
No fluoridation	1.62 (1.18 to 2.22); 0.003	--
6 to 15 years		
Fluoridation	--	Ref (1)
No fluoridation	--	2.13 (1.52 to 2.96); < 0.001

[a] Adjusted for age, gender, sealants, Aboriginality, SES, interval between dental checkup, region, inflammation
RR = rate ratio

- Children living in the non-fluoridated areas had 62% higher risk of deciduous tooth decay and over 200% higher risk of permanent tooth decay than those living in the fluoridated areas.

CONCLUSION	
Authors' conclusion	*"Poor dental health was associated with living in non-fluoridated areas"*(p.333) [74]
Reviewer's note	

Chalub 2016[80]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Sample was taken from the 2010 National Oral Health Survey conducted by the Brazilian Ministry of Health in the five large regions (north, northeast, central west, southeast and south) of the country. Population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	The sample was obtained through the random selection of municipalities and census sectors, configuring multi-stage cluster sampling with probability proportional to size.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of selection was adequately described. Response rate was 98%. Inclusion/exclusion criteria were not explicit.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Fluoridated water supply (absent or present) was a contextual variable.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Oral health coverage, gender, self-declared skin colour, schooling, monthly household income, age group, self-rated treatment need, dental appointment in the previous 12 months and dental services. No oral health habit.
2.5	Is the setting applicable to Canada?	-	Set in Brazil. Not applicable to Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Oral examinations were conducted according to the WHO criteria by trained examiners.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Oral health outcomes: WHO functional dentition (FDWHO), well-distributed teeth (WDT), functional dentition classified by esthetics and occlusion (FD_{class5}), functional dentition classified by esthetics, occlusion and periodontal status (FD_{class6})
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	

Item	Question	Rating	Comment
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	+	Yes, but not described in details.
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multi-level mixed-effect Poisson regression analysis.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good in sample selection, data analysis, but unclear about inclusion/exclusion criteria and outcome measures.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study conducted in Brazil with different in socio-economic characteristics and healthcare than in Canada. The findings have limited generalizability to the Canadian population.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Functional dentition in Brazilian adults: An investigation of social determinants of health (SDH) using a multilevel approach
Author(s)	Chalub et al.
Publication year	2016
Country (where the study was conducted):	Brazil
Funding sources	The Brazilian fostering agencies FAPEMIG and CNPq funded publication fee
Reported conflict of interest	☑ Yes ☐ No
Objectives	To estimate the prevalence of functional dentition among Brazilian adults using four different definitions and identity associated factors.
Study design	Cross-sectional
Study location	The five large regions (north, northeast, central west, southeast, and south) of Brazil.
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures	With CWF and without CWF (Fluoride levels not reported)
Setting	Community-based
Source of population	Adults aged 35 to 44 years who participated in the 2010 National Oral Health Survey
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	Random selection of municipalities and census sectors
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS			
Number of adults available for analysis	9,564	Mean schooling, years	8.5 (95% CI 8.1 to 8.9)
Age, years	35 to 44	Number of sound teeth	13.6 (95% CI 13.0 to 14.1)
Gender	36.6% male	Mean DMFT	16.7 (95% CI 16.2 to 17.3)
Race	87.5% brown or white	Mean of MFT	7.4
Monthly income (US$285 to US$852)	53.4%	Adults with edentulous in the mandible and/or maxilla	10.1% (95% CI 8.5 to 12.0)

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Four oral health outcomes: • **WHO functional dentition (FDWHO)**: ≥ 20% teeth presence • **Well-distributed teeth (WDT)**: ≥ 10 teeth in each arch • **Functional dentition classified by esthetics and occlusion (FD$_{class5}$)**: ≥ 1 tooth in each arch, ≥ 10 teeth in each arch, all maxillary and mandibular anterior teeth, 3 or 4 premolar POPs, and ≥ 1 molar POP (pair of antagonist posterior) bilaterally • **Functional dentition classified by esthetics, occlusion and periodontal status (FD$_{class6}$)**: FD$_{class5}$ plus shallow pockets and/or clinical attachment level (CAL) of 5 mm (community periodontal index [CPI] ≤ 3 or CAL ≤ 1).
Number of participants analysed	9,564
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Multi-level mixed-effect Poisson regression analysis.
Results	(see below)

Results

Prevalence of four oral health outcomes

Oral health outcome	Prevalence, % (95% CI)	
	Without CWF	With CWF
FDWHO	70.7 (65.1 to 75.8)	78.9 (76.3 to 81.3)
WDT	64.6 (58.1 to 70.6)	74.0 (71.2 to 76.7)
FD$_{class5}$	36.1 (28.8 to 44.0)	43.5 (40.7 to 46.4)
FD$_{class6}$	33.5 (26.4 to 41.5)	41.8 (38.9 to 44.8)

- The prevalence of all two oral health outcomes (FDWHO and WDT) were significantly higher (from non-overlapping 95% CI) in areas with fluoridated water supply compared to areas without water fluoridation.

Unadjusted multilevel mixed-effect Poisson regression analyses.

Oral health outcome	Unadjusted prevalence ratio (95% CI)	
	Without CWF	With CWF
FDWHO	Ref (1)	1.21 (1.12 to 1.30)
WDT	Ref (1)	1.24 (1.14 to 1.35)
FD$_{class5}$	Ref (1)	1.36 (1.18 to 1.58)
FD$_{class6}$	Ref (1)	1.37 (1.17 to 1.59)

	Adjusted multilevel mixed-effect Poisson regression analyses. <table><tr><th rowspan="2">Oral health outcome</th><th colspan="2">Adjusted prevalence^a ratio (95% CI)</th></tr><tr><th>Without CWF</th><th>With CWF</th></tr><tr><td>FDWHO</td><td>Ref (1)</td><td>1.18 (1.10 to 1.27)</td></tr><tr><td>WDT</td><td>Ref (1)</td><td>1.21 (1.12 to 1.31)</td></tr><tr><td>FD_{class5}</td><td>Ref (1)</td><td>1.20 (1.04 to 1.38)</td></tr><tr><td>FD_{class6}</td><td>Ref (1)</td><td>1.22 (1.05 to 1.41)</td></tr></table>[a] Adjusted by gender, self-declared skin colour, schooling, monthly household income, age group, self-rated treatment need, dental appointment in the previous 12 months, dental services and 2010 Municipal Human Development Index. • In both adjusted and adjusted final multiple models, significantly higher prevalence rates of the four outcomes were found for fluoridated water supply.
CONCLUSION	
Authors' conclusion	*"The presence of fluoridated water supply was associated with higher prevalence of all four oral health outcomes."*[80] p.2
Reviewer's note	Behavioral habits were not collected.

Cho 2016[82]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Data was from the National Health Insurance Service National Sample Cohort 2002 to 2013. No population demographics described.
1.2	Is the eligible population or area representative of the source population or area?	++	A random sample of 1,025,340 individuals, about 2.2% of the overall South Korean in 2002.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Stratified by age, sex, type of insurance, and income. Data was made through using probability sampling methods and the model used proportional allocation from total medical claims of 1,025,340 individuals.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Patients who lived in non-metropolitan areas (water fluoridation) and metropolitan areas (non-water fluoridation). Unclear if there is any cross-over of patients between areas. Water fluoride level not determined.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis based on previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Patient variables: Age, sex, income, type of insurance coverage, study year, dental care expenditures in the previous year, dental care visits in the previous year, dentofacial anomalies, and disorders of tooth development and eruption. Regional variables: Period from introduction of water fluoridation, number of dentists per 1,000 people and the financial independence rate of the local government.

Item	Question	Rating	Comment
2.5	Is the setting applicable to Canada?	-	Set in South Korea; may not be applicable to Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Not reported in the published article. But data were from the National Health Insurance Service National Sample Cohort, where the utilization of dental care was recorded including dental caries.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Outpatient dental care visit, dental expenditure.
3.4	Was there a similar follow-up time in exposure and comparison groups?	++	Used person-years
3.5	Was follow-up time meaningful?	++	Average follow-up time was 9.12 years
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Cox proportional hazard model, negative binomial regression, and regression analysis for dental care expenditures.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good in population selection and selection of exposure. Adequate in outcome measures and good data analysis. However, water fluoride level and migration not determined. Risk of selection bias.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Not generalizable to the Canadian population due to differences in SES, healthcare, resource and policy implications.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	The differences in healthcare utilization for dental caries based on the implementation of water fluoridation in South Korea
Author(s)	Cho et al.
Publication year	2016
Country (where the study was conducted):	South Korea
Funding sources	Not supported by funding
Reported conflict of interest	☑ Yes ☐ No

STUDY CHARACTERISTICS	
Objectives	To examine the relationship between the implementation of water fluoridation and the utilization of dental care.
Study design	Ecological
Study location	South Korea
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	CWF (fluoride level NR)
• Comparator	Non-CWF (fluoride level NR)
Setting	National
Source of population	National Health Insurance Service National Sample Cohort 2003 to 2013. Individuals aged 19 to < 70 years.
Inclusion/exclusion criteria	Inclusion: patients who lived in the non-metropolitan areas (having CWF programs) Exclusion: patients first diagnosed with dental caries before 2003.
Recruitment or sampling procedure	A random sample of 472,250 individuals (about 2.2% of the overall South Korea in 2002) from the National Health Insurance Service National Sample Cohort 2002 to 2013.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	472,250	49,122	423,128
Age	<19 years (30.24%) to >70 years (6.17%)	NR	NR
Gender	Male (50.7%) Female (49.3%)	NR	NR
Subgroups reported			
Income (percentile)	<10% (10.55%) to >91% (10.86%)	NR	NR
Types of insurances	Medical Aid (3.94%) NHI, self-employed insured (45.3%) NHI, employee insured (50.76%)	NR	NR
Year of baseline	2003 (87.27%) to 2013 (1.03%)	NR	NR
Dental facial abnormalities	Yes (0.02%) No (99.98%)	NR	NR
Disorder of tooth development and eruption	Yes (0.19%) No (99.81%)	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Percentage of patients experienced an outpatient dental visit Number of dental care visits Dental care costs
Number of participants analysed	Varied depending on outcome measures
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR

Statistical method of data analysis	Cox proportional hazard model, negative binomial regression, and regression analysis.
Results	• 46.98% and 48.66% of patients experienced an outpatient dental visit in area with and without water fluoridation, respectively, (*p* < 0.0001). The significant difference between fluoridation and non-fluoridation was observed across all aged groups (< 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and > 70 years). • From the Kaplan-Meier Survival curve, the mean (SE) for time to first diagnosis of dental caries was significantly greater in areas with water fluoridation compared to areas without water fluoridation: 1515.08 days (1104.16) vs 1498.74 days (1092.55), *p* < 0.0001. [Individuals living in areas with water fluoridation were less likely to visit dental care than those living in areas without water fluoridation] • The hazard ratio of dental care visits in areas with water fluoridation was 0.95 (95% CI 0.93 to 0.97); *p* < 0.0001 • The mean dental care visits and dental care costs were significantly lowered in areas with water fluoridation compared to areas without water fluoridation (*p*<0.0001) • After adjustment for regional variables and individual variables, there was a significant inverse relationship between dental care visit and water fluoridation (β coefficient = -0.029; p=0.043).
CONCLUSION	
Authors' conclusion	*"The implementation of water fluoridation programs and these periods are associated with reducing the utilization of dental health care.*"(p.1)[82]
Reviewer's note	Water fluoride level and migration not determined.

Crocombe 2016[70]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data were the 2004 to 2006 Australian National Survey of Adult Oral Health of capital city and non-capital city residents. Population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	A clustered stratified random sampling design was used select participants of 15 years and older. Eligible population was representative of the source.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Survey participants were interviewed by telephone followed by standardized oral epidemiological examinations. Australian postcodes were used to create two groups. Out of 5505 examined, 4170 completed the questionnaire, and 3700 people were included for lifetime fluoridation exposure calculation. Inclusion/exclusion criteria were appropriate.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Measured by mean lifetime fluoridation exposure was calculated using fluoridation database maintained by the Australian Research Centre for Population Oral Health that recorded fluoride concentration of public water supplies, classified geographically by postcode. Unclear how selection bias was minimized.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes

Item	Question	Rating	Comment
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	++	Confounders: age, gender, country of birth, SES, brushing with fluoride toothpaste, using sugar-free gum, smoking diabetes, and access to dental care.
2.5	Is the setting applicable to Canada?	+	Set in Australia, which has similar socio-economic factors and healthcare to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Examiners (dentists) were trained in the survey methods for standardized oral epidemiological examinations. Not report on the reliability and validity of outcome measures.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	DMFT
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multivariable regression models with adjustment for confounders.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Some aspects not reported. Unclear risk of selection and recall biases.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Set in Australia, which has similar level of fluoride fluoridated water as in Canada. Also similar in socio economic factors and healthcare. May be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Does lower lifetime fluoridation exposure explain why people outside capital cities have poor clinical oral health?
Author(s)	Crocombe et al.
Publication year	2016
Country (where the study was conducted):	Australia
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No

STUDY CHARACTERISTICS	
Objectives	To determine whether the greater dental caries experience of adults living outside Australian capital cities compared to adults living in the capital cities was associated with lower exposure to fluoridated water.
Study design	Ecological
Study location	Australia
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Person's proportion of lifetime exposed to the equivalent of 1 ppm fluoride in drinking water.
• Intervention	Capital cities (mean lifetime exposure = 59.1%; 95% CI 56.9 to 61.4)
• Comparator	Outside capital cities (mean lifetime exposure = 42.3%; 95% CI 36.9 to 47.6)
Setting	Dental clinic
Source of population	The 2004 to 2006 Australian National Survey of Adult (≥ 15 years) Oral Health.
Inclusion/exclusion criteria	Adults (≥ 15 years) who had one or more natural teeth were asked to attend a nearby dental clinic for an oral epidemiological examinations.
Recruitment or sampling procedure	A clustered stratified random sampling design was used select participants of 15 year and older.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention (capital city)**	**Comparator (outside capital city)**
Number of participants enrolled	3,770	2,514	1,256
Age, years	15 to 75+		
Gender			
Male	48.5%	47.6%	50.3%
Female	51.5%	52.4%	49.6%
Household income			
< $30,000	23.1%	20.0%	29.3%
$30,000 to $60,000	30.5%	29.3%	33.1%
$60,000+	46.4%	50.6%	37.7%

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Mean DMFT (decayed, missing or filled permanent teeth)
Number of participants analysed	3,770

<table>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>NA</td></tr>
<tr><td>Imputing of missing data</td><td>NA</td></tr>
<tr><td>Statistical method of data analysis</td><td>Multivariable regression models</td></tr>
<tr><td>Results</td><td>
Dental caries experience
<table>
<tr><th rowspan="2"></th><th rowspan="2">Total</th><th colspan="2">Mean</th><th rowspan="2"><i>P</i> value</th></tr>
<tr><th>Capital city</th><th>Outside</th></tr>
<tr><td>DMFT</td><td>13.4</td><td>12.9</td><td>14.3</td><td>0.02</td></tr>
<tr><td>DT</td><td>0.5</td><td>0.4</td><td>0.6</td><td><0.01</td></tr>
<tr><td>MT</td><td>4.5</td><td>4.1</td><td>5.3</td><td><0.01</td></tr>
<tr><td>FT</td><td>8.4</td><td>8.5</td><td>8.4</td><td>0.85</td></tr>
</table>

People living outside the capital city (42.3% mean lifetime fluoridation exposure) had significant higher caries experience (DMFT), decayed (DT) and missing teeth (MT), but not more filled teeth compared to those living in the capital city (59.1% mean lifetime fluoridation exposure).

Multivariable regression models for dental caries analyzed with regional location
<table>
<tr><th rowspan="2"></th><th colspan="2">β coefficient</th><th rowspan="2"><i>P</i> value</th></tr>
<tr><th>Capital city</th><th>Outside</th></tr>
<tr><td>DMFT</td><td>Ref</td><td>0.8</td><td>0.01</td></tr>
<tr><td>DT</td><td>Ref</td><td>0.1</td><td>0.10</td></tr>
<tr><td>MT</td><td>Ref</td><td>0.8</td><td><0.01</td></tr>
<tr><td>FT</td><td>Ref</td><td>-0.1</td><td>0.64</td></tr>
</table>

After adjustment for age, income, education, time brushed and access to dental care, there was a significant positive relationship between caries experience (DMFT) and outside capital city (β coefficient = 0.8; <i>P</i> = 0.01), which was mainly reflected by higher in missing teeth.

Multivariable regression models for dental caries analyzed with regional location plus proportion lifetime fluoridation exposure
<table>
<tr><th rowspan="2"></th><th colspan="2">β coefficient</th><th rowspan="2"><i>P</i> value</th></tr>
<tr><th>Capital city</th><th>Outside</th></tr>
<tr><td>DMFT</td><td>Ref</td><td>0.6</td><td>0.09</td></tr>
<tr><td>DT</td><td>Ref</td><td>0.1</td><td>0.11</td></tr>
<tr><td>MT</td><td>Ref</td><td>0.9</td><td><0.01</td></tr>
<tr><td>FT</td><td>Ref</td><td>-0.5</td><td>0.09</td></tr>
</table>

With additional adjustment of lifetime fluoride exposure, significant difference between regions was no longer observed for DMFT.
The model indicated that for a one unit increase in the percentage lifetime exposure to water fluoridation, there was a 1.3 reduction in the mean DMFT (β coefficient = -1.3; <i>P</i> < 0.01)

</td></tr>
<tr><th colspan="2">CONCLUSION</th></tr>
<tr><td>Authors’ conclusion</td><td><i>“With lifetime fluoridation exposure included in the regression model, there was no longer a significant difference in dental caries experience between people residing inside and outside Australian state capital cities. This study indicates that increasing lifetime fluoride exposure living outside Australian state capital cities would play a large role in removing the clinical oral health gap between people inside and outside capital cities.”</i>(p.99)[70]</td></tr>
<tr><td>Reviewer’s note</td><td>The study did not capture differences in rural areas and different levels of remoteness.</td></tr>
</table>

Crouchley 2016[68]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data of schoolchildren aged 5 to 12 years in 2011 and 2012 at Dental treatment Centres in fluoridated area (Perth metropolitan) and non-fluoridated areas (south West of western Australia)
1.2	Is the eligible population or area representative of the source population or area?	++	Yes
1.3	Do the selected participants or areas represent the eligible population or area?	++	Children (5 to 12 years old) were selected based on birth data (on 28th, 29th, 30th and 31st of the month); presented at Dental Treatment Centres; during period January 2011 to December 2012.
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Participants were selected based on residing in fluoridated and non-fluoridated areas. Selection bias was minimized by selecting children based on birth date.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis derived from previous studies
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, sex, Aboriginal status and having record at an initial examination at a DTC. Likely miss other important confounders.
2.5	Is the setting applicable to Canada?	+	Set in Australia, may be applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Dental outcomes were assessed by dental examiners at the Dental Treatment Centres based on WHO criteria. Not report on the reliability and validity of outcome measures.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	DMFT, dmft
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multivariable regression models with adjustment for confounders.

Item	Question	Rating	Comment
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Some aspects not reported. Other important and potential confounders not controlled.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Set in Australia, which has similar level of fluoride fluoridated water as in Canada. Also similar in socio economic factors and healthcare. May be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Dental Health Outcomes of Children Residing in Fluoridated and Non-Fluoridated Areas of Western Australia
Author(s)	Crouchley and Trevithick
Publication year	2016
Country (where the study was conducted):	Australia
Funding sources	Department of Health, Western Australia
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To determine if access to fluoridated water is associated with a difference in the prevalence of dental health outcomes among children in Western Australia.
Study design	Ecological
Study location	Australia
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	Perth metropolitan, fluoridated over 40 years – Fluoride level NR
• Comparator	Non-fluoridated areas in the southwest of Western Australia – Fluoride level NR
Setting	Dental Treatment Centres (DTC)
Source of population	Children 5 to 12 years old who presented at selected DTC in both non-fluoridated and the fluoridated areas from January 2011 to December 2012.
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	Children who had birth date on the 28th, 29th, 30th or 31st of the month and presented at selected DTC in both areas from January 2011 to December 2012. Evaluation data were collected by the Dental Health Services, which provided information of the first clinical examination in a calendar year.
Applicability to Canadian context (based on conditions such as fluoridation level, health and dental care system, and socio-economic factors [e.g., income and education levels])	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	10,825	9,972	853
Age	5 to 12 years	5 to 12 years	5 to 12 years
Gender	NR	NR	NR
Subgroups reported			
Aboriginal	2.5%	2.5%	3.0%
Unknown aboriginal	1.9%	1.6%	5.0%
Initial DTC examination	28.8%	29.2%	24.5%

REPORTED OUTCOMES	
Definition (with units) and method of measurement	dmft = decayed, missing or filled deciduous teeth – maximum score of 20. DMFT = decayed, missing or filled permanent teeth – maximum score of 28 or 32 if wisdom teeth are included. Significant Caries Index 10% (SiC^{10}) = Average caries experiences in the top one-tenth of individuals within a population group.
Number of participants analysed	10,825
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	Cases with missing date of birth or sex were excluded
Statistical method of data analysis	Univariate logistic regression and multivariate logistic regression models.
Results	See below

Results

Proportions of caries-free of deciduous teeth in children aged 5 to 9 years

Age (year)	Fluoridated	Non-fluoridated	*P* value
5	71.4% (1,213/1,700)	59.7% (89/149)	<0.001
6	64.7% (837/1,293)	56.0% (61/109)	NS
7	56.4% (729/1,292)	44.5% (49/110)	0.02
8	51.9% (630/1,214)	41.1% (45/102)	NS
9	49.5% (561/1,133)	43.3% (45/104)	NS

Caries prevalence of deciduous teeth (≥1 dmft) in children aged 5 to 9 years

Age (year)	Fluoridated	Non-fluoridated	*P* value
5	28.7% (487/1,700)	40.3% (60/149)	NR
6	35.3% (456/1,293)	44.0% (48/109)	NR
7	43.6% (563/1,292)	55.5% (61/110)	NR
8	48.1% (584/1,214)	55.9% (57/102)	NR
9	50.5% (572/1,133)	56.7% (59/104)	NR

Mean dmft in children aged 5 to 9 years

Age (year)	Fluoridated	Non-fluoridated	Significant difference* (Y/N)
	Mean (95% CI)		
5	1.1 (0.95 to 1.15)	1.6 (1.27 to 1.88)	Y
6	1.3 (1.17 to 1.43)	1.8 (1.21 to 2.33)	N
7	1.6 (1.44 to 1.72)	2.2 (1.65 to 2.80)	N
8	1.6 (1.49 to 1.74)	2.0 (1.54 to 2.50)	N
9	1.5 (1.40 to 1.64)	2.0 (1.52 to 2.48)	N

*Determined by comparing the overlapping of confidence intervals (CI); Y = no overlapping of CIs; N = overlapping of CIs

Proportions of caries-free of permanent teeth in children aged 6 to 12 years

Age (year)	Fluoridated	Non-fluoridated	*P* value
6	97.1% (1,256/1,293)	92.7% (101/109)	NS
7	91.9% (1,187/1,292)	90.0% (99/110)	NS
8	87.4% (1,060/1,213)	82.4% (84/102)	NS
9	85.1% (964/1,133)	77.9% (81/104)	0.05
10 to 11	77.1% (1,796/2,330)	67.4% (116/172)	< 0.001
11 to 12	71.4% (1,574/2,206)	60.7 % (105/173)	< 0.001

Caries prevalence of permanent teeth (≥1 DMFT) in children aged 6 to 12 years

Age (year)	Fluoridated	Non-fluoridated	*P* value
6	2.9% (37/1,293)	7.3% (8/109)	NR
7	8.1% (105/1,292)	10% (11/110)	NR
8	12.6% (153/1,213)	17.6% (18/102)	NR
9	14.9% (169/1,133)	22.1% (23/104)	NR
10 to 11	22.9% (534/2,330)	32.6% (56/172)	NR
11 to 12	28.6% (632/2,206)	39.3% (68/173)	NR

Mean DMFT in children aged 6 to 12 years

Age (year)	Fluoridated	Non-fluoridated	Significant difference* (Y/N)
	Mean (95% CI)		
6	0.05 (0.03 to 0.07)	0.11 (0.02 to 0.20)	N
7	0.13 (0.10 to 0.16)	0.20 (0.05 to 0.35)	N
8	0.22 (0.18 to 0.26)	0.28 (0.14 to 0.43)	N
9	0.25 (0.21 to 0.30)	0.40 (0.23 to 0.58)	N
10 to 11	0.44 (0.39 to 0.49)	0.67 (0.46 to 0.88)	N
11 to 12	0.60 (0.54 to 0.66)	0.82 (0.62 to 1.01)	N

*Determined by comparing the overlapping of confidence intervals (CI); Y = no overlapping of CIs; N = overlapping of CIs

SiC^{10} scores

Age (year)	For deciduous teeth in children 5 to 9 years		For permanent teeth in children 6 to 12 years	
	Fluoridated	Non-fluoridated	Fluoridated	Non-fluoridated
5	6.7	7.9	--	--
6	7.5	9.4	0.5	1.1
7	5.7	9.4	1.3	2.0
8	4.4	7.2	1.9	2.1
9	2.9	2.8	2.5	2.8
10 to 11	--	--	3.0	3.8
11 to 12	--	--	2.7	3.7

Effect estimates on the likelihood of one or more dmft or DMFT for children living in the non-fluoridated areas (Fluoridated area as Ref)

Participant category	Adjusted OR* (95% CI)	*P* value
Aged 5 to 9 years (dmft)	1.54 (1.35 to 1.75)	0.000
Aged 6 to 12 years (DMFT)	1.62 (1.33 to 1.98)	< 0.001

*Adjusted for age, sex, aboriginal status and having a record of an initial examination at a DTC.

CONCLUSION	
Authors' conclusion	"*Children living in non-fluoridated areas (South West) had poorer dental health than children from fluoridated areas (metropolitan) in WA, and this finding persisted even when age, sex, and Aboriginal status were accounted for.*"[68] p.24
Reviewer's note	Confounding factors not accounted for: socio-economic status, diet and dental and oral hygiene. Sample size of the non-fluoridated areas was smaller than that of the fluoridated area; may limit power of descriptive statistics to detect small differences between groups as statistically significant.

Ha 2016[77]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	The study was part of Child Dental Health Survey in Australia including children enrolled in School Dental Services. All South Australian children in school age are eligible.
1.2	Is the eligible population or area representative of the source population or area?	++	This study was conducted for indigenous children aged 5 to 15 years only.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Data were from routine examination records of children attending School Dental Services from 2001 to 2010. Not report on % of selected individuals or clusters agreed to participate.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selected based fluoridation areas. Unclear how selection bias was minimized.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	.Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Time trend, SES and remoteness. Other important confounders were likely not identified.
2.5	Is the setting applicable to Canada?	+	Set in Australia, but SES of aboriginal children and social services for aboriginal people are likely different between Australia and Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Diagnosis and reporting of caries experience followed the WHO criteria.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	dmft, DMFT
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multivariable mixed regression models.
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Potential risk of selection bias; likely missed important confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	May partially be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Trend in caries experience and associated contextual factors among indigenous children
Author(s)	Ha et al.
Publication year	2016
Country (where the study was conducted):	Australia
Funding sources	Australian Institute of Health and Welfare
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To assess the trends in dental caries among indigenous children in South Australia; and contribution of area-level socio-economic status (SES), remoteness and water fluoridation status.
Study design	Ecological
Study location	South Australia
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	With water fluoridation (>0.5 ppm)
• Comparator	Without water fluoridation (≤0.5 ppm)
Setting	School-based
Source of population	Indigenous children aged 5 to 15 years
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	Data from routine examination records of children attending School Dental Services from 2001 to 2010.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	18,067	NR	NR
Age, years	5 to 15	NR	NR
Gender	NR	NR	NR
Subgroups reported	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	dmft = decayed, missing or filled deciduous teeth (for children aged 5 to 10 years) DMFT = decayed, missing or filled permanent teeth (for children aged 6 to 15 years)
Number of participants analysed	Varied depending on outcome measure
Number of participants excluded or missing (with reasons)	NR

Imputing of missing data	NR
Statistical method of data analysis	Multivariable mixed regression models.
Results	- From 2001 to 2010, there was a non-significant trend of higher caries experience in the deciduous and permanent dentition in areas without water fluoridation compared to areas with water fluoridation. - After adjustment for time trend, SES and remoteness, there was a non-significant inverse relationship between both dmft (β coefficient [SE]: -0.10 [0.36]; NS), DMFT (β coefficient [SE]: -0.02 [0.21]; NS) and water fluoridation. - Indigenous children living in areas of lowest SES (β coefficient [SE] = 0.83 [0.28]; *P* < 0.05) and remoteness (β coefficient [SE] = 1.25 [0.45]; *P* < 0.05) had significantly higher caries experience for deciduous teeth than those living in areas of highest SES and major cities.
CONCLUSION	
Authors' conclusion	*"The dental caries trend increased in South Australian indigenous children over the study period, and was associated with area-level SES and remoteness."*[77] p.184
Reviewer's note	

Peres 2016[72]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data were from a population-based cohort study in a city of southern of Brazil, which was initiated in 2009 as baseline and carried out in 2012 including dental examination and face-to-face questionnaire.
1.2	Is the eligible population or area representative of the source population or area?	++	2 stage (census and households) clustered sample; adults 20 to 59 years of age
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of selection was described in the previous publication. 85.3% participants were selected in the first stage and 66% had dental examination in the second stage. However, sample of participants entering the analysis was small (only 18% of those had dental examination). Inclusion/exclusion criteria were not explicit.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Percent of lifetime exposure of the recommended level 0.8 ppm was calculated from the information of residential status, participant's age, and year of implementation of water fluoridation. Potential risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Fluoride can prevent dental caries in adults
2.3	Was the contamination acceptably low?	+	Based on lifetime access to fluoridation water. Unclear if there was contamination between groups.
2.4	How well were likely confounding factors identified and controlled?	+	Sex, age, SES, education, income, pattern of dental attendance, and smoking.
2.5	Is the setting applicable to Canada?	-	Set in Brazil. May not be applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental caries was assessed according to the WHO criteria. Dental examiners were subjected to rigorous training and standardization.

Item	Question	Rating	Comment
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	DMFT and DFT
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multiple negative binomial regression models
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Limitation in participant recruitments, small sample size, potential risk of selection bias, good statistical analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study conducted in only one city of southern of Brazil. Could not be generalizable to the Canadian context differences in socio-economic factors and healthcare systems.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Access to fluoridated water and adult dental caries: A natural experiment
Author(s)	Peres et al.
Publication year	2016
Country (where the study was conducted):	Brazil
Funding sources	CNPq. Brazil
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To investigate whether lifetime access to fluoridated water is associated with dental caries experience among adults from Florianopolis, Brazil.
Study design	Cross-sectional
Study location	A city of southern of Brazil
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Life time residential access to fluoridated water: > 75%; 50 to 75%; < 50%

Setting	Urban			
Source of population	Adults aged 20 to 59 years			
Inclusion/exclusion criteria	Those individuals residing at the same address since 7 years of age or younger were eligible for inclusion in the primary analysis			
Recruitment or sampling procedure	Two-stage (census tracts and households) clustered sample. Out of 2,016 target participants, 1,720 were investigated in 2009 (85.3%) and 1,222 were interviewed and 1,140 received dental examinations in 2012. 209 were eligible for inclusion			
Applicability to Canadian context	☐ High	☐ Partial	☑ Limited	
PARTICIPANT CHARACTERISTICS				
	Total	**>75%**	**50 to 75%**	**<50%**
Number of participants	209	78	75	56
Age, years	23 to 62	NR	NR	NR
Gender	44% male	NR	NR	NR
REPORTED OUTCOMES				
Definition (with units) and method of measurement	DMFT (decayed, missing or filled permanent teeth)			
Number of participants analysed	209			
Number of participants excluded or missing (with reasons)	NR			
Imputing of missing data	NR			
Statistical method of data analysis	Multiple negative binomial regression models			
Results	**DMFT rate ratio**			

Water fluoridation exposure	Unadjusted RR (95% CI)	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)	Model 3[c] RR (95% CI)
>75%	Ref (1)	Ref (1)	Ref (1)	Ref (1)
50% to 75%	1.93 (1.39 to 2.68)	1.20 (0.87 to 1.66)	1.19 (0.89 to 1.59)	1.11 (0.85 to 1.44)
<50%	2.70 (2.01 to 3.63)	1.37 (1.01 to 1.85)	1.35 (1.03 to 1.77)	1.39 (1.05 to 1.85)

RR = rate ratio

[a] Adjusted for sex, age, education, and income

[b] Adjusted for sex, age, education, income, and SES

[c] Adjusted for sex, age, education, income, SES, pattern of dental attendance, and smoking

- In unadjusted analyses, lower lifetime water fluoridation exposure (i.e., < 50%, 50% to 75%) had significant higher rate of DMFT compared to more than 75% lifetime water fluoridation exposure.
- After adjustment for various variables in model 1, 2 and 3, only the lowest lifetime water fluoridation exposure (i.e., < 50%) had significant higher rate of DMFT compared to more than 75% lifetime water fluoridation exposure.

	DFT rate ratio

Water fluoridation exposure	Unadjusted RR (95% CI)	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)	Model 3[c] RR (95% CI)
>75%	Ref (1)	Ref (1)	Ref (1)	Ref (1)
50% to 75%	1.25 (0.95 to 1.64)	1.09 (0.81 to 1.47)	1.34 (1.02 to 1.75)	ND
<50%	1.38 (0.98 to 1.94)	1.32 (0.93 to 1.87)	1.47 (1.05 to 2.04)	ND

CI = confidence interval; ND = not determined; RR = rate ratio
[a] Adjusted for sex, age, education, income
[b] Adjusted for sex, age, education, income, SES
[c] Adjusted for sex, age, education, income, SES, pattern of dental attendance, and smoking

- Moderate (50% to 75%) and lowest lifetime water fluoridation exposure (< 50%) had significant higher rate of DFT compared to > 75% lifetime water fluoridation exposure, after adjustment for sex, age, education, income and SES (Model 2[b]).

CONCLUSION	
Authors' conclusion	*"Longer residential access to fluoridated water was associated with less dental caries even in a context of multiple exposures to fluoride."*(p.868)[72]
Reviewer's note	Small sample size; risk of selection bias; no actual level of fluoride in water supply.

Schluter 2016[78]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	National aggregated data collected from children's routine child oral health service dental examinations with demographic information from Statistics New Zealand.
1.2	Is the eligible population or area representative of the source population or area?	++	All children aged 5 years and 12 to 13 years who had their oral health status recorded when they received dental treatment in New Zealand's child oral health services between 2004 and 2013.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Selection method was well described. National cross-sectional registry. Inclusion/exclusion criteria were explicit.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Children's CWF status was defined by public water supply status of their school. Risk of selection bias due to misclassification.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, ethnicity, and fluoridation area. Omit other important confounding variables (e.g., SES)
2.5	Is the setting applicable to Canada?	+	Set in New Zealand. May be applicable to Canada.

Item	Question	Rating	Comment
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Dental caries data are collected a part of the provision routine dental care by dental therapists, not from trained and calibrated examiners.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	dmft and DMFT
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Unweighted linear regression models
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good population recruitment. Risk of selection bias due to misclassification. Limitations in data analysis with unmeasured other important confounding variables.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study conducted in New Zealand. May partially be generalizable to the Canadian population.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Water fluoridation and ethnic inequities in dental caries profiles of New Zealand children aged 5 and 12-13 years: analysis of national cross-sectional registry databases for the decade 2004-2013
Author(s)	Schluter and Lee
Publication year	2016
Country (where the study was conducted):	New Zealand
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To undertake analyses of the associations between caries prevalence, CWF and ethnicity in New Zealand children aged 5 years and in school year 8 (generally aged 12-13 years).
Study design	Ecological
Study location	New Zealand
Study duration	NA

<table>
<tr><td>Exposure duration</td><td colspan="3">Lifetime</td></tr>
<tr><td colspan="4">Fluoride levels or Exposures:</td></tr>
<tr><td>• Intervention</td><td colspan="3">CWF – fluoride level NR</td></tr>
<tr><td>• Comparator</td><td colspan="3">Non-CWF – fluoride level NR</td></tr>
<tr><td>Setting</td><td colspan="3">School-based</td></tr>
<tr><td>Source of population</td><td colspan="3">All children aged 5 years and in school year 8 (~ 12 to 13 years of age)</td></tr>
<tr><td>Inclusion/exclusion criteria</td><td colspan="3">Extractions and fillings not due to caries and carious lesions were excluded.</td></tr>
<tr><td>Recruitment or sampling procedure</td><td colspan="3">National cross-sectional registry databases combined with Statistics New Zealand population estimates for 2004 to 2013 were used.</td></tr>
<tr><td>Applicability to Canadian context</td><td colspan="3">☐ High ☑ Partial ☐ Limited</td></tr>
<tr><th colspan="4">PARTICIPANT CHARACTERISTICS</th></tr>
<tr><td></td><td>Total</td><td>Intervention</td><td>Comparator</td></tr>
<tr><td>Number of participants enrolled</td><td>5 years old: 417,318 12 to 13 years old: 417,333
Māori = indigenous</td><td>NR</td><td>NR</td></tr>
<tr><td>Age</td><td>5 and 12 to 13 years</td><td>5 and 12 to 13 years</td><td>5 and 12 to 13 years</td></tr>
<tr><td>Gender</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Subgroups reported</td><td></td><td></td><td></td></tr>
<tr><td>Māori</td><td>5 years old: 93,715
12 to 13 years old: 94,001</td><td>NR</td><td>NR</td></tr>
<tr><td>Non-Māori</td><td>5 years old: 323,603
12 to 13 years old: 323,332</td><td>NR</td><td>NR</td></tr>
<tr><th colspan="4">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td colspan="3">dmft = decayed, missing or filled deciduous teeth
DMFT = decayed, missing or filled permanent teeth
Caries prevalence = % with deft/DMFT > 0</td></tr>
<tr><td>Number of participants analysed</td><td colspan="3">Varied depending on outcome measure</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td colspan="3">NR</td></tr>
<tr><td>Imputing of missing data</td><td colspan="3">NR</td></tr>
<tr><td>Statistical method of data analysis</td><td colspan="3">Unweighted linear regression models were used for statistical investigations of trends over time. Statistical significance was assessed based on Type III score statistic and Wald's chi-square test.</td></tr>
<tr><td>Results</td><td colspan="3">Caries-free prevalence (dmft = 0) for children aged 5 years in 2004
<table>
<tr><th></th><th colspan="2">Percent (95% CI)</th></tr>
<tr><th></th><th>Fluoridated areas</th><th>Non-fluoridated areas</th></tr>
<tr><td>Non-Māori</td><td>60.7 (58.4 to 62.9)</td><td>53.3 (51.1 to 55.6)</td></tr>
<tr><td>Māori</td><td>37.8 (35.6 to 40.1)</td><td>23.0 (20.7 to 25.2)</td></tr>
</table>

Carries-free prevalence for both non-Māori and Māori children aged 5 years was significant higher in fluoridated areas compared to non-fluoridated areas (judging from non-overlapping CIs).
In both areas, carries-free prevalence for Māori children was significantly lower compared to that for non-Māori children (judging from non-overlapping CIs).
Over the study period (2004 to 2013), caries-free prevalence improved by an average of 0.5% (95% CI, 0.1 to 0.9) per year for children in fluoridated areas, and by an average of 1.4% (95% CI, 1.1 to 1.8) per year for children in non-fluoridated areas.
</td></tr>
</table>

Mean dmft values for children aged 5 years in 2004

	Mean dmft (95% CI)	
	Fluoridated areas	Non-fluoridated areas
Non-Māori	1.50 (1.36 to 1.64)	2.01 (1.87 to 2.15)
Māori	3.01 (2.86 to 3.15)	4.60 (4.46 to 4.74)

- Mean dmft for both non-Māori and Māori children aged 5 years was significantly lower in fluoridated areas compared to non-fluoridated areas (judging from non-overlapping CIs).
- In both areas, mean dmft for Māori children was significantly higher compared to that for non-Māori children (judging from non-overlapping CIs).
- Over the study period (2004 to 2013)
  - In fluoridated areas:
    - No significant change in mean dmft for non-Māori children
    - Mean dmft decreased by 0.05 (95% CI, 0.02 to 0.08) per year for Māori children
  - In non-fluoridated areas:
    - Mean dmft decreased by 0.07 (95% CI, 0.04 to 0.09) per year for non-Maori children
    - Mean dmft decreased by 0.12 (95% CI, 0.10 to 0.15) per year for Maori children
  - Regression analysis on mean dmft (covariates = age, ethnicity, fluoridation status, and year of data collection) revealed significant differences between Māori and non-Māori ethic groups ($P < 0.001$), fluoridated and non-fluoridated areas ($P < 0.001$), and significant interaction between ethnicity and fluoridation status ($P < 0.001$), fluoridation status and time ($P < 0.001$), and ethnicity and time ($P = 0.001$).

Caries-free prevalence (DMFT = 0) for children aged 12 to 13 years in 2004

	Percent (95% CI)	
	Fluoridated areas	Non-fluoridated areas
Non-Māori	51.4 (49.4 to 53.4)	42.4 (40.4 to 44.4)
Māori	38.0 (35.9 to 40.0)	25.3 (23.3 to 27.3)

- Carries-free prevalence for both non-Māori and Māori children aged 12 to 13 years was significantly higher in fluoridated areas compared to non-fluoridated areas (judging from non-overlapping CIs).
- In both areas, carries-free prevalence for Māori children was significantly lower compared to that for non-Maori children (judging from non-overlapping CIs).
- Over the study period (2004 to 2013), caries-free prevalence improved by an average of 1.1% (95% CI, 0.7 to 1.4) per year for children in fluoridated areas, and by an average of 1.6% (95% CI, 1.3 to 2.0) per year for children in non-fluoridated areas.

Mean DMFT values for children aged 12 to 13 years in 2004

	Mean DMFT (95% CI)	
	Fluoridated areas	Non-fluoridated areas
Non-Māori	1.26 (1.17 to 1.36)	1.69 (1.58 to 1.77)
Māori	2.01 (1.91 to 2.10)	2.95 (2.86 to 3.05)

- Mean DMFT for both non-Māori and Māori children aged 12 to 13 years was significantly lower in fluoridated areas compared to non-fluoridated areas (judging from non-overlapping CIs).
- In both areas, mean DMFT for Māori children was significantly higher compared to that for non-Māori children (judging from non-overlapping CIs).
- Over the study period (2004 to 2013)
  - In fluoridated areas:
    - Mean DMFT decreased by 0.07 (95% CI, 0.06 to 0.09) per year for non-Māori children
    - Mean DMFT decreased by 0.07 (95% CI, 0.05 to 0.09) per year for Māori children
  - In non-fluoridated areas:
    - Mean DMFT decreased by 0.07 (95% CI, 0.04 to 0.09) per year for non-Māori children

	▪ Mean DMFT decreased by 0.11 (95% CI, 0.09 to 0.13) per year for Māori i children ○ Regression analysis on mean DMFT (covariates = age, ethnicity, fluoridation status, and year of data collection) revealed significant differences between Māori and non-Māori ethic groups ($P < 0.001$), fluoridated and non-fluoridated areas ($P < 0.001$), and significant interaction between ethnicity and fluoridation status ($P < 0.001$), fluoridation status and time ($P < 0.001$), and ethnicity and time ($P = 0.001$).
CONCLUSION	
Authors' conclusion	*"Significant and important gains in New Zealand children's oral health profiles appear to have been made over the last decade. Maori children continued carry a disproportionate oral health burden, even for those in CWF regions."*(p.1)[78]
Reviewer's note	No Adjustment for SES Dental coverage in Māori children was 10.9% (95% CI, 7.1 to 14.7) less than non-Māori children. Adjustment for differential coverage pattern worsened the caries-free and mean dmft/DMFT estimates.

Babarto 2015[81]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	The study population included adults aged 20 to 59 years residing in the city of Florianopolis, Southern Brazil. Population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	The study used cluster sampling. The first-stage units were census tracts and households were used as second-stage units.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Methods of selection were well described. Response rate was 85.3%. Inclusion/exclusion criteria not reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selection based on period of availability of fluoridated water. Company responsible for the distribution of treated water in the region was consulted about the period of availability of treated water in each of the city's census tract. Not known if the time exposure was the same at the individual level as the availability of fluoridated water. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Based on the effect of fluoridated water in the prevention of dental caries ad tooth loss in adults.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	SES, gender, age, years of education, household income per capita and length of residence in the same location. Likely miss other confounders.
2.5	Is the setting applicable to Canada?	-	Set in Brazil. Not applicable in Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Through interviews and questionnaire.
3.2	Were all outcome measurements complete?	NR	

Item	Question	Rating	Comment
3.3	Were all important outcomes assessed?	+	Edentulous status (tooth loss)
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	Yes
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multilevel logistic regression analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Potential risk of selection bias. Risk of recalling bias due to self-reporting tooth loss.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study was conducted in Brazil. Not applicable to the Canadian population.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Contextual and individual indicators associated with the presence of teeth in adults
Author(s)	Babarto et al.
Publication year	2015
Country (where the study was conducted):	Brazil
Funding sources	Conselho Nacional de Desenvolvimento Científico e Tecnológico
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To analyze whether socio-economic conditions and the period availability of fluoridated water are associated with the number of teeth present
Study design	Cross-sectional
Study location	City of Florianópolis, Southern Brazil
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	CWF availability = 27 years
• Comparator	CWF availability = 13 years
Setting	Communities
Source of population	Adults aged 20 to 59 years residing in the city of Florianopolis, Southern Brazil.

<table>
<tr><td>Inclusion/exclusion criteria</td><td colspan="3">NR</td></tr>
<tr><td>Recruitment or sampling procedure</td><td colspan="3">Cluster sampling was used. The first-stage units were census tracts and households were used as second-stage units.</td></tr>
<tr><td>Applicability to Canadian context</td><td colspan="3">☐ High ☐ Partial ☑ Limited</td></tr>
<tr><th colspan="4">PARTICIPANT CHARACTERISTICS</th></tr>
<tr><th></th><th>Total</th><th>Intervention</th><th>Comparator</th></tr>
<tr><td>Number of participants enrolled</td><td>1,720</td><td>NR</td><td>NR</td></tr>
<tr><td>Age, years</td><td>20 to 59</td><td>NR</td><td>NR</td></tr>
<tr><td>Gender</td><td>44.2% male</td><td>NR</td><td>NR</td></tr>
<tr><th colspan="4">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td colspan="3">Edentulous status (tooth loss)</td></tr>
<tr><td>Number of participants analysed</td><td colspan="3">1,720</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td colspan="3">NR</td></tr>
<tr><td>Imputing of missing data</td><td colspan="3">NR</td></tr>
<tr><td>Statistical method of data analysis</td><td colspan="3">Multilevel logistic regression analysis</td></tr>
<tr><td>Results</td><td colspan="3">Prevalence of tooth loss
<table>
<tr><th>CWF availability</th><th>Fewer teeth present % (95% CI)</th><th>OR (95% CI)[a]</th></tr>
<tr><td>27 years</td><td>18.4 (16.3 to 20.7)</td><td>Ref (1)</td></tr>
<tr><td>13 years</td><td>19.8 (16.5 to 23.5)</td><td>1.02 (1.01 to 1.02)</td></tr>
</table>
[a] Adjusted for SES, gender, age, years of education, household income per capita and length of residence in the same location</td></tr>
<tr><th colspan="4">CONCLUSION</th></tr>
<tr><td>Authors’ conclusion</td><td colspan="3"><i>“Poor socio-economic conditions and a shorter period of availability of fluoridated water were associated with the probability of having fewer teeth in adulthood.”</i>(p.1)[81]</td></tr>
<tr><td>Reviewer’s note</td><td colspan="3">Potential risk of selection bias. Risk of recalling bias due to self-reporting tooth loss.</td></tr>
</table>

Blinkhorn 2015[67]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Primary school children aged 5 to7 years in the first year of Public and Catholic Schools in three areas of New South Wales, Australia. Population demographic were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Yes
1.3	Do the selected participants or areas represent the eligible population or area?	++	The schools were randomly drawn from master school lists. Response rate was 70%.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on fluoridation and non-fluoridation areas.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Indigenous status, cardholder status, mother’s country of birth, gender and age identified and controlled for in multivariable analysis.
2.5	Is the setting applicable to Canada?	+	Set in Australia; may be applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental outcomes were assessed by two trained and calibrated dental examiners. The diagnostic system was based on a visual examination of air dried tooth.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Mean dmft, caries-free prevalence, mean SiC[30]
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	Yes
4.2	Were multiple explanatory variables considered in the analyses?	+	Yes
4.3	Were the analytical methods appropriate?	++	Multivariable analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good selection methods and data analysis. Sample size calculation was performed. Unlikely to introduce high risk of bias. Miss other important confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study conducted in Australia, which has similar socio-economic factors and healthcare. The findings may be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION				
Title	The Dental Health of primary school children living in fluoridated, pre-fluoridated and non-fluoridated communities in New South Wales, Australia			
Author(s)	Blinkhorn et al.			
Publication year	2015			
Country (where the study was conducted):	Australia			
Funding sources	Centre for Oral Health Strategy (NSW Health), The Australian Dental Association (NSW Branch), and Northern Sydney & Central Coast Area health Service.			
Reported conflict of interest	☑ Yes ☐ No			
STUDY CHARACTERISTICS				
Objectives	To compare the oral health of 5 to 7 years old living in fluoridated and non-fluoridated communities in New South Wales, Australia			
Study design	Cross-sectional			
Study location	New South Wales, Australia			
Study duration	NA			
Exposure duration	Lifetime			
Fluoride levels or Exposures:				
• Intervention	CWF (F level NR)			
• Comparator	Pre-CWF and non-CWF (F level NR)			
Setting	School-based			
Source of population	Primary school children aged 5 to 7 years in the first year of Public and Catholic Schools in three areas of New South Wales, Australia			
Inclusion/exclusion criteria	5 to 7 years old schoolchildren living in three areas.			
Recruitment or sampling procedure	A random number of schools were drawn from a master list of schools until individual school roles added up to 900 per area			
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited			
PARTICIPANT CHARACTERISTICS				
	Total	**Fluoridated**	**Pre-fluoridated**	**Non-fluoridated**
Number of participants enrolled	2,129	825	781	523
Age, years	5 to 7	5 to 7	5 to 7	5 to 7
Gender	49.9% male	50.7% male	48.7% male	50.2% male
REPORTED OUTCOMES				
Definition (with units) and method of measurement	Mean dmft, caries-free prevalence, mean significant caries index (SiC)			
Number of participants analysed	2,129			
Number of participants excluded or missing (with reasons)	NR			
Imputing of missing data	NR			
Statistical method of data analysis	Multivariable analysis			

Results

Mean dmft, caries-free prevalence and mean SiC index

Fluoridation status	dmft Mean (95% CI)	Caries-free % (95% CI)	SiC^{30} index Mean (95% CI)
Fluoridated	1.40 (1.22 to 1.58)	62.6 (59.2 to 65.9)	4.42 (4.04 to 4.81)
Pre-fluoridated	2.02 (1.80 to 2.23)**	50.8 (47.3 to 54.3)**	5.85 (5.47 to 6.22)
Non-fluoridated	2.09 (1.84 to 2.35)**	48.6 (44.3 to 52.9)**	5.97 (5.58 to 6.37)

**$P < 0.001$ compared to fluoridated
SiC^{30} = the dmft of the 30% of children with high levels of caries

- Fluoridated area had significantly lower mean dmft and higher caries-free prevalence than those in the pre-fluoridated and non-fluoridated areas.
- Fluoridated area had lower SiC score than the other areas.

Multivariate analysis

Fluoridation status	dmft[a] IRR (95% CI)	Caries experience[a] OR (95% CI); *P* value
Fluoridated	Ref (1)	Ref (1)
Pre-fluoridated	1.38 (1.14 to 1.67)**	1.62 (1.31 to 2.01)**
Non-fluoridated	1.53 (1.23 to 1.89)**	1.86 (1.46 to 2.37)**

[a] Adjusted for age, gender, Indigenous status, cardholder status and mother's country of birth
**$P < 0.001$
IRR = incidence rate ratio

- Children living in the pre-fluoridated and non-fluoridated areas had significantly higher risk of dental caries compared to those living in the fluoridated areas, after adjustment for age, gender, Indigenous status, cardholder status and mother's country of birth.

CONCLUSION

Authors' conclusion

"The children living in the well-established fluoridated area had less dental caries and a higher proportion free from disease when compared with the other two areas which were not fluoridated. Fluoridation demonstrated a clear benefit in terms of better oral health for young children."(p.1)[67]

Reviewer's note

Table 64: Research Question 2 Quality Assessment and Data Extraction

McLaren 2017[83]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Grade 2 children (~7 years old) from public or catholic school systems in two big cities (i.e., Calgary and Edmonton) in Alberta.
1.2	Is the eligible population or area representative of the source population or area?	++	These two school systems captured more than 90% of the Alberta schoolchildren in Alberta in 2013/14.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Data were collected from population-based sample as part of health region surveillance activities. For pre cessation (2004/05), in Calgary, a stratified random sample was used, with strata based on neighborhood income level of school location. Response rate was 60%. In Edmonton, all elementary school were invited to participate. Response rate was 89%. For post cessation, in both Calgary and Edmonton, a stratified random sample was used, with strata based on neighborhood income level of school location. Overall student-level response rates were 49.1% in Calgary and 47.0% in Edmonton. Sampling weights for each survey were developed, so that each survey was the representative of the underlying target population at that time.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on area of fluoridation status. Characteristics of the participants in both cities were similar. Measurement of biomarker for fluoride intake and questionnaire to gather information on sociodemographic, dental related and behavioral variables were conducted only for 2013/14, not for 2004/05.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	++	General health of child’s mouth, brush twice daily, visit dentist only for emergency or never, last visit dentist within the last year, fruit and vegetable at least once a day, sugar drink at least once a day, fluoride treatment at dentist office, household education of bachelor’s degree or higher, home ownership, ethno-cultural background, and age were measured and controlled in multivariable analysis.
2.5	Is the setting applicable to Canada?	++	Set in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Oral examinations were performed at school by trained and calibrated assessment teams consisting of a registered dental hygienist and a clerk. DMFT and deft were recorded, using the WHO criteria.

Item	Question	Rating	Comment
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	deft/DMFT and defs/DMFS.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multivariable analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good selection methods and thorough data analysis. Low response rates for post-cessation. Not reported on the proportion of participants completed oral examinations/questionnaires.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	++	Study conducted in Canada
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	Exploring the short-term impact of community water fluoridation cessation on children’s dental caries: a natural experiment in Alberta, Canada
Author(s)	McLaren et al.
Publication year	2017
Country (where the study was conducted):	Canada
Funding sources	Canadian Institutes of Health Research, Alberta Health, and Alberta Health Services
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To explore the short-term impact of fluoridation cessation on children’s dental caries, by examining change in caries experience in population-based samples of schoolchildren in two Canadian cities: Calgary (CWF cessation in 2011) and Edmonton (CWF continued)
Study design	Pre-post cross-sectional
Study location	Canada
Study duration	NA
Exposure duration	Lifetime

Fluoride levels or Exposures:			
- Intervention	Calgary, fluoridated (ranged 0.59 to 0.89 ppm) until 2011; post-cessation (ranged 0.07 to 0.30 ppm)		
- Comparator	Edmonton, continued fluoridation (average 0.7 ppm)		
Setting	School-based		
Source of population	Schoolchildren of grade 2 (approximately 7 years old) attending Public or Catholic schools in Calgary and Edmonton		
Inclusion/exclusion criteria	NR		
Recruitment or sampling procedure	Data were collected from population-based samples drawn during the pre-cessation period (2004/05) as part of surveillance activities and post-cessation period (2013/14). A stratified random sample was used, with strata based on neighborhood income level of school location.		
Applicability to Canadian context	☑ High	☐ Partial	☐ Limited
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled (sample sizes for primary teeth)	11,689	Calgary 3,337 599 in 2004/05 and 2,778 in 2013/14	Edmonton 8,352 6,445 in 2004/05 and 1,907 in 2013/14
Age	7 years	7 years	7 years
Gender	NR	NR	NR
Subgroups reported	NR	NR	NR
REPORTED OUTCOMES			
Definition (with units) and method of measurement	dmft = decayed, missing or filled deciduous teeth DMFT = decayed, missing or filled permanent teeth Caries prevalence = % with deft/DMFT > 0		
Number of participants analysed	Varied depending on outcome measures		
Number of participants excluded or missing (with reasons)	NR		
Imputing of missing data	NR		
Statistical method of data analysis	Differences between the two cities in change over time were confirmed using Poisson regression (regular or zero-inflated) or logistic regression with outcome measure regressed over year, city, age, and year x city interaction.		

Results

Dental caries index	Difference between 2013/14 (post-cessation) and 2004/05 (pre-cessation)		Year x city interaction term: RR or OR (95% CI); *P* value
	Calgary (stop fluoridation)	Edmonton (continued fluoridation)	
Mean deft	1.05*	0.34*	RR[a] = 1.37 (1.25 to 1.51); *P* < 0.001
Mean deft (those with deft>0)	1.38*	0.26	RR[b] = 1.34 (1.23 to 1.46); *P* < 0.001
Caries prevalence of deciduous teeth (≥1 dmft)	8%*	4%	OR[c] = 1.18 (0.92 to 1.51); *P* = 0.19
Mean DMFT	-0.24*	-0.01	RR[a] = 0.70 (0.51 to 0.95); *P* = 0.024
Mean DMFT (those with DMFT>0)	-0.21	-0.04	RR[b] = 0.88 (0.77 to 1.01); *P* = 0.062
Caries prevalence of permanent teeth (≥1 DMFT)	-12%*	-1%	OR[c] = 0.37 (0.28 to 0.49); *P* < 0.001
Complete caries care	13%*	-6%*	OR[c] = 2.53 (2.04 to 3.13); *P* < 0.001
No caries care	-5%*	4*	OR[c] = 0.38 (0.28 to 0.52); *P* < 0.001

CI = confidence interval; OR = odds ratio; RR = rate ratio
*Statistical significant at *P* < 0.05
[a]zero-inflated Poisson regression; [b]Poisson regression; [c]logistic regression

Adjusted deft and DEFT estimates (mean or %, 95% CI) for the post-cessation period (2013/14) of Calgary and Edmonton were not different compared to the unadjusted estimates. The confounding variables were general health of child's mouth, brush twice a day, visit dentist only for emergencies or never, last visit dentist within the last year, fruit or vegetable at least once a day, sugary drinks at least once a day, fluoride treatment at dentist office, household education of bachelor's degree or higher, home ownership, ethno-cultural background, and age.

CONCLUSION

Authors' conclusion	*"Our results suggest an increase in dental caries in primary teeth during a time period when community fluoridation was ceased. That we did not observe a worsening for permanent teeth in the comparative analysis could reflect the limited time since cessation."*(p.57)[83]
Reviewer's note	The sample size for Calgary in the pre-cessation (2004/05) period was much smaller than that for Edmonton. Due to lacking of questionnaire data of the pre-cessation period, adjusted estimates could not be computed.

McLaren 2016a[85]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Study set in Calgary and Edmonton
1.2	Is the eligible population or area representative of the source population or area?	++	Grade 2 children, representative of the source population of the area
1.3	Do the selected participants or areas represent the eligible population or area?	++	Stratified random sample for Calgary and all schools for Edmonton invited to participate. School level participation was low for post-cessation cohort.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)			
2.1	Allocation to intervention (or comparison). How was selection bias minimised?	+	CWF in Edmonton, non-CWF in Calgary
2.2	Were interventions (and comparisons) well described and appropriate?	++	CWF vs. non-CWF cities
2.3	Was the allocation concealed?	NA	
2.4	Were participants or investigators blind to exposure and comparison?	NA	
2.5	Was the exposure to the intervention and comparison adequate?	NA	
2.6	Was contamination acceptably low?	NR	
2.7	Were other interventions similar in both groups?	NR	
2.8	Were all participants accounted for at study conclusion?	NR	
2.9	Did the setting reflect usual Canadian practice?	++	Study set in Canada
2.10	Did the intervention or control comparison reflect usual Canadian practice?	++	Study set in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	defs and DMFS by calibrated examiners
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	No harms assessed
3.4	Were outcomes relevant?	++	defs, DMFS
3.5	Were there similar follow-up times in exposure and comparison groups?	NA	
3.6	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Were exposure and comparison groups similar at baseline? If not, were these adjusted?	NR	
4.2	Was intention to treat (ITT) analysis conducted?	NR	
4.3	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.4	Were the estimates of effect size given or calculable?	NR	
4.5	Were the analytical methods appropriate?	+	Mean differences calculated
4.6	Was the precision of intervention effects given or calculable? Were they meaningful?	++	CIs and p-values provided

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good selection and data collection methods. Low response rates for post-cessation. Confounders were not identified and controlled in data analysis. No multivariable analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	++	Study conducted in Canada
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	Measuring the short-term impact of fluoridation cessation on dental caries in Grade 2 children using tooth surface indices
Author(s)	McLaren et al.
Publication year	2016
Country (where the study was conducted):	Canada
Funding sources	Canadian Institutes of Health Research, Alberta Health, and Alberta Health Services
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To examine the short-term impact of fluoridation cessation on children’s caries experience measured by tooth surfaces.
Study design	Pre-post cross-sectional
Study location	Canada
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	Calgary, fluoridated (ranged 0.59 to 0.89 ppm) until 2011 (ranged 0.07 to 0.30 ppm)
• Comparator	Edmonton, continued fluoridation (average 0.7 ppm)
Setting	School-based
Source of population	Schoolchildren of grade 2 (approximately 7 years old) attending Public or Catholic schools in Calgary and Edmonton
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	Data were collected from population-based samples drawn during the pre-cessation period (2004/05) and post-cessation period (2013/14). A stratified random sample was used, based on neighborhood income level of school location.
Applicability to Canadian context	☑ High ☐ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention (Calgary)**	**Comparator (Edmonton)**
Number of participants enrolled (sample sizes for primary teeth)	12,581	3,829 599 in 2004/05 and 3,230 in 2013/14	8,752 6,445 in 2004/05 and 2,307 in 2013/14
Age	7 years	7 years	7 years
Gender	NR	NR	NR
Subgroups reported	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	defs = decayed, extracted (due to caries) or filled deciduous tooth surface DMFS = decayed, missing or filled permanent tooth surface

<table>
<tr><td>Number of participants analysed</td><td>Varied depending on outcome measure</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>NR</td></tr>
<tr><td>Imputing of missing data</td><td>NR</td></tr>
<tr><td>Statistical method of data analysis</td><td>Differences between the two cities in change over time were confirmed using zero-inflated Poisson regression with outcome measure regressed over year x city interaction.
Weighted analyses</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th rowspan="2">Dental caries index</th><th colspan="2">Difference between 2013/14 (post-cessation) and 2004/05 (pre-cessation)</th><th rowspan="2">Year x city interaction term: Rate ratio (95% CI); *P* value</th></tr>
<tr><th>Calgary (stop fluoridation)</th><th>Edmonton (continued fluoridation)</th></tr>
<tr><td colspan="4">a) All tooth surfaces</td></tr>
<tr><td>Mean defs</td><td>3.8*</td><td>2.1*</td><td>1.6 (1.4 to 1.8); *P* < 0.01[a]</td></tr>
<tr><td>Mean defs (those with defs>0)</td><td>5.9*</td><td>2.9*</td><td>1.6 (1.4 to 1.8); *P* < 0.01</td></tr>
<tr><td>Mean DMFS</td><td>-0.3*</td><td>-0.04</td><td>0.8 (0.6 to 1.1); *P* = 0.3[a]</td></tr>
<tr><td>Mean DMFS (those with DMFS>0)</td><td>-0.2</td><td>-0.2</td><td>0.96 (0.8 to 1.2); *P* = 0.6</td></tr>
<tr><td colspan="4">b) Smooth surface only[b]</td></tr>
<tr><td>Mean defs</td><td>2.9*</td><td>1.6*</td><td>1.8 (1.6 to 2.2); *P* < 0.01[a]</td></tr>
<tr><td>Mean defs (those with defs>0)</td><td>5.3*</td><td>3.0*</td><td>1.7 (1.5 to 2.0); *P* < 0.01</td></tr>
<tr><td>Mean DMFS</td><td>-0.02</td><td>0.0</td><td>2.7 (1.0 to 7.4); *P* = 0.06[a]</td></tr>
<tr><td>Mean DMFS (those with DMFS>0)</td><td>0.3</td><td>0.0</td><td>1.2 (0.8 to 1.8); *P* = 0.3</td></tr>
</table>
CI = confidence interval; RR = rate ratio
*Statistical significant based on non-overlapping 95% CI
[a] Interaction terms based on zero-inflated Poisson regression.
[b] Omits occlusal surfaces whenever present; omits buccal (vestibular) surfaces for teeth 46 and 36; omits lingual surfaces for teeth 16 and 26.
</td></tr>
<tr><th colspan="2">CONCLUSION</th></tr>
<tr><td>Authors’ conclusion</td><td>*“Trends observed for primary teeth were consistent with an adverse effect of fluoridation cessation on children’s tooth decay, 2.5-3 years post-cessation. Trends for permanent teeth hinted at early indication of an adverse effect.”*(p.274)[85]</td></tr>
<tr><td>Reviewer’s note</td><td>Differences in dental caries between cities at the tooth surface levels were observed for primary teeth only, but not for permanent teeth.
The sample size for Calgary in the pre-cessation (2004/05) period was much smaller than that for Edmonton.

The model did not include any adjustment for confounding variables.</td></tr>
</table>

McLaren 2016b[86]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Grade 2 children (~7 years old) from public or catholic school systems in the city of Calgary, Alberta.
1.2	Is the eligible population or area representative of the source population or area?	++	Yes
1.3	Do the selected participants or areas represent the eligible population or area?	++	Data in 2009/10 were collected from population-based sample as part of health region surveillance activities. Data in 2013/14 were collected as part of a joint research – surveillance initiative to evaluate the impact of CWF cessation in Calgary children's dental caries. A stratified random sample was used, with strata based on neighborhood income level of school location. The response rate in 2009/10 was 81%. The overall student-level response rate in 2013/14 was 49%.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on area of fluoridation status. Characteristics of the participants in both time periods were similar. Sampling weights were developed to account for both probability of selection and probability of non-response.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	SES: dental insurance and material deprivation (Pampalon index based on income, employment and education).
2.5	Is the setting applicable to Canada?	++	Set in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Oral examinations were performed at school by trained and calibrated assessment teams consisting of a registered dental hygienist and a clerk. deft and DMFT were recorded, using the WHO criteria.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	deft and DMFT
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	

Item	Question	Rating	Comment
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Zero-inflated Poisson regression or logistic regression.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good selection method, data collection method and data analysis. Low response rates for post-cessation. Unclear in some aspects due to not reporting.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	++	Study conducted in Canada
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	Equity in children’s dental caries before and after cessation of community water fluoridation: differential impact by dental insurance status and geographic material deprivation
Author(s)	McLaren et al.
Publication year	2016
Country (where the study was conducted):	Canada
Funding sources	Canadian Institutes of Health Research, Alberta Health, and Alberta Health Services
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To compare the socio-economic patterns of children’s dental caries in Calgary, Canada, between pre-cessation (2009/10) and post-cessation (2013/14) periods of CWF.
Study design	Pre-post cross-sectional
Study location	Canada
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	Post-cessation (2013/14) of CWF (fluoride levels ranged 0.07 to 0.30 ppm)
• Comparator	Pre-cessation (2009/10) of CWF (fluoride levels ranged 0.59 to 0.89 ppm)
Setting	School-based
Source of population	Schoolchildren of grade 2 (approximately 7 years old) attending Public or Catholic schools in Calgary and Edmonton
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	Data were collected from population-based samples drawn during the pre-cessation period (2009/10) and post-cessation period (2013/14). A stratified random sample was used, based on neighborhood income level of school location.
Applicability to Canadian context	☑ High ☐ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention (post-cessation)**	**Comparator (pre-cessation)**
Number of participants enrolled (sample sizes for primary teeth)	3,787	3,230 in 2013/14	557 in 2009/10
Age	7 years	7 years	7 years
Gender	NR	NR	NR
Subgroups reported			
Dental insurance	3,692	3,164	528
Small area material deprivation	3,491	2,980	511

REPORTED OUTCOMES	
Definition (with units) and method of measurement	deft = decayed, extracted or filled deciduous teeth DMFT = decayed, missing or filled permanent teeth Caries prevalence = % with deft/DMFT > 0
Number of participants analysed	Varied depending on outcome measures
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Differences between surveys were confirmed using zero-inflated Poisson regression or logistic regression with outcome measure regressed over year x socio-economic indicator interaction term.
Results	

Dental caries index	Effect estimates of absence (vs presence) of dental insurance on dental caries outcomes		Year x no dental insurance interaction term: RR or OR (95% CI); *p* value
	2009/10 (pre)	**2013/14 (post)**	
deft[a]	RR = 1.05 (0.94 to 1.17); $P = 0.40$	RR = 0.94 (0.86 to 1.03); $P = 0.18$	RR = 0.90 (0.78 to 1.04); $P = 0.14$
DMFT[a]	RR = 0.87 (0.65 to 1.16); $P = 0.33$	RR = 1.56 (1.05 to 2.33); $P = 0.03$*	RR = 1.80 (1.10 to 2.39); $P = 0.02$*
2 or more teeth (primary or permanent) with untreated decay[b]	OR = 1.76 (1.34 to 2.32); $P < 0.001$*	OR = 2.0 (1.57 to 2.53); $P < 0.001$*	OR = 1.13 (0.81 to 1.58); $P = 0.46$

CI = confidence interval; RR = rate ratio

*Statistical significance at $P < 0.05$

[a] Zero-inflated Poisson regression.

[b] Logistic regression

Dental caries index	Effect estimates of high or middle deprivation (vs low deprivation) on dental caries outcomes		Year x highest or middle deprivation interaction terms: RR or OR (95% CI); *P* value
	2009/10 (pre)	**2013/14 (post)**	
deft[a]			
Highest deprivation	RR = 1.07 (0.93 to 1.23); $P = 0.34$	RR = 1.19 (1.08 to 1.30); $P < 0.001$*	RR = 1.11 (0.95 to 1.30); $P = 0.20$
Middle deprivation	RR = 1.03 (0.88 to 1.19); $P = 0.73$	RR = 1.15 (1.02 to 1.30); $P = 0.02$*	RR = 1.12 (0.91 to 1.37); $P = 0.27$

Dental caries index	Effect estimates of high or middle deprivation (vs low deprivation) on dental caries outcomes		Year x highest or middle deprivation interaction terms: RR or OR (95% CI); *P* value
	2009/10 (pre)	**2013/14 (post)**	
DMFT[a]			
Highest deprivation	RR = 1.42 (0.74 to 2.69); $P = 0.27$	RR = 1.04 (0.68 to 1.59); $P = 0.85$	RR = 0.74 (0.36 to 1.50); $P = 0.40$
Middle deprivation	RR = 1.08 (0.61 to 1.91); $P = 0.77$	RR = 0.80 (0.49 to 1.30); $P = 0.37$	RR = 0.74 (0.36 to 1.51); $P = 0.41$
2 or more teeth (primary or permanent) with untreated decay[b]			
Highest deprivation	OR = 2.95 (0.89 to 9.82); $P = 0.07$	OR = 2.23 (1.66 to 2.98); $P < 0.001$*	OR = 0.75 (0.24 to 2.36); $P = 0.63$
Middle deprivation	OR = 0.90 (0.31 to 2.62); $P = 0.83$	OR = 1.43 (1.05 to 1.94); $P = 0.02$*	OR = 1.59 (0.57 to 4.43); $P = 0.37$

CI = confidence interval; RR = rate ratio
*Statistical significant at $P < 0.05$
[a] Zero-inflated Poisson regression.
[b] Logistic regression

CONCLUSION	
Authors' conclusion	*"Statistically significant inequities by dental insurance status and by small area material deprivation were more apparent in 2013/14 than in 2009/10."*[86] p.1
Reviewer's note	Absence of comparison community. Did not adjust for confounding variables such as fluoride varnish, dental sealants which are publicly funded for school-aged children. Another confounding variable is regular brushing with fluoride toothpaste.

PHE 2015[84]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data from dental survey of children aged 5 years and 12 years living in Bedford Borough in 2008 (water fluoridation) and in 2015 (water fluoridation cessation), conducted by the National Dental Public Health Epidemiology Programme in England
1.2	Is the eligible population or area representative of the source population or area?	+	Small number of children examined
1.3	Do the selected participants or areas represent the eligible population or area?	+	Dental surveys were performed according to the national protocol for dental surveys. Percent of selected individuals agreed to participate and inclusion/exclusion criteria were not reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selected at the time of the presence of water fluoridation and the time of water fluoridation cessation.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis was from previous studies
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors were controlled
2.5	Is the setting applicable to Canada?	+	Set in UK. May partially applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dmft and dt based on specified diagnostic criteria – BASCD. Trained and calibrated examiners.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dmft, dental fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No multivariable analysis conducted.

Item	Question	Rating	Comment
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Unclear in many aspects due to not reporting. No multivariable analysis conducted to control for confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study was conducted in UK. Similar in healthcare system and sociodemographic characteristics to Canada. May partially be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Dental health impact of water fluoridation in children living in Bedford Borough Council in 2008, 2009 and 2015
Author(s)	Public Health England
Publication year	2016
Country (where the study was conducted):	England
Funding sources	Department of Health, England
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	a) To understand through data comparison the dental health of five-year-old children and the level of change to dental health with water fluoridation in 2008 and without water fluoridation in 2015. b) To understand the dental health of five-year-old children living in areas of advantage/disadvantage with and without water fluoridation in Bedford Borough and the level of change when water fluoridation was suspended in the same areas of advantage/disadvantage. c) To assess the perception of fluorosis in twelve year-old children in Bedford Borough in areas where water fluoridation was present.
Study design	Pre-post cross-sectional
Study location	England
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	Water fluoridation (0.51 to 0.83 ppm) in 5 year period prior to 2008 Water fluoridation (0.61 to 0.73 ppm, mean 0.69 ppm) during first 6 months of 2008
• Comparator	Water fluoridation cessation (0.24 to 0.26 ppm) in 5 year period prior to 2015 Water fluoridation (0.26 to 0.27 ppm, mean 0.27 ppm) during first 6 months of 2015
Setting	School-based
Source of population	Data from dental survey of children aged 5 years living in Bedford Borough in 2008 (water fluoridation) and in 2015 (water fluoridation cessation), conducted by the National Dental Public Health Epidemiology Programme in England.
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	Dental surveys were performed according to the national protocol for dental surveys.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	1,873	1,010 in 2008	863 in 2015
Age	5 years	5 years	5 years
Gender	NR	NR	NR
Index of Multiple Deprivation:			
1 (most deprived)	220	104	106
2	366	193	173
3	250	103	147
4	220	57	163
5 (most affluent)	246	97	149

REPORTED OUTCOMES	
Definition (with units) and method of measurement	dmft = decayed, missing or filled deciduous teeth Caries prevalence = % with dmft > 0
Number of participants analysed	Varied depending on outcome measures
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	CIs and *p* values reported. Did not conduct any multivariable analysis to adjust for confounders.
Results	

	2008	**2015**	**2008**	**2015**	**2008**	**2015**
	Mean dmft		Mean dmft > 0		% dmft > 0	
n=1,010 in 2008 (fluoridation) n=863 in 2015 (no fluoridation)	0.85	0.97	3.26	3.57	26.2	27.1
Difference	+0.12, *P* = 0.18		+0.31, *P* = 0.21		+0.9%, *P* = 0.51	
	Mean dt		**Mean dt > 0**		**% dt > 0**	
n=1,010 in 2008 (fluoridation) n=863 in 2015 (no fluoridation)	0.65 (0.55 to 0.75)	0.73 (0.61 to 0.85)	2.81 (2.49 to 3.14)	3.09 (2.74 to 3.43)	23.1 (20.6 to 25.7)	23.6 (20.8 to 26.4)
Difference	+0.08		+0.28		+0.5%	
	Mean mt		**Mean mt > 0**		**% mt > 0**	
n=1,010 in 2008 (fluoridation) n=863 in 2015 (no fluoridation)	0.07 (0.03 to 0.10)	0.12 (0.07 to 0.17)	3.16 (2.34 to 3.98)	3.70 (2.77 to 4.63)	2.2 (1.3 to 3.1)	3.2 (2.1 to 4.4)
Difference	+0.05		+0.54		+1.0%	

		Mean dmft		Mean dmft > 0		% dmft > 0	
2008, F <0.7 ppm (n=446)	2015, no fluoridation (n=297)	0.57 (0.42 to 0.72)	0.56 (0.38 to 0.74)	3.16 (2.67 to 3.66)	2.95 (2.26 to 3.64)	18.0 (14.41 to 21.69)	19.0 (14.55 to 23.47)
Difference		-0.01		-0.21		+1.0%	
2008, F ≥0.7 ppm (n=564)	2015, no fluoridation (n=439)	1.16 (0.95 to 1.36)	1.36 (1.11 to 1.60)	3.41 (2.96 to 3.86)	3.72 (3.26 to 4.17)	34.0 (30.0 to 37.9)	36.5 (31.80 to 41.17)
Difference		+0.2		+0.31		+2.5%	

IMD National Quintile	**Mean dmft**		**% dmft > 0**	
	2008 F ≥ 0.7 ppm	**2015 no fluoridation**	**2008 F ≥ 0.7 ppm**	**2015 no fluoridation**
1 (most deprived)	1.40 (0.91 to 1.90)	1.51 (1.06 to 1.95) *P* = 0.75	34.2 (25.5 to 42.9)	40.6 (31.2 to 49.9) *P* = 0.33
2	1.56 (1.18 to 1.95)	1.57 (1.14 to 1.98) *P* = 0.98	44.0 (37.0 to 51.0)	39.9 (32.4 to 47.4) *P* = 0.43
3	0.72 (0.39 to 1.05)	1.03 (0.53 to 1.53) *P* = 0.31	27.2 (18.6 to 35.8)	30.8 (19.5 to 42.0) *P* = 0.62
4	0.74 (0.27 to 1.20)	0.72 (0.19 to 1.25) *P* = 0.96	24.6 (13.4 to 35.7)	22.0 (10.5 to 33.5) *P* = 0.75
5 (most affluent)	0.22 (0.10 to 0.34)	0.58 (0.23 to 0.93) *P* = 0.06	14.4 (7.4 to 21.4)	21.8 (10.9 to 32.7) *P* = 0.25

IMD National Quintile	**Mean dmft**		**% dmft > 0**	
	2008 F < 0.7 ppm	**2015 no fluoridation**	**2008 F < 0.7 ppm**	**2015 no fluoridation**
1 (most deprived)	-	-	-	-
2	*	*	*	*
3	0.86 (0.55 to 1.17)	0.72 (0.3 to 1.11) *P* = 0.57	23.7 (16.9 to 30.4)	23.2 (14.0 to 32.3) *P* = 0.93
4	0.48 (0.27 to 0.69)	0.37 (0.16 to 0.59) *P* = 0.48	18.4 (12.0 to 24.8)	14.2 (7.7 to 20.6) *P* = 0.36
5 (most affluent)	0.23 (0.10 to 0.35)	0.55 (0.26 to 0.84) *P* = 0.05	9.0 (4.3 to 13.6)	20.2 (12.1 to 28.3) *P* = 0.01

IMD = Index of Multiple Deprivation
-, no data; * number of children below 20

Summary of findings:
In whole population,

- Mean dmft slightly increased by 0.12 points from 2008 to 2015 (not statistically significant, NS)
- Mean dmft > 0 (obvious sign) increased by 0.31 points (NS)
- Caries prevalence (% dmft > 0) increased by 0.9% (NS)

	• There was no difference in mean dt or mean mt between 2008 and 2015 • Mean dt > 0 and mean mt > 0 increased by 0.28 points (NS) and 0.54 points (NS), respectively. • Prevalence of decay teeth (% dt > 0) and prevalence of missing teeth (% mt>0) increased by 0.5% (NS) and 1% (NS), respectively. In subpopulation (2008, F ≥ 0.7 ppm versus 2015, no fluoridation), • Mean dmft increased by 0.2 points from 2008 to 2015 (NS) • Mean dmft > 0 increased by 0.31 points (NS) • Caries prevalence (% dmft > 0) increased by 2.5% (NS) • Mean dmft and dental caries prevalence increased from most affluent group to most deprived group according to the Index of Multiple Deprivation classification. • However, there was no statistically significant difference in mean dmft and caries prevalence within groups between 2008 and 2015. In subpopulation (2008, F < 0.7 ppm versus 2015, no fluoridation), • There was no difference in mean dmft or mean dmft > 0 between 2008 and 2015 • Caries prevalence (% dmft > 0) increased by 1% (NS) • Mean dmft and caries prevalence were lowest in the most affluent groups compared to others. • In the most affluent group, mean dmft and caries prevalence significantly increased in 2015 compared to 2008. Perception of fluorosis among 12 years old children (n = 240) living in 2008/2009, • 19.1% said "yes" of having white marks • 58.9% said "no" of having white marks • 21.6% said "don't know" of having white marks
CONCLUSION	
Authors' conclusion	*"There was no statistically significant change in dental health of five years old children between 2008 and 2015. However, the data suggested that dental health deteriorated over the time period although this was not statistically significant"* (p.24)[84]
Reviewer's note	No adjustment for confounders

Table 65: Research Question 3 Quality Assessment and Data Extraction

Chafe 2018[129]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Study set in Newfoundland and Labrador
1.2	Is the eligible population or area representative of the source population or area?	++	Includes provincial level data
1.3	Do the selected participants or areas represent the eligible population or area?	+	All cases of diabetes registered included; no inclusion exclusion criteria
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	12 water quality measurements taken between January 2000 and December 2012
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Concentration of drinking water components and diabetes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounders adjusted for
2.5	Is the setting applicable to Canada?	++	Study conducted in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Patients with diabetes from the Newfoundland and Labrador Pediatric Diabetes Research Unit, more details of how they were diagnosed not reported
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Only harms assessed not benefits
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	-	No sample size calculation
4.2	Were multiple explanatory variables considered in the analyses?	-	No confounders or SES variables included in the model
4.3	Were the analytical methods appropriate?	+	Linear regression
4.4	Was the precision of association given or calculable? Is association meaningful?	+	P values but no confidence intervals

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations due to retrospective review of cases, adequate confounders not adjusted for, no sample size calculation
5.2	Are the findings generalizable to the source population (i.e., externally valid)?	++	Study set in Canada
Overall quality rating		(-,++)	Low

Data Extraction

GENERAL INFORMATION	
Title	Association of type 1 diabetes and concentrations of drinking water components in Newfoundland and Labrador, Canada
Author(s)	Chafe et al.
Publication year	2018
Country (where the study was conducted):	Canada
Funding sources	Grants from Janeway Hospital Research Foundation and the Lesley Harris Centre RBC drinking water and outreach research fund, Memorial University
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To determine the association between drinking water quality and rates of type 1 diabetes in Newfoundland and Labrador
Study design	Case-control
Study location	Newfoundland and Labrador, Canada
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Components in public water supply including fluoride ion
Setting	Community, regional
Source of population	Children 0 to 14 years. Cases of type 1 diabetes were obtained from the Newfoundland and Labrador Pediatric Diabetes Database.
Inclusion/exclusion criteria	Inclusion: Cases consisted of children with type 1diabetes. The controls had no type 1 diabetes.
Recruitment or sampling procedure	Communities with at least one case of type 1 diabetes and communities had no cases. Total 240 communities were included.
Applicability to Canadian context	☑ High ☐ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of cases and controls	Cases: 499 Controls: NR	NR	NR
Age	0 to 14 years	NR	NR
Gender	NR	NR	NR
Subgroups	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Type 1 diabetes
Number of participants analysed	NR
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	One-way ANOVA, linear regression analysis Three level of analysis: 1) Compared between communities with cases and controls for any difference in each component of eater quality (by ANOVA), 2) Regression analysis of water quality indicator levels ant type 1 diabetes incidence rate at community level 3) Regression analysis of water quality indicator levels ant type 1 diabetes incidence rate at regional level
Results	• Incidence rate of type 1 diabetes for province at time of study: 51.7/100,000 • Incidence rate of type 1 diabetes in communities reporting at least one case of type 1 diabetes: 154.1/100,000 (± 175.2 SD); ranged from 16.2 to 1,282.1/100,000. • When comparing communities with cases and controls by ANOVA, levels of ammonia, barium, copper, lead, magnesium, uranium and zinc were significantly higher in communities that reported cases of type 1 diabetes. However, there was no difference in the level of fluoride or arsenic between communities with cases and controls. • Linear regression analyses of water quality indicator and type 1 diabetes incidence rate showed that arsenic (β coefficient = 0.268; *P* = 0.013) and fluoride (β coefficient = 0.202; *P* = 0.005) in drinking water were positively associated with higher incidence of type 1 diabetes at the community level, but not at the regional level. • Barium (β coefficient = -0.478; *P* = 0.009) and nickel (β coefficient = -0.354; *P* = 0.050) were negatively associated with incidence of type 1 diabetes at the regional level, but not at the community level. • No component was found to have a significant association across the three different levels of analysis performed.
CONCLUSION	
Authors' conclusion	*"We confirmed the high incidence of type 1 diabetes in NL. We also found that concentrations of some components in drinking water were associated with higher incidence of type 1 diabetes, but no component was found to have a significant association across the three different levels of analysis performed."* (p.1) [129]
Reviewer's note	No adjustment for confounding variables.

Khandare 2018[112]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Schoolchildren aged 8 to 14 years in villages of Nalgonda district, India. Population demographic not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	-	Cross-sectional study. Recruitment not defined. Unclear as whether the eligible population representative of the source.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Villages were randomly selected. Unclear how the random process was carried out. % of selected individuals or clusters agreed to participate not described Inclusion: All participants were born and had lived in the area since birth.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	NR	
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Evidence for hypothesis was not all based on previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No adjustment for confounding factors
2.5	Is the setting applicable to Canada?	-	Set in India
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis assessed by a dental specialist using the modified Dean index. Biochemical markers (total ALP, PTH, T3, T4, TSH, vitamin D) were measured from blood tests.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis and biochemical parameters
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	-	No multivariable analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	SDs and *p*-values reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Population and method of selection not well described. Risk of selection bias. No adjustment for confounders in data analysis
5.2	Are the findings generalizable to the source population (i.e., externally valid)?	-	Set in India, where socio-economic factors and healthcare differ from those in Canada.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Dose-dependent effect of fluoride on clinical and subclinical indices of fluorosis in school going children and its mitigation by supply of safe drinking water for 5 years: an Indian study
Author(s)	Khandare et al.
Publication year	2018
Country (where the study was conducted):	India
Funding sources	UNICEF
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To assess the fluoride dose-dependent clinical and subclinical symptoms of fluorosis and reversal of disease by providing safe drinking water
Study design	Cross-sectional
Study location	Villages of Nalgonda district, Telangana, India
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	2.53 ppm, 3.77 ppm, < 1 ppm (initial was 4.515 ppm followed by intervention with safe drinking water for 5 years)
• Comparator	0.877 ppm
Setting	School-based
Source of population	8 to 14 years old schoolchildren living in areas having different fluoride levels
Inclusion/exclusion criteria	Inclusion: Born and resided in area since birth
Recruitment or sampling procedure	Villages were randomly selected. Details not reported
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS					
	Total	**3.77 ppm**	**2.53 ppm**	**< 1 ppm (initial 4.515 ppm)**	**0.877 ppm**
Number of participants enrolled	1,934	416	546	327	645
Age	8 to 14 years	8 to 14 years	8 to 14 years	8 to 14 years	8 to 14 years
Gender	46.7% boys	51.2% boys	44.9% boys	42.8% boys	47.4% boys
Subgroups by age (n)					
8 to 10 years	484	108	129	147	100
11 to 13 years	786	190	224	70	302
>13 years	664	118	193	110	243

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis assessed by a dental specialist using the modified Dean index. Biochemical markers (total ALP, PTH, T3, T4, TSH, vitamin D) were measured from blood tests.
Number of participants analysed	1,934
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Chi-square test
Results	**Prevalence and severity of dental fluorosis in children aged 8 to 14 years**

Fluoride level	Modified Dean's index					Fluorosis
	0	1	2	3	4	
3.77 ppm (N=416)	38.2%	40.1%	19.7%	1.9%	0.0%	61.8%
2.53 ppm (N=546)	18.1%	56.6%	22.5%	2.4%	0.4%	81.9%
<1 ppm (N=327)	18.7%	52.3%	26.9%	2.1%	0.0%	81.3%
0.877 ppm (N=645)	78.8%	18.8%	2.3%	0.2%	0.0%	21.2%

- The prevalence of dental fluorosis was higher in higher fluoride levels (i.e., 3.77 ppm, 2.53 ppm, <1 ppm [previous 4.515 ppm 5 years ago]) compared to low fluoride levels (0.877 ppm)
- Within each fluoride category, there was no difference in the prevalence and severity of dental fluorosis between age subgroups.

Biomarkers measured from blood tests

	Water fluoride level (ppm)				Normal range
	3.77	**2.53**	**< 1**	**0.877**	
	mean (SD)				
PTH (pg/mL)	20.0 (4.8)^{a*b*}	17.6 (4.4)^{a*}	14.5 (2.9)^{b*c*}	13.7 (3.8)	9 to 55
T3 (ng/mL)	1.34 (0.32)^{a*b*}	1.57 (0.36)^{a*}	1.46 (0.38)^{a*}	2.17 (0.42)	0.8 to 2.0
T4 (ng/dL)	132.8 (21.9) ^{a*b*}	116.0 (17.3)	84.4 (21.6)^{a*b*c*}	112.7 (22.0)	61 to 118
TSH (μIU/mL)	2.65 (1.04)^{a*b*}	1.85 (0.46)	1.58 (0.44)^{c*}	1.66 (0.49)	0.17 to 11.05

	Water fluoride level (ppm)				Normal range
	3.77	**2.53**	**< 1**	**0.877**	
	mean (SD)				
Alkaline phosphatase (IU/L)	479.2 (141.7)^{a*b*}	275.7 (64.4)	246.8 (58.3)^{c*}	242.0 (88.2)	98 to 279
25-(OH) vitamin D (ng/mL)	25.57 (4.60)^{a*}	24.31 (4.21)^{a*}	35.31 (8.07)^{b*c*}	35.34 (12.37)	30 to 74
1,25-(OH)$_2$ vitamin D (pg/mL)	116.7 (34.3)^{a*b*}	91.8 (46.3)^{a*}	98.4 (22.5)^{a*c*}	37.2 (29.1)	24 to 86

* $P < 0.05$

[a] compared to 0.877 ppm

[b] compared to 2.53 ppm

[c] compared to 3.77 ppm

PTH = parathyroid hormone; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

- At 3.77 ppm, PTH, T4, TSH, alkaline phosphatase and 1, 25-(OH)$_2$ vitamin D levels were significantly higher and T3 level was significantly lower than those at 2.53 and 0.877 ppm.
- PTH, T3 and TSH in all groups were within normal range.
- After 5 years of removal excess fluoride (i.e., < 1 ppm), the levels of PTH, T4, TSH, alkaline phosphatase, 25-(OH) vitamin D and 1, 25-(OH)$_2$ vitamin D were significantly lower than those at 3.77 ppm.

CONCLUSION	
Authors' conclusion	*"the biochemical indices were altered in a dose-dependent manner and intervention with safe drinking water for 5 years in intervention group-mitigated clinical and subclinical symptoms of fluorosis."*[112] p.1
Reviewer's note	No adjustment for confounders.

Kheradpisheh 2018[123]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	The cases and controls were from the Yazd Healthy Study (YaHS) project. Yazd is a warm and dry city of Iran. Population demographics not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear how cases and controls were selected. "*Out of the 8,724 YaHS participants, 693 people reported various thyroid diseases diagnosed by a doctor. Of these, 198 cases and 213 controls were selected*"
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of selection of participants and % of selected individuals or clusters agreed to participate were not described. Inclusion: Cases consisted of participants with thyroid diseases. The controls did not have any thyroid disease.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)			
2.1	Allocation to intervention (or comparison). How was selection bias minimised?	-	Water samples from sites of cases and controls were selected to determine the fluoride concentrations. Likely confounded by other minerals that might affect thyroid diseases.
2.2	Were interventions (and comparisons) well described and appropriate?	-	No
2.3	Was the allocation concealed?	-	No
2.4	Were participants or investigators blind to exposure and comparison?	-	No
2.5	Was the exposure to the intervention and comparison adequate?	NR	
2.6	Was contamination acceptably low?	NR	
2.7	Were other interventions similar in both groups?	NR	
2.8	Were all participants accounted for at study conclusion?	NA	
2.9	Did the setting reflect usual Canadian practice?	-	Set in Iran. Sources of drinking water are from wells.
2.10	Did the intervention or control comparison reflect usual Canadian practice?	+	Drinking water fluoride levels (0 to 0.5 ppm) were lower than Health Canada recommended optimum level (0.7 ppm)
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	T3, T4 and TSH were measured using radioimmunoassay method. Colorimetric method was used to measure fluoride concentrations in water.
3.2	Were all outcome measurements complete?	++	Yes

Item	Question	Rating	Comment
3.3	Were all important outcomes assessed?	++	Yes
3.4	Were outcomes relevant?	++	Yes
3.5	Were there similar follow-up times in exposure and comparison groups?	NA	
3.6	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Were exposure and comparison groups similar at baseline? If not, were these adjusted?	NR	
4.2	Was intention to treat (ITT) analysis conducted?	NA	
4.3	Was the study sufficiently powered to detect an intervention effect (if one exists)?	+	No clear description. Report that sample size was calculated based on a previous study
4.4	Were the estimates of effect size given or calculable?	++	Yes
4.5	Were the analytical methods appropriate?	++	Multiple logistic regression models adjusted for gender, family history of thyroid disease, amount of water consumption, exercise, diabetes, hypertension and drinking water fluoride
4.6	Was the precision of intervention effects given or calculable? Were they meaningful?	++	95% CIs and *p*-values reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Risk of multiple biases
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Could not be generalized to the Canadian population due to difference in socio-economic characteristics, water regulation and healthcare system
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Impact of drinking water fluoride on human thyroid hormones: A case-control study
Author(s)	Kheradpisheh et al.
Publication year	2018
Country (where the study was conducted):	Iran
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No

STUDY CHARACTERISTICS	
Objectives	To study the impacts of drinking water fluoride on T3, T4, and TSH hormones
Study design	Case-control
Study location	Yazd Greater Area, Iran
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	NOF: 0.3 to 0.5 ppm
• Comparator	NOF: 0 to 0.29 ppm
Setting	Community
Source of population	Participants 20 to 70 years from the Yazd Healthy Study project
Inclusion/exclusion criteria	Inclusion: Cases consisted of participants with thyroid diseases. The controls did not have any thyroid disease.
Recruitment or sampling procedure	Unclear how cases and controls were selected
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention (0.3 to 0.5 ppm)**	**Comparator (0.0 to 0.29 ppm)**
Number of cases and controls	411 Cases: 198 Controls: 213	Cases: 139 Controls: 148	Cases: 59 Controls: 65
Age	20 to 60 years	20 to 60 years	20 to 60 years
Gender	Cases: 19.2% male Controls: 41.3% male	NR	NR
Subgroups	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	T3, T4 and TSH were measured using radioimmunoassay method. Colorimetric method was used to measure fluoride concentrations in water.
Number of participants analysed	411
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Multivariable logistic regression analysis

Results

T3, T4 and TSH levels among cases and controls in two levels of fluoride in drinking water

	T3, ng/dL		T4, µg/dL		TSH, mIU/L	
	Mean (SD)		Mean (SD)		Mean (SD)	
	0 to 0.29 ppm	0.3 to 0.5 ppm	0 to 0.29 ppm	0.3 to 0.5 ppm	0 to 0.29 ppm	0.3 to 0.5 ppm
Case	115.3 (22)	117.8 (36.6); *P* = 0.19	6.56 (2.2)	7.6 (4.3); *P* = 0.17	11.85 (7)	20.5 (12.8); *P* = 0.003
Control	135 (18.4)	138.5 (21.6); *P* = 0.026	8.5 (1.2)	8.6 (1.2); *P* = 0.45	2.2 (0.95)	2.8 (0.9); *P* = 0.001
Normal range	78 to 180		5.5 to 12.5		0.17 to 4.5	

- All values of T3 and T4 were within the normal ranges.
- Mean TSH values were significantly higher in 0.3 to 0.5 ppm compared to 0 to 0.29 ppm in both cases and controls
- Among cases, there were no significant differences between fluoride levels for T3 and T4 mean values.

Multivariable logistic regression analysis for factors affecting hypothyroidism in cases and control groups

Drinking water fluoride: 0.3 to 0.5 ppm vs 0.0 to 0.29 ppm

- OR 1.034 (95% CI, 0.7 to 1.53); *P* = 0.86 (0 to 0.29 ppm as Ref)
  (Adjustment for gender, family history of thyroid disease, amount of water consumption, exercise, diabetes and hypertension)
- Drinking water fluoride levels did not significantly associated with hypothyroidism
- Gender, family history of thyroid disease, amount of water consumption, exercise, diabetes and hypertension significantly associated with hypothyroidism

CONCLUSION	
Authors’ conclusion	No concrete conclusion
Reviewer’s note	Gender was imbalanced between cases and controls The authors claimed that amount of water consumption (4 to 5 glasses) was significantly associated with hypothyroidism. However, no significant effect was observed with more than 5 glasses.

Moghaddam 2018[126]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Study conducted in, Iran. Two cities Sarayan county and Poldasht county
1.2	Is the eligible population or area representative of the source population or area?	+	Health records of individuals, however recruitment and eligible population not reported
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of selection not reported, exclusion criteria provided
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Varying fluoride concentrations (≤2.00ppm, 2.01 to 3ppm and 3+ ppm)
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	-	No theoretical basis for selecting explanatory variables
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	Important confounders not included – socio-economic factors, lifestyle, diet, other fluoride products, oral health habits
2.5	Is the setting applicable to Canada?	-	Not applicable to Canada because of different health care context and SES factors
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Data from health records, may be potential biases due to missing data, recall bias, incorrect data entry
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Only harms assessed
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	-	No sample size calculation
4.2	Were multiple explanatory variables considered in the analyses?	+	Not all confounders included in the model
4.3	Were the analytical methods appropriate?	++	Multivariate logitistic regression
4.4	Was the precision of association given or calculable? Is association meaningful?	++	P values and Cis provided

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Retrospective review of medical records, confounders not adjusted for, no sample size calculation
5.2	Are the findings generalizable to the source population (i.e., externally valid)?	-	Not applicable to the Canadian context due to different SES and health care context
Overall quality rating		(-,-)	Low

Data Extraction

GENERAL INFORMATION	
Title	High concentration of fluoride can be increased risk of abortion
Author(s)	Moghaddam et al.
Publication year	2018
Country (where the study was conducted):	Iran
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	Evaluate the effect of drinking fluoride levels on spontaneous abortion in high and low fluoride regions
Study design	Cross-sectional
Study location	Two regions of low and high drinking water fluoride levels
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	Groundwater: ≥ 3 ppm, 1.5 to 3.00 ppm
• Comparator	Groundwater: ≤ 1.5 ppm
Setting	Rural
Source of population	Pregnant women living in areas having different fluoride levels
Inclusion/exclusion criteria	Inclusion: Pregnant women
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS				
	Total	**≤ 1.5 ppm**	**1.5 to 3.00 ppm**	**≥ 3 ppm**
Number of participants enrolled	2,601	2488	43	70
Age	NR	NR	NR	NR
Subgroups	NR	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Number of spontaneous abortion was collected from health centres in those areas
Number of participants analysed	2601
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Multilevel Poisson regression analysis
Results	**Association between water fluoride levels and incidence rate of abortion**

Association between water fluoride levels and incidence rate of abortion

Fluoride level	IRR (95% CI)	*P* value
≤1.5 ppm	Ref (1)	
1.5 to 3.00 ppm	0.85 (0.37 to 1.93	0.693
≥3 ppm	2.06 (1.11 to 3.83)	0.022

IRR = incidence rate ratio

CONCLUSION	
Authors' conclusion	*"The results showed that there is a relationship between the concentration of fluoride in drinking water and abortion, so that the risk of abortion increased at high concentrations of fluoride."*[126] p.1
Reviewer's note	Imbalance in number of participants between groups. No adjustment for confounding variables in the analysis.

PHE 2018[79]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Study set in England
1.2	Is the eligible population or area representative of the source population or area?	++	Study includes all of England, multiple registers used for all the outcomes
1.3	Do the selected participants or areas represent the eligible population or area?	++	Area level analysis including all of Englad
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Fluoridation levels grouped in to 5 categories
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Most important confounders adjusted for
2.5	Is the setting applicable to Canada?	+	May be applicable to Canada due to similar health care context
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Trained dental examiner for dental outcomes, registers for other outcomes may be potential bias
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	++	Benefits and harms assessed
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	+	No sample size calculation , country wide study
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multivariate analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	P-values and CIs provided

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	++	Most confounders adjusted for, representative of the general population, appropriate statistical methods
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	May be applicable to the Canadian population
Overall quality rating		(++,+)	Acceptable

Data Extraction

GENERAL INFORMATION	
Title	Water fluoridation: Health monitoring report for England 2018
Author(s)	Public Health England
Publication year	2018
Country (where the study was conducted):	England
Funding sources	Government of UK
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To determine the association between concentration of fluoride in public water supply in England and selected health outcomes
Study design	Ecological
Study location	England
Study duration	NA
Exposure duration	Lifetime since birth
Fluoride levels or Exposures:	
• Intervention and comparator	Fluoride level in water supply (regardless of source): < 0.1 ppm, 0.1 to < 0.2 ppm, 0.2 to < 0.4 ppm, 0.4 to < 0.7 ppm, ≥ 0.7 ppm
Setting	National
Source of population	Dental fluorosis: children aged 11 to 14 years in 2015 Hip fracture: participants aged 0 to 80+ years (2007 to 2015) Kidney stone: age not reported (2007 to 2015) Down’s syndrome: live births 2012 to 2014 Bladder cancer: age not reported (2007 to 2015) Osteosarcoma: participants aged 0 to 49 years (1995 to 2015)
Inclusion/exclusion criteria	Populations in receipt of public water supplies
Recruitment or sampling procedure	Population data obtained from the Census and related mid-year estimates computed by the Office of National Statistics
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

<table>
<tr><th colspan="2">PARTICIPANT CHARACTERISTICS</th></tr>
<tr><td>Number of participants</td><td>Dental fluorosis: N = 1,899 from 4 cities
Hip fracture: N = 477,610,000 person-years
Kidney stone: N = 477,610,000 person-years
Down’s syndrome: N = 2,020,259 live births
Bladder cancer: N = 827,660,000 person-years
Osteosarcoma: N = 710,260,000 person-years</td></tr>
<tr><td>Gender</td><td>NR</td></tr>
<tr><td>Subgroups</td><td>Male and female for hip fracture</td></tr>
<tr><th colspan="2">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td>Dental fluorosis: TF index
Hip fracture: Data from hospital episode statistics
Kidney stone: Data from hospital episode statistics
Down’s syndrome: The National Congenital Anomaly and Rare Disease Registration Service
Bladder cancer: English Cancer Registration
Osteosarcoma: English Cancer Registration</td></tr>
<tr><td>Number of participants analysed</td><td>Dental fluorosis: N = 1,899</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>45 (did not have a fluoride concentration or fluoridation status allocated)</td></tr>
<tr><td>Imputing of missing data</td><td>NR</td></tr>
<tr><td>Statistical method of data analysis</td><td>Multivariable analysis adjusting for confounders
Hip fracture: gender was stratified; so, adjusted for age, deprivation, ethinicity
Down’s syndrome: adjusted for maternal age
Kidney stone, bladder cancer, osteosarcoma: adjusted for age, gender, deprivation and ethnicity</td></tr>
<tr><td>Results</td><td>

Dental fluorosis: This outcome was reported in Pretty et al. 2016, which was included in the review. The findings are therefore not reported here.
Hip fracture

Incidence of hip fractures between 2007 and 2017, by fluoride levels
<table>
<tr><th>Fluoride level (ppm)</th><th>Crude incidence (per 100,000 person-years)</th><th>Crude IRR (95% CI)</th><th><i>P</i> value</th></tr>
<tr><td><0.1</td><td>121.0 (120.4 to 121.5)</td><td>Ref (1)</td><td>--</td></tr>
<tr><td>0.1 to <0.2</td><td>97.6 (97.1 to 98.1)</td><td>0.81 (0.75 to 0.87)</td><td>< 0.001</td></tr>
<tr><td>0.2 to <0.4</td><td>117.0 (116.2 to 117.8)</td><td>0.97 (0.91 to 1.03)</td><td>0.279</td></tr>
<tr><td>0.4 to <0.7</td><td>123.2 (117.1 to 119.0)</td><td>1.02 (0.93 to 1.12)</td><td>0.699</td></tr>
<tr><td>≥0.7</td><td>97.8 (59.7 to 151.1)</td><td>0.98 (0.89 to 1.07)</td><td>0.597</td></tr>
</table>
Compared with fluoride level of <0.1 ppm, there was no difference in crude rate ration of hip fracture admission at all fluoride levels, except 0.1 to <0.2 ppm, at which hip fracture rate was 19% lower.
</td></tr>
</table>

Adjusted incidence rate ratios of hip fracture admission, stratified by age group, fluoride levels and gender, England (2007 to 2015)

Age (years)	Fluoride level (ppm)	Adjusted IRR in females (95% CI)*; *P* value	Adjusted IRR in males (95% CI)*; *P* value
0 to 49	< 0.1	Ref (1)	Ref (1)
	0.1 to < 0.2	0.82 (0.76 to 0.89); < 0.001	0.86 (0.81 to 0.92); < 0.001
	0.2 to < 0.4	0.87 (0.79 to 0.96); 0.004	0.87 (0.81 to 0.94); < 0.004
	0.4 to < 0.7	0.95 (0.81 to 1.12); 0.540	0.87 (0.79 to 0.96); 0.008
	≥ 0.7	0.87 (0.78 to 0.98); 0.019	0.89 (0.83 to 0.95); 0.001
50 to 64	< 0.1	Ref (1)	Ref (1)
	0.1 to < 0.2	0.92 (0.79 to 0.96); 0.001	0.95 (0.85 to 1.00); 0.064
	0.2 to < 0.4	0.95 (0.90 to 1.00); 0.072	0.89 (0.84 to 0.96); 0.001
	0.4 to < 0.7	0.95 (0.88 to 1.03); 0.211	0.91 (0.83 to 1.01); 0.073
	≥ 0.7	1.04 (0.96 to 1.12); 0.366	1.00 (0.89 to 1.13); 0.977
65 to 79	< 0.1	Ref (1)	Ref (1)
	0.1 to < 0.2	0.97 (0.95 to 1.00); 0.036	1.01 (0.97 to 1.04); 0.778
	0.2 to < 0.4	1.01 (0.98 to 1.04); 0.456	0.98 (0.94 to 1.02); 0.264
	0.4 to < 0.7	1.01 (0.97 to 1.05); 0.785	0.93 (0.89 to 0.98); 0.005
	≥ 0.7	1.06 (1.02 to 1.10); 0.003	1.08 (1.02 to 1.14); 0.009
≥80	< 0.1	Ref (1)	Ref (1)
	0.1 to < 0.2	1.03 (1.00 to 1.05); 0.006	1.04 (1.00 to 1.07); 0.028
	0.2 to < 0.4	1.03 (1.01 to 1.05); 0.001	1.05 (1.02 to 1.08); 0.002
	0.4 to < 0.7	1.03 (1.00 to 1.06); 0.033	1.05 (1.01 to 1.09); 0.008
	≥ 0.7	1.05 (1.02 to 1.09); 0.001	1.05 (0.99 to 1.12); 0.078

*Adjusted for deprivation status and ethnicity

- The association between fluoride levels and hip fracture varied by age group in both females and males.
- At age 0 to 49 years, water fluoride levels of ≥ 0.1 ppm were associated with lower risk of hip fracture admission in both males and females.
- At age 50 to 64 years, there was no clear relationship between water fluoride and fracture admission risk in both males and females.
- At age 65 to 79, fluoride levels at ≥ 0.7 ppm was associated with increased risk of hip fracture admission in both males and females.
- At age ≥ 80 years, the risk of hip fracture admission was significantly increased at all water fluoride levels greater than 0.1 ppm.

Adjusted incidence rate ratios of hip fracture admission, stratified by gender and fluoridation status, England (2007 to 2015)

Gender	Fluoridation status[a]	Adjusted IRR (95% CI)[b]	*P* value
Male	No	Ref (1)	--
	Yes	1.02 (1.00 to 1.05)	0.053
Female	No	Ref (1)	--
	Yes	1.04 (1.01 to 1.06)	0.001

[a] No = fluoride level < 0.2 ppm; Yes = fluoride level ≥ 2 ppm
[b] Adjusted for age, gender, ethnicity and deprivation status

- When compared to areas without water fluoridation scheme (i.e., < 0.2 ppm), there was weak association between fluoridation status (≥ 0.2 ppm) and hip fracture admission in males. In female, there was a small but significantly increased risk of hip fracture admission by 4% (95% CI, 1% to 6%). Adjusted confounders were age, gender, ethnicity and deprivation status.

3. Kidney stone

Adjusted incidence rate ratios of kidney stone admission, by fluoride levels, England 2007 to 2015

Fluoride levels	Adjusted IRR (95% CI)*	*P* value	*P* trend
< 0.1	Ref (1)	--	0.533
0.1 to < 0.2	1.22 (1.14 to 1.30)	< 0.001	
0.2 to < 0.4	1.17 (1.10 to 1.26)	< 0.001	
0.4 to < 0.7	1.07 (0.96 to 1.18)	0.214	
≥ 0.7	1.01 (0.86 to 1.13)	0.857	

* Adjusted for age, gender, ethnicity and deprivation status

- At fluoride levels of 0.1 to < 0.2 ppm and 0.2 to < 0.4 ppm, there was a significantly increased risk of kidney stone admission by 22% and 17% compared to fluoride level of < 0.1 ppm.
- There was no association between kidney stone admission and fluoride at higher levels (i.e., 0.4 to < 0.7 ppm and ≥ 0.7 ppm), after adjustment for age, gender, ethnicity and deprivation status.
- There was no evidence of a trend relationship between fluoride level and kidney stone admission incidence (*P* = 0.533).

Adjusted incidence rate ratios of kidney stone admission, by fluoridation status, England (2007 to 2015)

Fluoridation status[a]	Adjusted IRR (95% CI)[b]	*P* value
No	Ref (1)	--
Yes	0.90 (0.82 to 0.98)	0.020

[a] No = fluoride level < 0.2 ppm; Yes = fluoride level ≥ 2 ppm

[b] Adjusted for age, gender, ethnicity and deprivation status

- After adjustment for age, gender, ethnicity and deprivation status, the risk of admission for kidney stone was 10% lower (95% CI 2% to 18%) in areas with fluoride level of ≥ 2 ppm than in areas where fluoride level was < 2 ppm.

4. Down’s syndrome

Adjusted incidence rate ratios of Down’s syndrome, by fluoride levels, England 2012 to 2014

Fluoride levels	Adjusted IRR (95% CI)*	*P* value	*P* trend
< 0.1	Ref (1)	--	0.941
0.1 to < 0.2	1.11 (1.03 to 1.19)	0.003	
0.2 to < 0.4	0.96 (0.88 to 1.06)	0.446	
0.4 to < 0.7	1.21 (1.05 to 1.40)	0.009	
≥ 0.7	0.99 (0.88 to 1.12)	0.912	

* Adjusted for maternal age

- Compared to the lowest fluoride levels (< 0.1 ppm), there was a significant increase in incidence rate of Down’s syndrome at fluoride levels of 0.1 to < 0.2 ppm (by 11%) and 0.4 to < 0.7 ppm (by 21%), but not at fluoride levels of ≥ 0.7 ppm, after adjustment for maternal age.
- There was no evidence of a trend relationship between fluoride level and Down’s syndrome incidence (*P* = 0.941).

Adjusted incidence rate ratios of Down's syndrome, by fluoridation status, England (2012 to 2014)

Fluoridation status[a]	Adjusted IRR (95% CI)[b]	*P* value
No	Ref (1)	--
Yes	0.97 (0.89 to 1.07)	0.596

[a] No = fluoride level < 0.2 ppm; Yes = fluoride level ≥ 2 ppm

[b] Adjusted for age, gender, ethnicity and deprivation status

- There was no association between water fluoridation status and incidence of Down's syndrome.

5. Bladder cancer

Adjusted incidence rate ratios of bladder cancer, by fluoride levels, England 2007 to 2015

Fluoride levels	Adjusted IRR (95% CI)*	*P* value	*P* trend
< 0.1	Ref (1)	--	0.027
0.1 to < 0.2	0.99 (0.96 to 1.02)	0.434	
0.2 to < 0.4	1.00 (0.97 to 1.03)	0.897	
0.4 to < 0.7	1.00 (0.95 to 1.05)	0.902	
≥ 0.7	0.93 (0.88 to 0.98)	0.004	

* Adjusted for age, gender, ethnicity and deprivation status

- After adjustment for age, gender, ethnicity and deprivation status, fluoride level at ≥ 0.7 ppm was associated with 7% lower in the incidence rate of bladder cancer diagnosis compared to fluoride level of < 0.1 ppm.
- There was no association between water fluoride and bladder cancer incidence at other lower fluoride levels (i.e., 0.4 to < 0.7 ppm, 0.2 to < 0.4 ppm and 0.1 to < 0.2 ppm).
- Test of trend suggested a potential threshold effect above 0.7 ppm, rather than a linear relationship.
- Further analysis by subcategorized ≥ 0.7 ppm into two levels 0.7 to <0.9 ppm and ≥0.9 ppm showed similar risk of bladder cancer at both fluoride levels (IRR = 0.92; 95% CI, 0.86 to 0.98; *P* = 0.015 for 0.7 to < 0.9 ppm and IRR 0.94; 95% CI, 0.89 to 0.99; *P* = 0.017 for ≥ 0.9 ppm).

Adjusted incidence rate ratios of bladder cancer, by fluoridation status, England (2007 to 2015)

Fluoridation status[a]	Adjusted IRR (95% CI)[b]	*P* value
No	Ref (1)	--
Yes	0.94 (0.90 to 0.98)	0.002

[a] No = fluoride level < 0.2 ppm; Yes = fluoride level ≥2 ppm

[b] Adjusted for age, gender, ethnicity and deprivation status

- After adjustment for age, gender, ethnicity and deprivation status, the risk of bladder cancer incidence was 6% lower (95% CI, 2% to 10%) in areas with fluoride level of ≥ 2 ppm than in areas where fluoride level was < 2 ppm.

6. Osteosarcoma

Adjusted incidence rate ratios of osteosarcoma, by fluoride levels, England 1995 to 2015

Fluoride levels	Adjusted IRR (95% CI)*	*P* value	*P* trend
< 0.1	Ref (1)	--	0.569
0.1 to < 0.2	1.04 (0.93 to 1.15)	0.511	
0.2 to < 0.4	0.99 (0.86 to 1.13)	0.852	
0.4 to < 0.7	1.14 (0.94 to 1.39)	0.191	
≥ 0.7	0.90 (0.75 to 1.07)	0.228	

* Adjusted for age and gender

<table>
<tr><td></td><td>

- There was no association between fluoride concentration and osteosarcoma incidence, after adjustment for age and gender.

Adjusted incidence rate ratios of osteosarcoma, by fluoridation status, England (1995 to 2015)

Fluoridation status[a]	Adjusted IRR (95% CI)[b]	*P* value
No	Ref (1)	--
Yes	0.96 (0.90 to 1.11)	0.550

[a] No = fluoride level < 0.2 ppm; Yes = fluoride level ≥ 2 ppm
[b] Adjusted for age and gender

- After adjustment for age and gender, the risk of osteosarcoma incidence was similar in both fluoridation (≥ 2 ppm) and no fluoridation (< 2 ppm) areas.

</td></tr>
<tr><td colspan="2">CONCLUSION</td></tr>
<tr><td>Authors’ conclusion</td><td><i>“We have also been able to explore associations with potential adverse health effects in more detail: despite statistical evidence of associations between exposure to fluoridation and certain health effects in this report, the overall analysis and weight of evidence means causal associations are unlikely.”</i>(p.116)[79]</td></tr>
<tr><td>Reviewer’s note</td><td></td></tr>
</table>

Yousefi 2018[113]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Study conducted in West Azerbaijan Province, Iran. Four villages of the city of Poldasht; demographics of the population described
1.2	Is the eligible population or area representative of the source population or area?	+	Health records of individuals, however recruitment and eligible population not reported
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of selection not reported, exclusion criteria provided
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Areas with high fluoride in comparison to low fluoride (range from 0.79 to 10.15 ppm
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Theoretical basis for fluoride – accumulation of fluoride in the hard and soft tissues causes cardiovascular changes and
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	Important confounders not included – socio-economic factors, lifestyle, diet, other fluoride products, oral health habits
2.5	Is the setting applicable to Canada?	-	Not applicable to Canada because of different health care context and SES factors
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Data from health records, may be potential biases due to missing data, recall bias, incorrect data entry Method of measurement not reported

Item	Question	Rating	Comment
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Only harms assessed, benefits not assessed
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	-	No sample size calculation
4.2	Were multiple explanatory variables considered in the analyses?	+	Not all confounders included in the model
4.3	Were the analytical methods appropriate?	++	Multivariate logistic regression
4.4	Was the precision of association given or calculable? Is association meaningful?	++	P values and Cis provided
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Potential bias due to retrospective review of medical records, important confounders not adjusted for
5.2	Are the findings generalizable to the source population (i.e., externally valid)?	-	Not generalizable to Canada due to different SES and different health care context.
Overall quality rating		(-,-)	Low

Data Extraction

GENERAL INFORMATION	
Title	Association of hypertension, body mass index, and waist circumference with fluoride intake; water drinking in residents of fluoride endemic areas, Iran
Author(s)	Yousefi et al.
Publication year	2018
Country (where the study was conducted):	Iran
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To investigate the association between drinking water fluoride and hypertension, body mass index, and waist circumference
Study design	Cross-sectional
Study location	Two villages with low and high fluoride levels, Iran
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	High: 10.15 ppm

<table>
<tr><td>• Comparator</td><td colspan="3">Low: 0.79 ppm</td></tr>
<tr><td>Setting</td><td colspan="3">Rural</td></tr>
<tr><td>Source of population</td><td colspan="3">Residents aged 27 to 43 years living in two villages in the Northwest part of Iran</td></tr>
<tr><td>Inclusion/exclusion criteria</td><td colspan="3">NR</td></tr>
<tr><td>Recruitment or sampling procedure</td><td colspan="3">NR</td></tr>
<tr><td>Applicability to Canadian context</td><td colspan="3">☐ High ☐ Partial ☑ Limited</td></tr>
<tr><td colspan="4">PARTICIPANT CHARACTERISTICS</td></tr>
<tr><td></td><td>Total</td><td>Intervention (10.15 ppm)</td><td>Comparator (0.79 ppm)</td></tr>
<tr><td>Number of participants enrolled</td><td>346</td><td>190</td><td>156</td></tr>
<tr><td>Age</td><td>27 to 43 years</td><td>29 to 43 years</td><td>27 to 42 years</td></tr>
<tr><td>Male</td><td>45.7%</td><td>44.7%</td><td>46.8%</td></tr>
<tr><td colspan="4">REPORTED OUTCOMES</td></tr>
<tr><td>Definition (with units) and method of measurement</td><td colspan="3">Isolated systolic hypertension, ISH (SBP ≥ 140 mmHg and DBP ≤ 90 mmHg)
Isolated diastolic hypertension, ISH (SBP ≤ 140 mmHg and DBP ≥ 90 mmHg)
Isolated systolic-diastolic hypertension, ISH (SBP ≥ 140 mmHg and DBP ≥ 90 mmHg)</td></tr>
<tr><td>Number of participants analysed</td><td colspan="3">346</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td colspan="3">NR</td></tr>
<tr><td>Imputing of missing data</td><td colspan="3">NR</td></tr>
<tr><td>Statistical method of data analysis</td><td colspan="3">Chi-square test, multivariable logistic regression</td></tr>
<tr><td>Results</td><td colspan="3">Blood pressure (mean ± SE) of participants in two areas
<table>
<tr><th rowspan="2"></th><th colspan="2">Fluoride level</th><th rowspan="2"><i>P</i> value</th></tr>
<tr><th>0.79 ppm</th><th>10.15 ppm</th></tr>
<tr><td>SBP (mmHg)</td><td>111.6 ± 1.33</td><td>118.7 ± 1.06</td><td><0.001</td></tr>
<tr><td>DBP (mmHg)</td><td>71.4 ± 0.622</td><td>74.3 ± 0.787</td><td>0.005</td></tr>
</table>
Prehypertension prevalence: [No definition for prehypertension provided]
• High fluoride (10.15 ppm): 48.94% (93/190)
• Low fluoride (0.79 ppm): 6.41 % (10/156)

Regression analysis on hypertension:
• High fluoride (10.15 ppm): OR 2.3 (95% CI, 1.03 to 5.14); <i>P</i> = 0.041
• Low fluoride (0.79 ppm): Ref
(Adjustment for age, sex, BMI and waist circumference)</td></tr>
<tr><td colspan="4">CONCLUSION</td></tr>
<tr><td>Authors' conclusion</td><td colspan="3"><i>"This study declared a significant correlation between exposure to excess fluoride in drinking water and the prevalence of hypertension in people living in fluoride endemic areas."</i>[113] p. 5</td></tr>
<tr><td>Reviewer's note</td><td colspan="3">No adjustment for confounding variables related to hypertension.</td></tr>
</table>

Aggeborn 2017[69]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data from Swedish registers for cohort born 1985-1992 and information on fluoride levels in CWF.
1.2	Is the eligible population or area representative of the source population or area?	++	Yes
1.3	Do the selected participants or areas represent the eligible population or area?	++	Method of selection of participants (aged 16 and older) was well described. Inclusion/exclusion criteria were explicit.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on fluoride levels in drinking water (from the Swedish Geological Survey data and drinking water data from municipalities), and fluoride exposure since birth.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Evidence for hypothesis derived from previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Sex, marital status, parent's education, parent's income, father's cognitive and non-cognitive ability, parent immigrant, cohort mean education (at birth, at school start, at 16 years age). No dental habit or diet.
2.5	Is the setting applicable to Canada?	+	Set in Sweden. May be applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Dental health data were from The National Board of Health and Welfare. Cognitive and non-cognitive ability measures were assessed according to the Stanine scale. Labour market outcome data were from the Swedish tax agency.
3.2	Were all outcome measurements complete?	+	All participants born between 1985 and 1992 eligible.
3.3	Were all important outcomes assessed?	++	Dental outcomes, cognitive ability, non-cognitive ability, math test scores, and labour market outcomes
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	

Item	Question	Rating	Comment
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Weightened regression analysis.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs and p values reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	++	Good in population recruitment, method of selection of exposure, outcome measure and data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study conducted in Sweden. May be generalizable to the Canadian Context due to comparable fluoride levels.
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	The effect of fluoride in the drinking water
Author(s)	Aggeborn and Öhman
Publication year	2017
Country (where the study was conducted):	Sweden
Funding sources	U-CARE
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To study the effect of fluoride exposure through the drinking water throughout life on cognitive and non-cognitive ability, math test scores and labour market outcomes
Study design	Ecological
Study location	Sweden
Study duration	NA
Exposure duration	Lifetime since birth
Fluoride levels or Exposures:	
• Intervention and comparator	Non-artificially fluoridated water with fluoride levels in the community water ≤ 1.5 ppm. Naturally occurring fluoride in drinking water ranges between 0 and 4 ppm, where the absolute majority of Swedish water plants have fluoride levels below 1.5 ppm. The water authorities may reduce the fluoride levels in the water if the level exceeds 1.5 ppm.
Setting	National
Source of population	Individuals of age 16 and older
Inclusion/exclusion criteria	Cohorts born between 1985 and 1992. Individuals immigrated to Sweden during childhood were excluded.
Recruitment or sampling procedure	Cognitive and non-cognitive ability measures were from the Swedish military enlistment. Labour market outcome data were from the Swedish tax agency.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS	
Number of observations	
Cognitive ability	17,864 to 81,776
Non-cognitive ability	14,408 to 66,375
Math test in the ninth grade	119,233 to 499,892
Annual income	140,663 to 634,793
Employment status	158,504 to 728,074
REPORTED OUTCOMES	
Definition (with units) and method of measurement	Cognitive and non-cognitive ability measures were assessed according to the Stanine scale (a Stanine point ~ 6 to 8 IQ points). For cognitive ability, a test was used to measure the underlying intelligence. For non-cognitive ability, the individual was evaluated the ability to function in a war scenario, i.e., willingness to take initiative emotional balance. Math test was taken in the ninth grade. Average number of points on the test was 27 points. Labour market outcomes (i.e., annual income, employment status); 2014 data on annual income from the Swedish tax agency. Employment status is a dummy variable taking the value of 1 if the individual was defined as employed in 2014.
Number of participants analysed	NR
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Regression analysis.
Results	

Outcomes	**β-coefficient (SE); expressed in 0.1 ppm F**	
	Unadjusted[a]	Adjusted
Cognitive ability (up to age 18)	-0.0088 (0.0030)***	0.0058[b] (0.0041)
Non-cognitive ability (up to age 18)	0.0026 (0.0026)	0.0165[b] (0.0046)***
Math test in the ninth grade	-0.1031 (0.0099)***	-0.0205[c] (0.0088)**
Log annual labour income in 2014	0.0053 (0.0007)***	0.0044[b] (0.0010)***
Log employment status	0.0021 (0.0003)***	0.0022[b] (0.0004)***

[a] Without fixed effects and covariates

[b] With fixed effects and covariates of group 2

[c] With fixed effects and covariates of group 1 and group 2

Covariate group 1 = sex, marital status

Covariate group 2 = parent's education, parent's income, father's cognitive and non-cognitive ability, parent immigrant, cohort mean education [at birth, at school start, at 16 years age])

*** $P < 0.01$, ** $P < 0.05$

CONCLUSION	
Authors' conclusion	*"we find precisely estimated zero-effects on cognitive ability, non-cognitive ability and math test scores for fluoride levels in Swedish drinking water."*[69] p.1 *"we find that fluoride improves later labor market outcomes, which indicates that good dental health is a positive factor on the labor market."*[69] p.1
Reviewer's note	With regards to cognitive ability and non-cognitive ability, the results should be multiplied by 10 when expressed in 1 ppm F. With regards to annual labour income and employment status, the results should be multiplied by 1000 when expressed in 1 ppm F.

Arora 2017[91]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data from the National Survey of Oral Health of US School Children (aged 4 to 22 years) 1986 to 1987. Population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Yes. Children aged 7 to 17 years with a history of single continuous residence were included.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Yes
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on the level of fluoride in water fluoridation.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis derived from previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	++	Age, gender, race/ethnicity, other sources of fluoride, region.
2.5	Is the setting applicable to Canada?	+	Set in US. Likely applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Dental fluorosis was assessed using Dean's index. Measurement validity not reported.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	+	Reported elsewhere.
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multinomial logistic regression models.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported.

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	++	Good in population recruitment, method of selection of exposure and data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study conducted in USA. Could be generalizable to the Canadian Context.
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION			
Title	Does water fluoridation affect the prevalence of enamel fluorosis differently among racial and ethnic groups?		
Author(s)	Arora et al.		
Publication year	2017		
Country (where the study was conducted):	USA		
Funding sources	NR		
Reported conflict of interest	☐ Yes	☑ No	
STUDY CHARACTERISTICS			
Objectives	To assess whether the effect of water fluoride level on enamel fluorosis is different among different race/ethnicity groups among US school children.		
Study design	Ecological		
Study location	USA		
Study duration	NA		
Exposure duration	Lifetime		
Fluoride levels or Exposures:			
• Intervention	0.3 to < 0.7 ppm 0.7 to 1.2 ppm		
• Comparator	< 0.3 ppm		
Setting	National survey		
Source of population	Children aged 7 to 11 years and 12 to 17 years		
Inclusion/exclusion criteria	Children aged 7 to 17 years with a history of single continuous residence were included in the analysis.		
Recruitment or sampling procedure	National survey of oral health in US school children 1986 to 1987		
Applicability to Canadian context	☐ High	☑ Partial	☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total		**Total**
Number of participants enrolled	16,060	Other source of fluoride, %	
Age, years	7 to 17	Yes	77.1
Gender, %		No	22.9
Male	51.8	Region, %	
Female	48.2	Midwest	23.5

Race/ethnicity, %		New England	5.0
Black, Non-Hispanic	22.2	Northeast	18.8
Other, Non-Hispanic	3.4	Northwest	5.2
White, Non-Hispanic	60.5	Pacific	10.6
White/Black, Hispanic	13.9	Southeast	27.7
Water fluoridation, %		Southwest	9.2
<0.3 ppm	36.9		
0.3 to <0.7 ppm	10.8		
0.7 to 1.2 ppm	52.3		
REPORTED OUTCOMES			
Definition (with units) and method of measurement	Dental fluorosis was assessed using Dean’s index. Criteria: 0: normal; 1: questionable; 2: very mild; 3: mild; 4: moderate; 5: severe		
Number of participants analysed	16,060		
Number of participants excluded or missing (with reasons)	NA		
Imputing of missing data	NA		
Statistical method of data analysis	Fitted Multinomial Regression Models.		
Results			

Dental fluorosis as a function of water fluoridation

Water fluoridation (ppm)	Weighted prevalence (%) of dental fluorosis (95% CI)			Maximum likelihood estimates
	Normal	Questionable	Fluorosis present	
<0.3	62.9 (55.9 to 69.8)	24.7 (19.2 to 30.1)	12.5 (8.9 to 16.1)	Ref
0.3 to <0.7	51.7 (37.4 to 66.1)	28.7 (22.6 to 34.8)	19.6 (7.3 to 31.9)	-0.12; *P* = 0.73
0.7 to 1.2	38.3 (30.0 to 46.6)	33.9 (26.1 to 41.6)	27.9 (21.4 to 34.3)	0.79; *P* = 0.00

Adjusted for age, gender, race/ethnicity, other sources of fluoride, region.

Dental fluorosis as a function of race/ethnicity

	Weighted prevalence (%) of dental fluorosis (95% CI)			Maximum likelihood estimates
	Normal	Questionable	Fluorosis present	
Race/ethnicity				
White, Non-Hispanic	50.9 (43.8 to 57.9)	28.3 (22.9 to 33.8)	20.8 (15.4 to 26.3)	Ref
Black, Non-Hispanic	40.7 (29.6 to 51.8)	33.6 (26.4 to 40.7)	25.7 (15.5 to 36.5)	0.07; *P* = 0.86
Hispanic	51.6 (40.8 to 62.4)	30.8 (22.8 to 38.7)	17.7 (9.3 to 26.0)	-0.66; *P* = 0.04
Other	57.4 (48.0 to 66.9)	28.3 (20.9 to 35.6)	14.3 (9.0 to 19.6)	-0.13; *P* = 0.55

	Weighted prevalence (%) of dental fluorosis (95% CI)			Maximum likelihood estimates
	Normal	Questionable	Fluorosis present	
Interaction				
White, Non-Hispanic x (0.3 to <0.7 ppm)				Ref
White, Non-Hispanic x (0.7 to 1.2 ppm)				Ref
Black Non-Hispanic x (0.3 to <0.7 ppm)				0.54; *P* = 0.25
Black Non-Hispanic x (0.7 to 1.2 ppm)				0.23; *P* = 0.60
Hispanic x (0.3 to <0.7 ppm)				1.70; *P* = 0.00
Hispanic x (0.7 to 1.2 ppm)				0.51; *P* = 0.15
Other x (0.3 to <0.7 ppm)				0.61; *P* = 0.33
Other x (0.7 to 1.2 ppm)				-0.30; *P* = 0.35

Adjusted for age, gender, water fluoridation, other sources of fluoride, region.

CONCLUSION	
Authors' conclusion	*"Enamel fluorosis was not associated with race/ethnicity. Our analysis suggests that exposure to similar levels of fluoride in the water does not appear to place certain race/ethnic groups at a higher risk for developing enamel fluorosis, and lowering the optimal range of drinking water fluoride to a single value of 0.7 ppm will provide a level of protection against enamel fluorosis that will benefit all race/ethnicity groups."*(p.1) [91]
Reviewer's note	Old data set (30 years old)

Barberio 2017a[120]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data source was from Cycles 2 (2009 to 2011) and 3 (2012 to 2013) of the Statistics Canada's Canadian Health Measures Survey. Population demographics were well described.
1.2	Is the eligible population or area representative of the source population or area?	++	Cross-sectional survey of a nationally representative sample of Canadians that consists of a household interview followed by physical health measurements. Target population was Canadians aged 3 to 79 years leaving in 10 provinces. Data from children 3 to 12 years were analyzed.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Complex random sampling was used to select respondents. The overall respond rates were 55.5% (Cycle 2) and 51.7% (Cycle 3). Data from children aged 3 to 12 years old were analyzed.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	• Urine fluoride levels: unadjusted, creatinine-adjusted and specific gravity-adjusted. • Tap water fluoride levels.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Diagnosis of learning disability from health professional, but little information provided on ICD codes or methods used to diagnose, ,may be at risk of bias.
2.3	Was the contamination acceptably low?	NR	

Item	Question	Rating	Comment
2.4	How well were likely confounding factors identified and controlled?	+	Sex, age, household education and household income were included as potential confounders. May miss other important confounders.
2.5	Is the setting applicable to Canada?	++	Set in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	-	Learning disability assessed by a single item from household survey. Follow-up question about type of disability was omitted in Cycle 3. Diagnosis of learning disability was based on self-reported; but little information provided on ICD codes or methods used to diagnose. Risk of reporting bias.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Learning disability (only answered as Yes or No)
3.4	Was there a similar follow-up time in exposure and comparison groups	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	SES factors, fluoridation exposure
4.3	Were the analytical methods appropriate?	++	Logistic regression
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Major limitation due to self –reported diagnosis of disability; no confounders, water fluoridation from data collection site.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	++	Study conducted in Canada
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Fluoride exposure and reported learning disability diagnosis among Canadian children: Implications for community water fluoridation
Author(s)	Barberio et al.
Publication year	2017
Country (where the study was conducted):	Canada
Funding sources	CIHR, Public Health Agency of Canada, and Alberta Innovates – Health Solutions
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To examine the association between fluoride exposure and parental- or self-reported diagnosis of a learning disability among a population-based sample of Canadian children ages 3 to 12 years.
Study design	Ecological
Study location	Canada
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Determined from urine fluoride levels (Cycle 2 [2009 to 2011]) and tap water fluoride levels (Cycle 3 [2012 to 2013])
Setting	Survey of a nationally representative sample consists of a household interview followed by physical health measurements taken at a mobile examination clinic.
Source of population	Canadians aged 3 to 79 years living in private households in the 10 provinces.
Inclusion/exclusion criteria	Children aged 3 to 12 years
Recruitment or sampling procedure	Complex random sampling was used to select respondents.
Applicability to Canadian context	☑ High ☐ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS		
	Cycle 2	**Cycle 3**
Number of participants enrolled	1,844	1,726
Age	3 to 12 years	3 to 12 years
Gender	52% males	51% males

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Learning disability assessed by a single item from household survey ("*Do you have a learning disability?*"). Follow-up question about type of disability was omitted in Cycle 3. Diagnosis of learning disability was based on parental- or self-reported.
Number of participants analysed	N = 1,120 from Cycle 2 N = 1,101 from Cycle 3
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Logistic regression analysis
Results	1. **For Cycle 2 of the Canadian Health Measures Survey (CHMS)**

Predictor variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Parental- or self-reported learning disability among children aged 3 to 12 years		
Urinary fluoride	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.04)
Creatinine-adjusted urinary fluoride	0.99 (0.87 to 1.13)	1.04 (0.95 to 1.15)
Specific gravity-adjusted urinary fluoride	1.00 (0.99 to 1.02)	1.01 (0.99 to 1.02)
Parental- or self-reported diagnosis of ADHD among children aged 3 to 12 years		
Urinary fluoride	1.02 (0.97 to 1.08)	1.02 (0.97 to 1.09)
Creatinine-adjusted urinary fluoride	0.97 (0.71 to 1.32)	1.01 (0.85 to 1.21)
Specific gravity-adjusted urinary fluoride	1.01 (0.97 to 1.05)	1.01 (0.96 to 1.06)
Parental- or self-reported diagnosis of ADD among children aged 3 to 12 years		
Urinary fluoride	0.98 (0.93 to 1.04)	0.99 (0.93 to 1.05)
Creatinine-adjusted urinary fluoride	0.62 (0.47 to 0.83)***	0.79 (0.59 to 1.06)
Specific gravity-adjusted urinary fluoride	0.97 (0.92 to 1.03)	0.98 (0.94 to 1.03)

[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household
***$P < 0.01$

2. For Cycle 3 of the CHMS

Predictor variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Parental- or self-reported learning disability among children aged 3 to 12 years		
Urinary fluoride	1.01 (0.996 to 1.03)	1.02 (0.99 to 1.04)
Creatinine-adjusted urinary fluoride	1.01 (0.77 to 1.34)	1.03 (0.86 to 1.23)
Specific gravity-adjusted urinary fluoride	1.01 (0.99 to 1.02)	1.01 (0.99 to 1.03)
Fluoride concentration of tap water	1.41 (0.14 to 14.41)	0.88 (0.068 to 11.33)

[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household

3. For Cycles 2 and 3 of the CHMS

Predictor variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Parental- or self-reported learning disability among children aged 3 to 12 years		
Urinary fluoride	1.01* (1.00 to 1.03)	1.02** (1.00 to 1.03)
Creatinine-adjusted urinary fluoride	1.00 (0.91 to 1.10)	1.04 (0.98 to 1.10)
Specific gravity-adjusted urinary fluoride	1.01 (1.00 to 1.02)	1.01 (1.00 to 1.02)

[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household
**$P < 0.05$, *$P < 0.1$

Summary of findings:

- When Cycle 2 were examined, self-reported learning disability, self-reported diagnosis of ADHD and self-reported diagnosis of ADD were not significantly associated with fluoride exposure measured as urinary fluoride, creatinine-adjusted urinary fluoride or specific gravity-adjusted urinary fluoride.
- When Cycle 3 was examined, self-reported learning disability was not significantly associated with fluoride exposure measured as urinary fluoride, creatinine-adjusted urinary fluoride, specific gravity-

	adjusted urinary fluoride or fluoride concentration of tap water. - When Cycles 2 and 3 were combined, there was a small significant association between self-reported learning disability and urinary fluoride. However, the association was not observed with creatinine-adjusted urinary fluoride or specific gravity-adjusted urinary fluoride.
CONCLUSION	
Authors' conclusion	*"Overall, there did not appear to be a robust association between fluoride exposure and parental- or self-reported diagnosis of a learning disability among Canadian children."* (p.e229) [120]
Reviewer's note	The study did not capture the severity of the learning disability, ADHD or ADD. The outcomes were self-reported, risk of reporting and recalling biases.

Barberio 2017b[124]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Data source was from Cycles 2 (2009 to 2011) and 3 (2012 to 2013) of the Statistics Canada's Canadian Health Measures Survey. Population demographics were well described.
1.2	Is the eligible population or area representative of the source population or area?	++	Cross-sectional survey of a nationally representative sample of Canadians that consists of a household interview followed by physical health measurements. Target population was Canadians aged 3 to 79 years leaving in 10 provinces.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Complex random sampling was used to select respondents. The overall respond rates were 55.5% (Cycle 2) and 51.7% (Cycle 3). Data from participants aged 3 to 79 years old were analyzed.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	- Urine fluoride levels: unadjusted and creatinine-adjusted. - Tap water fluoride levels.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Sex, age, household education and household income were included as potential confounders. Risk of missing other potential confounders
2.5	Is the setting applicable to Canada?	++	Set in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Thyroid function measured subjectively and objectively: 1) Self-reported diagnosis of thyroid condition 2) TSH level 3) Blood test for primary hypothyroidism (TSH, free T4, antithyroid peroxidase, antithyroglobulin)

Item	Question	Rating	Comment
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Only harms assessed
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Logistic regression
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good source of population, acceptable selection methods and good data analysis. Risk of selection bias.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	++	Study conducted in Canada
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	Fluoride exposure and indicators of thyroid functioning in the Canadian population: Implications for community water fluoridation
Author(s)	Barberio et al.
Publication year	2017
Country (where the study was conducted):	Canada
Funding sources	CIHR, Public Health Agency of Canada, and Alberta Innovates – Health Solutions
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To examine the association between fluoride exposure and (1) diagnosis of a thyroid condition and (2) indicators of thyroid functioning among a national-based sample of Canadians
Study design	Ecological
Study location	Canada
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Determined from urine fluoride levels (Cycle 2 [2009 to 2011]) and tap water fluoride levels (Cycle 3 [2012 to 2013])
Setting	Survey of a nationally representative sample consisting of a household interview followed by physical health measurements taken at a mobile examination clinic.

Source of population	Canadians aged 3 to 79 years living in private households in the 10 provinces.
Inclusion/exclusion criteria	Exclusion: three territories, Aboriginal settlements, institutionalized residents, members of the Canadian Forces, and residents of certain remote areas. Pregnant women and those taking thyroid medications were excluded.
Recruitment or sampling procedure	Complex random sampling was used to select respondents.
Applicability to Canadian context	☑ High ☐ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS

	Cycle 2	**Cycle 3**
Number of participants enrolled	6,395	5,785
Age, mean (95% CI)	38.57 (38.35 to 38.80)	39.05 (38.40 to 39.70)
Gender	50.06% females	50.06% females

REPORTED OUTCOMES

Definition (with units) and method of measurement	Thyroid function measured subjectively and objectively: 4) Self-reported diagnosis thyroid condition (“*Do you have a thyroid condition?”)* 5) TSH level 6) Blood test for primary hypothyroidism (TSH, free T4, antithyroid peroxidase, antithyroglobulin)
Number of participants analysed	N = 2,530 from Cycle 2 N = 2,671 from Cycle 3
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Logistic regression analysis
Results	

1. **For Cycle 2**

	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)[a]**
Self-reported diagnosis of a thyroid condition		
Urinary fluoride	0.98 (0.94 to 1.03)	0.98 (0.95 to 1.02)
Creatinine-adjusted urinary fluoride	NS (data not shown)	NS (data not shown)

[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household

***$P < 0.01$

2. **For Cycle 3**

	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)[a]**
Self-reported diagnosis of a thyroid condition		
Urinary fluoride	1.00 (0.99 to 1.02)	1.00 (0.99 to 1.01)
Creatinine-adjusted urinary fluoride	NS (data not shown)	NS (data not shown)
Fluoride concentration of tap water	0.92 (0.22 to 3.94)	0.98 (0.28 to 3.45)
TSH levels		
Low TSH	1.01 (0.99 to 1.04)	1.01 (0.99 to 1.04)
Normal TSH	Ref	Ref
High TSH	0.99 (0.97 to 1.02)	0.99 (0.97 to 1.02)

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Creatinine-adjusted urinary fluoride	NS (data not shown)	NS (data not shown)
Fluoride concentration of tap water		
Low TSH	1.77 (0.20 to 15.86)	1.38 (0.08 to 24.49)
Normal TSH	Ref	Ref
High TSH	1.38 (0.07 to 27.00)	1.20 (0.14 to 10.08)

[a] Adjusted for age, sex, household income adequacy, and highest attained education in the household
OR = odds ratio; RRR = relative risk ratio

- There were no differences between individuals with or without primary hypothyroidism in urinary fluoride (31.78 µmol/L; 95% CI, 11.63 to 51.93 vs 29.23 µmol/L; 95% CI, 25.97 to 32.49 and in fluoride concentration of tap water (0.36 ppm; 95% CI, 0.16 to 0.57 vs 0.22 ppm; 95% CI, 0.15 to 0.30).

3. For the constrained subsamples of Cycles 2 and 3

<table>
<tr><th></th><th colspan="3">No thyroid condition</th><th colspan="3">With thyroid condition</th></tr>
<tr><td colspan="7"><i>Cycle 2</i>[a]</td></tr>
<tr><td>Urinary fluoride (µmol/L), mean (95% CI); <i>(n=~390)</i></td><td colspan="3">41.61 (34.50 to 48.72)</td><td colspan="3">38.60 (30.12 to 47.00)</td></tr>
<tr><td colspan="7"><i>Cycle 3 subsample</i>[b]</td></tr>
<tr><td>Urinary fluoride (µmol/L), mean (95% CI); <i>(n=~590)</i></td><td colspan="3">34.18 (26.30 to 42.06)</td><td colspan="3">39.58 (29.27 to 49.89)</td></tr>
<tr><th></th><th colspan="2">Low TSH</th><th colspan="2">Normal TSH</th><th colspan="2">High TSH</th></tr>
<tr><td colspan="7"><i>Cycle 3</i>[b]</td></tr>
<tr><td>Urinary fluoride (µmol/L), mean (95% CI); <i>(n=~820)</i></td><td colspan="2">40.01
(24.35 to 55.67)</td><td colspan="2">33.92
(26.79 to 41.05)</td><td colspan="2">30.76 (17.89 to 43.63)</td></tr>
<tr><td>Mean fluoride concentration of tap water (ppm), mean (95% CI); <i>(n=~820)</i></td><td colspan="2">0.34
(0.16 to 0.51)</td><td colspan="2">0.35
(0.21 to 0.49)</td><td colspan="2">0.38
(0.19 to 0.57)</td></tr>
</table>

[a] Refers to respondents who: (1) attend a fluoridated data collection site, (2) identified tap water was their primary source of drinking water at home and, (3) lived in their current home for three or more years.

[b] Refers to respondents who: (1) attend a fluoridated data collection site, (2) reported using fluoride-containing dental products at home and, (3) reported ever receiving fluoride treatment at the dentist.

Summary of findings:
- There was no association between the measures of fluoride exposure (urinary fluoride or fluoride concentration of tap water) and self-reported diagnosis of a thyroid condition.
- There was also no association between the measures of fluoride exposure (urinary fluoride or fluoride concentration of tap water) and abnormal (low or high) TSH level compared to normal TSH level.
- Individuals with a thyroid condition and those without did not differ in the mean of urinary fluoride or the mean of fluoride concentration of tap water.

CONCLUSION	
Authors' conclusion	*"at the population level, fluoride exposure is not associated with impaired thyroid functioning in a time and place where multiple sources of fluoride exposure, including CWF, exist."*[124] p.1019
Reviewer's note	Limitations: Risk of reporting bias. Family history of thyroid disease not available. Urine fluoride might fluctuate from spot urine sample measurement.

Bonola-Gallardo 2017[103]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Schoolchildren aged 9 to 12 years from public elementary schools located in the state of Morelos in South-Central Mexico. Population demographics not adequately described
1.2	Is the eligible population or area representative of the source population or area?	++	Children between 9 to 12 years of age from public elementary schools
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of selection not well described. Eligibility criteria provided, number of children who agreed to participate also provided.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selection based on community water fluoride concentration. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	-	Evidence for hypothesis based on toxicology study.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No
2.5	Is the setting applicable to Canada?	-	Set in Mexico, where socio-economic factors and healthcare differ from those in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Degree of dental fluorosis was assessed using the TF index. Measurements were performed by a trained and standardized dentist. No objective measurement.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No confounders adjusted for dental fluorosis

Item	Question	Rating	Comment
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported in dental fluorosis analysis
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Poor selection methods, poor data analysis. Potential risk of bias existed.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Set in Mexico, where socio-economic factors and healthcare differ from those in Canada. Comparator, not <0.4 ppm
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Enzymatic Activity of glutathione S-transferase and dental fluorosis among children receiving two different levels of naturally fluoridated water
Author(s)	Bonola-Gallardo et al.
Publication year	2017
Country (where the study was conducted):	Mexico
Funding sources	Grant from CONACYT-México
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To measure the activity of the enzyme glutathione S-transferase (GST) in saliva and to compare the activity of this enzyme in children with and without dental fluorosis in communities with different concentrations of naturally fluoridated water.
Study design	Cross-sectional
Study location	Public elementary schools located in a rural region in the southeast of the state of Morelos, Central Mexico.
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	1.8 ppm
• Comparator	0.4 ppm
Setting	School-based
Source of population	Schoolchildren aged 9 to 12 years
Inclusion/exclusion criteria	Inclusion: lifelong residents in respective communities and did not have systemic diseases
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

<table>
<tr><th colspan="4">PARTICIPANT CHARACTERISTICS</th></tr>
<tr><td></td><td>Total</td><td>Intervention</td><td>Comparator</td></tr>
<tr><td>Number of participants enrolled</td><td>141</td><td>70</td><td>71</td></tr>
<tr><td>Age, mean (SD)</td><td>10.6 years (1.03)</td><td>NR</td><td>NR</td></tr>
<tr><td>Gender</td><td>85 (60.2%) females</td><td>NR</td><td>NR</td></tr>
<tr><td>Subgroups reported</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><th colspan="4">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td colspan="3">Dental fluorosis was assessed using the TF index.
TFI 0 to 1: no or very low
TFI 2 to 3: mild
TFI ≥ 4: moderate to severe
GST was an irrelevant outcome.</td></tr>
<tr><td>Number of participants analysed</td><td colspan="3">141</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td colspan="3">NR</td></tr>
<tr><td>Imputing of missing data</td><td colspan="3">NR</td></tr>
<tr><td>Statistical method of data analysis</td><td colspan="3">For dental fluorosis, significance level was set at $p<0.05$</td></tr>
<tr><td>Results</td><td colspan="3">
<table>
<tr><th>Fluoride</th><th>TFI 0 to 1</th><th>TFI 2 to 3</th><th>TFI ≥4</th><th><i>p</i> value</th></tr>
<tr><td>0.4 ppm (n = 71)</td><td>69 (97%)</td><td>1 (1.4%)</td><td>1 (1.4%)</td><td><0.0001</td></tr>
<tr><td>1.8 ppm (n = 70)</td><td>4 (5.7%)</td><td>57 (81.4%)</td><td>9 (12.9%)</td><td></td></tr>
</table>

At 0.4 ppm, 97% of children had no or very low levels of dental fluorosis (TFI 0 to 1).
At 1.8 ppm, 81% of children had mild levels of dental fluorosis (TFI 2 to 3).

</td></tr>
<tr><th colspan="4">CONCLUSION</th></tr>
<tr><td>Authors’ conclusion</td><td colspan="3"><i>“Higher levels of GST were detected in children with more severe levels of fluorosis.”</i>[103] p.46</td></tr>
<tr><td>Reviewer’s note</td><td colspan="3">Only dental fluorosis data were extracted. The prevalence of dental fluorosis in the study was wrongly calculated. They were therefore re-calculated by dividing the affected number of individuals per TFI category to the number of individuals of each group.</td></tr>
</table>

Garcia-Perez 2017[104]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Schoolchildren aged 8 to 12 years from public elementary schools located in a rural region in the southeast of the state of Morelos, Central Mexico. Population demographics adequately described
1.2	Is the eligible population or area representative of the source population or area?	+	Cross-sectional study. Recruitment defined. Unclear how the communities were selected. Eligible population may not be representative of the source.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Children born in two rural communities of different water fluoride concentration were selected through consent of parents. Those who have lived outside the study region for more than 6 months during their 7 years of life or had fixed orthodontic appliances were excluded. Response rate was 91.7%.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selection based on community water fluoride concentration. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Variables included sex, age, tooth brushing frequency with fluoride toothpaste, Oral Hygiene Index, and dental caries. However, it is unclear if those had been included in the analysis of dental fluorosis.
2.5	Is the setting applicable to Canada?	-	Set in Mexico, where socio-economic factors and healthcare differ from those in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Degree of dental fluorosis was assessed using the TF index. Measurements were performed by a trained and standardized dentist.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	Yes

Item	Question	Rating	Comment
4.2	Were multiple explanatory variables considered in the analyses?	+	Unclear
4.3	Were the analytical methods appropriate?	+	Unclear
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p-values reported for analysis of dental fluorosis.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Some aspects unclear due to not being reported. Risk of selection bias.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Set in Mexico, where socio-economic factors and healthcare differ from those in Canada. Comparator, not <0.4 ppm (i.e., 0.7 ppm vs 1.6 ppm)
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Impact of caries and dental fluorosis on oral health-related quality of life: a cross-sectional study in schoolchildren receiving water naturally fluoridated at above-optimal levels
Author(s)	Garcia-Perez et al.
Publication year	2017
Country (where the study was conducted):	Mexico
Funding sources	NR
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To evaluate the impact of caries on oral health-related quality of life (OHRQoL) among schoolchildren living in areas with high concentrations of fluoride in water.
Study design	Cross-sectional
Study location	Public elementary schools located in a rural region in the southeast of the state of Morelos, Central Mexico.
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	1.61 ppm
• Comparator	0.7 ppm
Setting	School-based in rural region
Source of population	Schoolchildren aged 8 to 12 years
Inclusion/exclusion criteria	Children born in selected communities were included in the study; children who lived outside the study area for a period of 6 months during the first 7 years of life and/or those who had fixed orthodontic appliances were excluded.
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

<table>
<tr><th colspan="4">PARTICIPANT CHARACTERISTICS</th></tr>
<tr><td></td><td>Total</td><td>Intervention</td><td>Comparator</td></tr>
<tr><td>Number of participants enrolled</td><td>524</td><td>NR</td><td>NR</td></tr>
<tr><td>Age, mean (SD)</td><td>8 to 10 years old, mean 9.59 (0.51), n = 252
11 and 12 years old, mean 11.40 (0.55), n = 272</td><td>NR</td><td>NR</td></tr>
<tr><td>Gender</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Subgroups reported</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><th colspan="4">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td colspan="3">Dental fluorosis was assessed using the Thylstrup and Fejerskov (TF) index.
The OHRQoL was evaluated using the Child Perceptions Questionnaire.</td></tr>
<tr><td>Number of participants analysed</td><td colspan="3">NR</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td colspan="3">NR</td></tr>
<tr><td>Imputing of missing data</td><td colspan="3">NR</td></tr>
<tr><td>Statistical method of data analysis</td><td colspan="3">Chi-square test</td></tr>
<tr><td>Results</td><td colspan="3">Prevalence of fluorosis
<table>
<tr><th rowspan="2">Dental fluorosis</th><th colspan="2">Fluoride levels in drinking water</th></tr>
<tr><th>0.7 ppm</th><th>1.6 ppm</th></tr>
<tr><td>Overall</td><td>29.2%</td><td>53.4%</td></tr>
<tr><td>TFI ≥ 4 (moderate/severe)</td><td>9.5%</td><td>28.1%</td></tr>
</table>

For OHRQoL, there was no comparison between 0.7 ppm and 1.6 ppm fluoride levels. This study examined the relationship between dental fluorosis and OHRQoL in school children living in high fluoridated area only.
Children aged 11 to 12 years with dental fluorosis TFI ≥ 4 had higher risk of having deterioration on OHRQoL (OR 2.39; 95% CI, 2.12 to 2.69]) compared to no dental fluorosis (TFI = 0).
</td></tr>
<tr><th colspan="4">CONCLUSION</th></tr>
<tr><td>Authors' conclusion</td><td colspan="3"><i>"A negative impact on OHRQoL was observed in children with caries and fluorosis."</i>[104] p.1</td></tr>
<tr><td>Reviewer's note</td><td colspan="3">No OHRQoL data reported to allow for comparison between children living in the 0.7 ppm fluoridated area and the 1.61 ppm fluoridated area.</td></tr>
</table>

Ibiyemi 2017[109]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Schoolchildren aged 8 years living in lower and higher water fluoridation areas of rural and urban parts of Oyo state on south-west Nigeria. Population demographics not adequately described
1.2	Is the eligible population or area representative of the source population or area?	+	Cross-sectional study. Recruitment not defined.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Study locations were randomly selected. Unclear about % of selected individuals agreed to participate.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selection based on community water fluoride concentration. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis based on previous studies
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, gender, exclusive breastfeeding, age breastfeeding ceased, infant/childhood disease, age of tooth brushing, frequency of tooth brushing, amount of toothpaste used per brushing, fluoride toothpaste ingestion, normal birth, family history of tooth discoloration. Diet and SES missing.
2.5	Is the setting applicable to Canada?	-	Set in Nigeria, where socio-economic factors and healthcare differ from those in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Degree of dental fluorosis was assessed using the TF index. Measurements were performed by a trained and standardized dentist.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis prevalence
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	Yes
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	++	Binary logistic regression analysis.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	p values and 95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Limitation in recruitment methods. Acceptable population selection and data analysis. Risk of selection bias.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Set in Nigeria, where socio-economic factors and healthcare differ from those in Canada.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Prevalence and extent of enamel defects in the permanent teeth of 8-year-old Nigerian children
Author(s)	Ibiyemi et al.
Publication year	2017
Country (where the study was conducted):	Nigeria
Funding sources	Commonwealth School Commission and the Centre for Oral Health Research, Newcastle University
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To determine the prevalence and extent of developmental enamel defects and dental fluorosis in 8-year-old Nigerians and explore associations with key predictors.
Study design	Cross-sectional
Study location	Rural and urban parts of Oyo state in south-west Nigeria
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention, mean (SD)	Community water supply: Urban, higher F: 0.85 (0.19) ppm; Rural, higher F: 2.13 (0.64) ppm Drinking water actually consumed: Urban, higher F: 0.75 (0.76) ppm; Rural, higher F: 1.11 (1.00) ppm
• Comparator, mean (SD)	Community water supply: Urban, lower F: 0.07 (0.02) ppm; Rural, lower F: 0.09 (0.02) ppm Drinking water actually consumed: Urban, lower F: 0.25 (0.20) ppm; Rural, lower F: 0.27 (0.14) ppm
Setting	School-based
Source of population	8 years old children
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	NR

Applicability to Canadian context (based on conditions such as fluoridation level, health and dental care system, and socio-economic factors [e.g., income and education levels])	☐ High ☐ Partial ☑ Limited		
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	322	Urban, higher F (n = 81) Rural, higher F (n = 79)	Urban, lower F (n = 79) Rural, lower F (n = 83)
Age, mean (SD)	8.5 (0.3) years	NR	NR
Gender	48.1% males	NR	NR
Subgroups reported	NR	NR	NR
REPORTED OUTCOMES			
Definition (with units) and method of measurement	Degree of dental fluorosis in permanent teeth was assessed using the Thylstrup and Fejerskov (TF) index.		
Number of participants analysed	322		
Number of participants excluded or missing (with reasons)	3 (water and cooking water samples not provided)		
Imputing of missing data	NR		
Statistical method of data analysis	Multiple multilevel logistic regression		
Results	Prevalence of dental fluorosis (TFI > 0) • Urban, higher F: 20/81 (24.7%) • Rural, higher F: 65/79 (82.3%) • Urban, lower F: 4/79 (5.1%) • Rural, lower F: 7/83 (8.4%) • All areas: 96/322 (29.8%) Association between dental fluorosis and fluoride concentration in drinking water: OR = 1.57 (95% CI, 0.87 to 2.81), NS After adjustment for age, gender, exclusive breastfeeding, age breastfeeding ceased, infant/childhood disease, age of tooth brushing, frequency of tooth brushing, amount of toothpaste used per brushing, fluoride toothpaste ingestion, normal birth, family history of tooth discoloration.		
CONCLUSION			
Authors' conclusion	*"With 29.8% of these children exhibiting dental fluorosis…, drinking water F concentration was identified as a positive predictor"*(p.8)[109]		
Reviewer's note	Prevalence of dental fluorosis was highest in rural higher F areas (82.3%) and lowest in urban lower F areas (5.1%). After adjusting for independent variables, the association between dental fluorosis and fluoride concentration in drinking water was not statistically significant.		

Khandare 2017[96]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	School children aged 8 to 15 years from 8 rural areas of the Doda district, India, where drinking water had fluoride level of 1.85 to 3.84 ppm. Higher secondary school children (age not reported) from two schools in urban area (F 1.13 ppm; range 0.32 to 1.18 ppm) were used as control. The population characteristics not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	-	Cross-sectional study. Recruitment not defined. Unclear as whether the eligible population representative of the source.
1.3	Do the selected participants or areas represent the eligible population or area?	NR	
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Characteristics of comparison group may differ from those of the intervention group. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Evidence for hypothesis was not all based on previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No
2.5	Is the setting applicable to Canada?	-	Set in India, where socio-economic factors and healthcare differ from those in Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Dental fluorosis assessed by a dental specialist using Dean index. Markers for kidney function (creatinine), thyroid function (PTH, T3, T4, TSH, vitamin D), and bone metabolic indicators (osteocalcin) measured from blood tests.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis, kidney function, thyroid function, bone metabolic indicators.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	

Item	Question	Rating	Comment
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No
4.4	Was the precision of association given or calculable? Is association meaningful?	+	*P* values reported (not actual number)
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Population and method of selection not well described. Risk of selection bias. No adjustment for confounders in data analysis
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Set in India, where socio-economic factors and healthcare differ from those in Canada.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Dental fluorosis, nutritional status, kidney damage, and thyroid function along with bone metabolic indicators in school-going children living in fluoride-affected hilly areas of Doda district, Jammu and Kashmir, India
Author(s)	Khandare et al.
Publication year	2017
Country (where the study was conducted):	India
Funding sources	Indian Council of Medical Research
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To study the prevalence of dental fluorosis, nutritional status, and blood and urine parameters related to fluoride exposure kidney function, thyroid function and bone metabolism among schoolchildren living areas with different water fluoride levels.
Study design	Cross-sectional (not a case-control as reported)
Study location	8 rural and 2 urban schools from the Doda district of Jammu and Kashmir, India
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	1.43 to 3.84 ppm
• Comparator	1.13 ppm (0.32 to 1.18 ppm)
Setting	School-based
Source of population	8 to 15 years old schoolchildren living in high fluoride rural areas (intervention) Older school children (age not reported) from higher secondary school living in lower fluoride urban areas (comparator)
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	824	379	445
Age	NR	8 to 15 years	NR (older)
Gender	494 (60%) males 330 (40%) females	193 (50.9%) males 186 (49.1%) females	301 (67.6%) 144 (32.3%)
Subgroups reported	NR	NR	NR
REPORTED OUTCOMES			
Definition (with units) and method of measurement	Dental fluorosis assessed by a dental specialist using Dean index. Markers for kidney function (creatinine), thyroid function (PTH, T3, T4, TSH, vitamin D), and bone metabolic indicators (osteocalcin) measured through blood tests.		
Number of participants analysed	824		
Number of participants excluded or missing (with reasons)	NR		
Imputing of missing data	NR		
Statistical method of data analysis	Linear regression analysis; correlation coefficient (r); one-way ANOVA		
Results	**Prevalence of dental fluorosis**		

Water fluoride (ppm)	Gender	Dean's classification							Fluorosis
		0	0.5	1	1.5	2	3	4	
1.13	Males (n=301)	220 (73%)	45 (15%)	20 (7%)	11 (4%)	5 (2%)	0	0	27%
	Females (n=144)	99 (69%)	24 (17%)	16 (11%)	4 (3%)	1 (1%)	0	0	31%
1.43 to 3.84	Males (n=180)	101 (56%)	10 (6%)	20 (11%)	20 (11%)	12 (7%)	10 (6%)	7 (4%)	44%
	Females (n=185)	92 (50%)	15 (8%)	25 (14%)	19 (10%)	18 (10%)	6 (3%)	10 (5%)	50%

Markers for kidney function (creatinine), thyroid function (PTH, T3, T4, TSH, vitamin D), and bone metabolic indicators (osteocalcin) measured from blood tests

	Water fluoride level		Normal range
	1.43 to 3.84 ppm	0.32 to 1.18 ppm	
	mean ± SD		
Urinary fluoride level (mg/L)	3.28 ± 1.71*	1.91 ± 0.64	≤1.5
Serum creatinine (mg/dL)	0.85 ± 0.35*	0.45 ± 0.16	0.5 to 1.2
GFR (ml/min/1.73m^2)	84.1 ± 33.1*	120.9 ± 27.4	≥90
PTH (pg/mL)	49 ± 12*	27 ± 5	13 to 54
T3 (ng/mL)	0.63 ± 0.24	0.68 ± 0.35	0.8 to 2.0
T4 (µg/dL)	16.1 ± 2.9	16.9 ± 1.6	6.1 to 11.8
TSH (mU/L)	2.9 ± 0.6*	3.4 ± 0.5	0.3 to 4.0
Osteocalcin (ng/mL)	31.3 ± 13.2*	14.7 ± 3.3	9.0 to 42.0
Alkaline phosphatase (IU/L)	401 ± 125*	266 ± 70	98 to 279
25-(OH) vitamin D (ng/mL)	9.8 ± 5.9	13.0 ± 7.6	30 to 74
1,25-(OH)$_2$ vitamin D (pg/mL)	146.2 ± 38.8*	98.8 ± 38.1	24 to 86

* $P < 0.05$

GFR = glomerular filtration rate; PTH = parathyroid hormone; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

	Summary of findings: - The prevalence of dental fluorosis in the low fluoride areas (27% to 31%) was lower than that in the high fluoride areas (44% to 50%). - Serum creatinine of individuals in high fluoride areas was significantly higher than those in the low fluoride areas (0.85 vs 0.45 mg/dL). However, the values were within the normal range (0.5 to 1.2 mg/dL). - Similarly, although there were significant differences between groups in PTH, TSH and osteocalcin, the values of both groups were within the normal ranges. - No significant differences were observed between groups in T3, T4 and 25-(OH) vitamin D levels. The 1,25-$(OH)_2$ vitamin D values of both groups were beyond the normal range.
CONCLUSION	
Authors' conclusion	*"In conclusion, fluorotic area school children were more affected with dental fluorosis, kidney damage, along and some bone indicators as compared to control school children."*(p.2) [96]
Reviewer's note	Poor research methodology. School children aged 8 to 15 years from 8 rural areas with fluoride level of 1.85 to 3.84 ppm were compared with high school children (age not reported) from two schools in urban area (F 1.13 ppm; range 0.32 to 1.18 ppm). No confounders were adjusted for in data analyses. The findings did not support the authors' conclusion.

Mohammadi 2017[117]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Data and information of individuals living in six villages of Poldasht county, Iran were from the Health Record Department, Poldasht Health Centre. Population demographics were not described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear
1.3	Do the selected participants or areas represent the eligible population or area?	NR	
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on water fluoride concentration. Risk of selection bias. Individual mobility was not controlled.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Skeletal fluorosis caused by exposure to high fluoride level in drinking water.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, sex, fast food and dairy consumption. The villages had same SES and dietary habits. Other sources of fluoride not accounted.
2.5	Is the setting applicable to Canada?	-	Set in Iran. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	-	Skeletal fluorosis not measured radiographically, not clear if other bone diseases that can cause restricted ROM were ruled out. Unclear if tests used were validated

Item	Question	Rating	Comment
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Skeletal fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multiple multilevel logistic regression
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Participant selection was not adequately described. Risk of selection.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	No. Study conducted in Iran with much higher F levels compared to Canada
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Skeletal fluorosis in relation to drinking water in rural areas of West Azerbaijan, Iran
Author(s)	Mohammadi et al.
Publication year	2017
Country (where the study was conducted):	Iran
Funding sources	Tehran University of Medical Sciences and Poldasht Health Centre
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To evaluate the association between exposures to drinking water fluoride and skeletal fluorosis in five villages of Poldasht County, Iran.
Study design	Cross-sectional
Study location	Five villages of Poldasht County, Iran
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	High: 4.02 ppm, 7.63 ppm, 10.15 ppm
• Comparator	Low: 0.68 ppm, 0.79 ppm
Setting	Rural

Source of population	Adults: ≤ 40 years old and 41 to ≥ 70 years old		
Inclusion/exclusion criteria	NR		
Recruitment or sampling procedure	NR		
Applicability to Canadian context (based on conditions such as fluoridation level, health and dental care system, and socio-economic factors [e.g., income and education levels])	☐ High	☐ Partial	☑ Limited
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	915	445	470
Age, mean (SD)	NR	NR	NR
Gender	NR	NR	NR
Subgroups reported	NR	NR	NR
REPORTED OUTCOMES			
Definition (with units) and method of measurement	Skeletal fluorosis was assessed by physical examination.		
Number of participants analysed	915		
Number of participants excluded or missing (with reasons)	NR		
Imputing of missing data	NR		
Statistical method of data analysis	Multiple multilevel logistic regression		
Results	**Prevalence of skeletal fluorosis**		

Fluoride level	**Skeletal fluorosis**		***P* value**
	No	Yes	
High	351 (78.9%)	94 (21.1%)	< 0.001
Low	456 (97.0%)	14 (3.0%)	

Odds ratio of skeletal fluorosis in high fluoride area versus low fluoride area (reference)

		OR (95% CI)	***P* value**
All	Unadjusted	8.33 (5.56 to 12.5)	< 0.001
	Adjusted	9.09 (5.25 to 16.67)	< 0.001
Male	Unadjusted	11.59 (3.54 to 37.95)	< 0.001
	Adjusted	6.05 (3.59 to 10.19)	< 0.001
Female	Unadjusted	8.47 (4.42 to 16.24)	< 0.001
	Adjusted	8.73 (4.31 to 17.67)	< 0.001

Variables: Age, sex, fast food and dairy consumption.

- The prevalence of skeletal fluorosis increased with age (i.e., 8% at age ≤ 40 years versus 54.5% at age ≥ 71 years.
- The prevalence of skeletal fluorosis was higher in female (15%) than in male (8.6%).

CONCLUSION	
Authors' conclusion	*"The present study demonstrates a significant relationship between the fluoride concentrations in the water and the prevalence of skeletal fluorosis in an endemic fluorosis area."* (p.6) [96]
Reviewer's note	The study did not determine the severity of skeletal fluorosis. Radiographs were not taken to confirm skeletal fluorosis.

Rango 2017[107]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Area in the Ethiopian rift valley, rural communities, local groundwater wells of different fluoride concentrations. Participant demographics well described.
1.2	Is the eligible population or area representative of the source population or area?	++	Participants enrolled from 27 rural communities. Recruitment well defined. Eligible population may be representative of the source.
1.3	Do the selected participants or areas represent the eligible population or area?	++	In each sample community, households were selected by counting off every 2 or more households in the community, and 1 to 2 subjects from each household were enrolled. Inclusion criteria: age 10 to 59 years, lifelong residence, consumption of well water since the time of well construction. Samples were randomly selected to represent four age groups: 10 to 15, >15 to 25, >25 to 35, and >35 to 50 years.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Measurement of individuals' fluoride level from fingernail and 12-hour urine samples.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis based on previous study.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, sex, BMI. SES was not included.
2.5	Is the setting applicable to Canada?	-	Set in Ethiopia. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Dental fluorosis was evaluated using the TF Index. Data validation not reported.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis

Item	Question	Rating	Comment
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Yes, but missed other relevant variables such as SES.
4.3	Were the analytical methods appropriate?	++	Multivariable regression analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	P values and SE reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Source of population and participant selection well described. Weak in controlling of confounders and outcome measures. Appropriate data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	No. Study conducted in Ethiopia with much higher F levels compared to Canada,
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Biomarkers of chronic fluoride exposure in groundwater in a highly exposed population
Author(s)	Rango et al.
Publication year	2017
Country (where the study was conducted):	Ethiopia
Funding sources	NIEHS’s career development grant
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To examine in the Ethiopian Rift Valley population the relationship between fluoride (F^-) concentrations in fingernail clippings and urine, and the prevalence and severity of enamel fluorosis among those exposed to high levels of F^- in drinking water.
Study design	Cross-sectional
Study location	Area in the Ethiopian Rift Valley, rural communities, local groundwater wells of different fluoride concentrations.
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	0.6 to 15 ppm
• Intervention	
• Comparator	
Setting	Rural

Source of population	Individuals aged 10 to 50 years		
Inclusion/exclusion criteria	Inclusion criteria: age 10 to 50 years, lifelong residence, consumption of well water since the time of well construction.		
Recruitment or sampling procedure	Randomly sampled households in order to obtain equal representation across the four age groups		
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited		
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	386	NR	NR
Age, mean (SD)	24.5 (11.1) years	NR	NR
Gender	NR	NR	NR
Weight			
Subgroups reported	Four age groups: 10 to 15, > 15 to 25, > 25 to 35, and > 35 to 50 years.	NR	NR
REPORTED OUTCOMES			
Definition (with units) and method of measurement	Dental fluorosis was evaluated using the TF Index.		
Number of participants analysed	386		
Number of participants excluded or missing (with reasons)	NR		
Imputing of missing data	NR		
Statistical method of data analysis	ANOVA, Multivariable regression analysis		
Results	**Fluoride in drinking water and enamel fluorosis** • As F in drinking water increased from 0.6 ppm to 15 ppm, prevalence of severe enamel fluorosis increased and the prevalence of mild-to-moderate enamel fluorosis decreased. • At 0.6 ppm, the prevalence of fluorosis was 0. • Between 1.4 to 2.0 ppm the prevalence of fluorosis was 4.3%. As the concentration of F in the drinking water increased to 4 ppm and 15 ppm, the prevalence of severe fluorosis was 16% and 64%, respectively. • Mean TF scores increased in all age groups (10 to 15 years, > 15 to 25 years, > 25 to 35 years, and > 35 to 50 years) as individual exposed to increasing levels of fluoride in drinking water (< 2 ppm, > 2 to 5 ppm, > 5 to 8 ppm, > 8 to 12 ppm). • However, the mean TF scores (enamel fluorosis severity) decreased with increasing age, and individuals aged between 10 to 35 years (81%) had higher proportion of teeth with enamel fluorosis compared to those aged between 36 to 50 years (27.5% of teeth). [Older people might have lower exposure to fluoride during early years of enamel formation; i.e., born prior to the year of well installation]		

Correlation between fluoride in drinking water and enamel fluorosis, fingernail fluoride and urinary fluoride

	Correlation coefficient, *r*	*P* value
Enamel fluorosis severity (n=316)	0.42	< 0.001
Fingernail fluoride (n=258)	0.60	< 0.001
Urinary fluoride (n=287)	0.74	< 0.001

Multivariable regression analyses for the relationship between fluoride in water and biomarkers (enamel fluorosis, fingernail fluoride and urinary fluoride)

Biomarkers	β coefficient (SE)
Mean TF score	
Unadjusted	0.35** (0.055)
Adjusted[a]	0.37** (0.008)
Fingernail fluoride	
Unadjusted	0.61** (0.090)
Adjusted[a]	0.82** (0.020)
Urinary fluoride	
Unadjusted	0.79** (0.077)
Adjusted[a]	0.76** (0.026

**P < 0.01

[a] Adjusted for age, sex, BMI and community fixed effects

- A 1 unit increase in water concentration of fluoride is associated with a 0.4 unit increase in TF score and a 0.8 unit increase in fingernail and urinary fluoride.

CONCLUSION	
Authors' conclusion	*“The data indicate that both fingernail and urine measures are good biomarkers for fluoride exposure and enamel fluorosis outcome, the latter being slightly more sensitive.”*[107] p.1
Reviewer's note	The comparison between older and younger people for enamel fluorosis should be taken cautiously as older people might not be exposed to high fluoride levels in their childhood.

Razdan 2017[97]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Three villages in India of low (0.6 ppm), medium (1.70 ppm) and high (4.99 ppm) fluoride levels. Demographics not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	+	Children aged 12 to 14 years. Unclear if population sample was representative of the source.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Methods of selection not described. Unclear % of selected individuals agreed to participate. Appropriate inclusion/exclusion criteria.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	3 villages with differing levels of water fluoridation (0.6pmm, 1.70ppm, and 4.99pm. Risk of selection bias
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis based on previous studies
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors identified and controlled
2.5	Is the setting applicable to Canada?	-	Set in India. Not applicable to Canada due to different in socio-economic factors and healthcare.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis assessed using the Modified Dean's fluorosis index by calibrated and trained examiners. IQ was measured using SPM Test by John C Raven.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis, IQ
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No
4.4	Was the precision of association given or calculable? Is association meaningful?	++	P values and 95% CI reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Poor methods of selection and data analysis. Potential presence of risk of bias.

Item	Question	Rating	Comment
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study conducted in India areas with different in SES factors, healthcare and fluoride level in water. On area had fluoride level 0.6 ppm, which is similar to that in Canada. That level was used as a positive control.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Effect of fluoride concentration in drinking water on intelligence quotient of 12-14-year-old children in Mathura district: A cross-sectional study
Author(s)	Razdan et al.
Publication year	2017
Country (where the study was conducted):	India
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To assess and determine the correlation between concentration of fluoride in ingested water on the intelligence quotient (IQ) of 12 to 14 years old children in Mathura district.
Study design	Cross-sectional
Study location	Three villages in India of low (0.6 ppm), medium (1.70 ppm) and high (4.99 ppm) fluoride levels.
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	4.99 ppm, 1.70 ppm
• Comparator	0.6 ppm
Setting	Rural
Source of population	Children aged 12 to 14 years.
Inclusion/exclusion criteria	Inclusion: residents of the same village since birth, mothers lived in the same village since pregnancy, drinking same ground water. Exclusion: birth defects, genetic disorders, history of head injury, systemic diseases, children residing in another area for an extended period of time other than area of birth.
Recruitment or sampling procedure	Convenient sampling strategy
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS				
	Total	**4.99 ppm**	**1.70 ppm**	**0.6 ppm**
Number of participants enrolled	219	75	75	69
Age	12 to 14 years	NR	NR	NR
Gender	NR	NR	NR	NR
Subgroups reported	NR	NR	NR	NR

<table>
<tr><th colspan="2">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td>Dental fluorosis assessed using the Modified Dean’s fluorosis index.
IQ was measured using the Standard Progressive Matrices (SPM) Test by John C Raven.

Grade I: Intellectual superior (IQ score ≥ 95%)
Grade II: Definitely above average (IQ score > 75%)
Grade III: Intellectual average (IQ score 75 to 25%)
Grade IV: Definitely below average in intellectual capacity (IQ score ≤ 25%)
Grade V: Intellectually impaired (IQ score ≤ 5%)</td></tr>
<tr><td>Number of participants analysed</td><td>219</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>0</td></tr>
<tr><td>Imputing of missing data</td><td>NA</td></tr>
<tr><td>Statistical method of data analysis</td><td>Chi-square test, ANOVA</td></tr>
<tr><td>Results</td><td>Intellectual level

In the low 0.6 ppm water fluoride area, children were intellectually average (31.9%), above average (55.1%) or superior (13.0%). None were below average or intellectual impaired.
In the medium 1.7 ppm water fluoride area, children were intellectually average (81.3%), below average (13.3%) or intellectual impaired (5.3%). None were above average or superior.
In the high 4.99 ppm water fluoride area, children were intellectually average (33.3%), below average (46.7%) or intellectual impaired (20.0%). None were above average or superior.

Mean IQ scores
<table>
<tr><th>Fluoride level</th><th>Mean (95% CI)</th><th>Mean difference (95% CI)</th></tr>
<tr><td>A: 0.6 ppm</td><td>38.6 (37.1 to 40.1)</td><td>A-B: 19.7 (17.6 to 21.8)*</td></tr>
<tr><td>B: 1.7 ppm</td><td>18.9 (17.9 to 20.0)</td><td>A-C: 24.7 (22.6 to 26.8)*</td></tr>
<tr><td>C: 4.99 ppm</td><td>13.9 (12.8 to 15.1)</td><td>B-C: 5.00 (2.95 to 7.05)*</td></tr>
</table>
*<i>p</i> < 0.001

Children living in the 1.7 ppm and 4.99 ppm fluoride level areas had significantly lower mean IQ scores compared to those in the 0.6 ppm fluoride level area.

Dental fluorosis

All children living in 0.6 ppm fluoride area had normal teeth.
All children living in 1.7 ppm and 4.99 ppm areas had dental fluorosis.
The proportions of children with mild (18.7% vs 10.7%), moderate (53.3% vs 60.0%) and severe (28.0% vs 29.3%) dental fluorosis in 1.7 ppm compared with 4.99 ppm were similar.
</td></tr>
<tr><th colspan="2">CONCLUSION</th></tr>
<tr><td>Authors’ conclusion</td><td><i>“Concentration of fluoride in the ingested water was significantly associated with the IQ of children. It has also coined the proportional variability in mental output in accordance to the ingested fluoride level. As two sides of a coin, fluoride cannot be utterly blamed for a lower intelligence in a population; it puts forward a fact that intelligence is a multifactorial variable with a strategic role played by genetics and nutrition to develop cognitive and psychosomatic activities in an adult.”</i>(p.1)[97]</td></tr>
<tr><td>Reviewer’s note</td><td>The study did not conduct an analysis to study the association between fluoride and IQ. No confounders were identified and controlled.</td></tr>
</table>

Yousefi 2017[127]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Data and information of individuals living in five villages of Poldasht county, Iran, were from the Health Record of the areas. Population demographics were not described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear
1.3	Do the selected participants or areas represent the eligible population or area?	NR	
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on water fluoride concentration. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	-	Evidence for hypothesis based studies of surrogate outcomes.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors controlled
2.5	Is the setting applicable to Canada?	-	Set in Iran. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Fertility, infertility and abortion data were from health records.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Prevalence of fertility, infertility and abortion
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No multivariable regression analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Poor study design and methodology
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	No. Study conducted in Iran with much higher F levels compared to Canada
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION			
Title	Epidemiology off drinking water fluoride and its contribution to fertility, infertility, and abortion: An ecological study in west Azerbaijan province, Poldasht County, Iran		
Author(s)	Yousefi et al.		
Publication year	2017		
Country (where the study was conducted):	Iran		
Funding sources	NR		
Reported conflict of interest	☐ Yes	☑ No	
STUDY CHARACTERISTICS			
Objectives	To examine, in females living in areas with low and high drinking water fluoride level (means 1.90 and 8.10 ppm, respectively) the relationship between drinking water fluoride and (i) fertility, (ii) infertility without known etiology factors, and (iii) abortion without known etiology factors		
Study design	Ecological		
Study location	Five villages of Poldasht county, Iran		
Study duration	NA		
Exposure duration	Lifetime		
Fluoride levels or Exposures:			
• Intervention	8.10 ± 1.44 ppm (range 6.00 to 10.30 ppm)		
• Comparator	1.90 ± 0.37 ppm (range 1.46 to 2.81 ppm)		
Setting	Rural		
Source of population	Women aged 10 to 49 years living in five villages of Poldasht County, Iran		
Inclusion/exclusion criteria	Exclusion: conditions known to cause infertility such as diabetes mellitus, obesity, smoking, and consumption of alcohol.		
Recruitment or sampling procedure	NR		
Applicability to Canadian context	☐ High	☐ Partial	☑ Limited
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention (8.10 ppm)**	**Comparator (1.90 ppm)**
Number of participants enrolled	3,392	2,098	1,294
Age	10 to 49 years	NR	NR
Subgroups reported	NR	NR	NR

<table>
<tr><th colspan="2">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td>Fertility, infertility and abortion data were from health records.</td></tr>
<tr><td>Number of participants analysed</td><td>3,392</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>NR</td></tr>
<tr><td>Imputing of missing data</td><td>NR</td></tr>
<tr><td>Statistical method of data analysis</td><td>NR</td></tr>
<tr><td>Results</td><td>Rates of fertility, infertility and abortion
<table>
<tr><th rowspan="2"></th><th colspan="2">Fluoride level</th><th rowspan="2">Difference</th><th rowspan="2"><i>P</i> value</th></tr>
<tr><th>1.90 ppm</th><th>8.10 ppm</th></tr>
<tr><td>Fertility</td><td>5.3% (105/1,993)</td><td>5.7% (70/1,224)</td><td>0.3%</td><td>< 0.001</td></tr>
<tr><td>Infertility</td><td>0.9% (17/1,993)</td><td>2.0% (24/1,224)</td><td>1.1%</td><td>< 0.001</td></tr>
<tr><td>Abortion</td><td>5.7% (6/105)</td><td>15.7% (11/70)</td><td>10.0%</td><td>0.011</td></tr>
</table>

There was small difference in fertility between women living in high and low fluoride areas.
Women living in high fluoride areas had higher rates of infertility and abortion than those living in the low fluoride areas.
</td></tr>
<tr><th colspan="2">CONCLUSION</th></tr>
<tr><td>Authors’ conclusion</td><td><i>“There were no statistically significant differences in the reproductive parameters between the low and high F regions when the women were considered by 5-year age groups, but, when the data were pooled and all age groups were considered together in a group with ages 10 to 49 year, those in the low F group were more fertile (P < 0.05) and had lower rates of (i) infertility without known etiological factors (P < 0.001) and (ii) abortion without known etiological factors (P < 0.001).”</i> (p.342)[127]</td></tr>
<tr><td>Reviewer’s note</td><td>The conclusion did not reflect the findings. Substantial limitations in design and research methodology. No confounders were identified and adjusted in the data analysis.</td></tr>
</table>

Aravind 2016[121]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Three villages in India were selected based on water fluoride level: < 1.2 ppm (low), 1.2 to 2 ppm (medium), > 2 ppm (high). Children 10 to 12 years were selected from the villages. Setting and population demographics were not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	10-12 year old children over a period of 3 months were assessed for IQ.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Sample was selected using a formula, with no explanation. Purposive sampling was used to determine the villages. No report on % of selected individuals who agreed to participate. Exclusion criteria were provided.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Potential selection bias may exist.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis based on previous studies
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	Confounding factors were not considered in the analysis.
2.5	Is the setting applicable to Canada?	-	The setting was in India. Not applicable to Canada due to different in SES, healthcare and fluoride level in drinking water.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	IQ was assessed using the Raven's standard Progressive Matrices test.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	IQ
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	+	Unclear method
4.2	Were multiple explanatory variables considered in the analyses?	-	No

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	-	No
4.4	Was the precision of association given or calculable? Is association meaningful?	++	p values and SD provided
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Unclear in some aspects due to not being reported. Poor in methods of selection, outcome assessment and data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study conducted in India. Could not be generalizable to the Canadian context due to difference in water fluoride level and other aspects.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Effect of fluoride water on intelligence in 10 to 12-year-old school children
Author(s)	Aravind et al.
Publication year	2016
Country (where the study was conducted):	India
Funding sources	No source of funding
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To evaluate the relationship of drinking water fluoride levels with children's intelligence quotient (IQ)
Study design	Cross-sectional
Study location	Three villages in India
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	1.2 to 2 ppm, >2 ppm
• Comparator	<1.2 ppm
Setting	Rural
Source of population	Children 10 to 12 years from three villages in India were selected based on water fluoride level
Inclusion/exclusion criteria	Exclusion: children suffering from any development disorder related to psychiatric illness and children with defective audio, speech, or visual activity.
Recruitment or sampling procedure	Random sampling of government schools from all three village
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

<table>
<tr><th colspan="5">PARTICIPANT CHARACTERISTICS</th></tr>
<tr><td></td><td>Total</td><td>> 2 ppm</td><td>1.2 to 2 ppm</td><td>< 1.2 ppm</td></tr>
<tr><td>Number of participants enrolled</td><td>288</td><td>96</td><td>96</td><td>96</td></tr>
<tr><td>Age</td><td>10 to 12 years</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Gender</td><td>Male: 49%
Female: 51%</td><td>Male: 49%
Female: 51%</td><td>Male: 48%
Female: 52%</td><td>Male: 49%
Female: 51%</td></tr>
<tr><td>Subgroups reported</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><th colspan="5">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td colspan="4">Intelligence was assessed using the Raven’s Standard Progressive Matrices (SPM) test.
Grade I: Intellectual superior (IQ score ≥ 95%)
Grade II: Definitely above average (IQ score > 75%)
Grade III: Intellectual average (IQ score 75 to 25%)
Grade IV: Definitely below average in intellectual capacity (IQ score ≤ 25%)
Grade V: Intellectually impaired (IQ score ≤ 5%)</td></tr>
<tr><td>Number of participants analysed</td><td colspan="4">288</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td colspan="4">NR</td></tr>
<tr><td>Imputing of missing data</td><td colspan="4">NR</td></tr>
<tr><td>Statistical method of data analysis</td><td colspan="4">ANOVA, Student’s <i>t</i>-test, Spearman’s rank correlation coefficient.</td></tr>
<tr><td>Results</td><td colspan="4">Mean IQ scores
<table>
<tr><th rowspan="2">Fluoride level</th><th colspan="3">Mean IQ (SD)</th></tr>
<tr><th>All</th><th>Males</th><th>Females</th></tr>
<tr><td><1.2 ppm</td><td>41.03 (16.36)***</td><td>41.47 (14.93)***</td><td>40.62 (17.77)***</td></tr>
<tr><td>1.2 to 2 ppm</td><td>56.68 (14.51)</td><td>56.30 (13.14)</td><td>57.03 (15.78)</td></tr>
<tr><td>>2 ppm</td><td>31.59 (16.81)</td><td>30.92 (16.09)</td><td>32.24 (17.62)</td></tr>
</table>
***<i>P</i> < 0.0001 when compared based on fluoride levels
NS when comparing males versus females

Intellectual level

In all three regions with low, medium and high fluoride level in drinking water, none of the children were intellectual superior or impaired.
Intellectually below average was highest in high fluoride area (59.4%) compared to medium fluoride area (0%) or low fluoride area (15.6%).
Intellectual average was lowest in high fluoride area (40.6%) compared to medium fluoride area (81.3%) or low fluoride area (81.3%).
None of the children in the high fluoride area were intellectually above average (0%) compared to medium fluoride area (8.3%) or low fluoride area (3.1%).

Correlation

IQ level was negatively and significantly correlated with fluoride level in drinking water ($r = -0.204$, $P < 0.0001$)
</td></tr>
<tr><th colspan="5">CONCLUSION</th></tr>
<tr><td>Authors’ conclusion</td><td colspan="4"><i>“IQ level was negatively correlated with fluoride level in drinking water. Factors that might affect children’s IQ need to be considered and it is necessary to devise solutions for preventing the harmful effects of excessive intake of fluoride ion in the body.”</i>[121] p.1</td></tr>
<tr><td>Reviewer’s note</td><td colspan="4">Confounding factors were not considered in the analysis.</td></tr>
</table>

Archer 2016[115]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Population-based case-control studies. Cases included Texas children and adolescents aged 0 to 19 years who reported to the Texas Cancer Registry and were diagnosed with primary malignant osteosarcoma between January 1, 1996 and December 31, 2006. Controls were sample from Texas children and adolescents (0 to 19 years) with either central nervous system tumours or leukemia during the same time period. Population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Data obtained from Texas Cancer Registry.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Geocoded address information at the time of diagnosis was mapped onto certificates of convenience and necessity water service area boundary shapefiles. Additional information on public water system locations were obtained from the Texas Commission on environmental Quality Water Utility Database. 87% of the cases and 87.5% of the controls were geocodable and included in the analysis. Inclusion and exclusion criteria were explicit.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)			
2.1	Allocation to intervention (or comparison). How was selection bias minimised?	+	Case-control. Controls to cases were 4 to 1 ratio. Two CNS tumor controls and two leukemia controls were randomly selected for each osteosarcoma case.
2.2	Were interventions (and comparisons) well described and appropriate?	++	Yes
2.3	Was the allocation concealed?	NR	
2.4	Were participants or investigators blind to exposure and comparison?	NR	
2.5	Was the exposure to the intervention and comparison adequate?	+	Patient’s fluoride exposure was estimated based on fluoride level in their residence’s public water system.
2.6	Was contamination acceptably low?	+	Unclear about any contamination in exposure. Geocoded address and water service area information was used to determine exposure. Some bias may exist.
2.7	Were other interventions similar in both groups?	NR	
2.8	Were all participants accounted for at study conclusion?	++	All cases and controls included in the analysis were accounted for at study conclusion.
2.9	Did the setting reflect usual Canadian practice?	++	Set in USA. Public drinking water fluoridation either naturally occurring or added.

Item	Question	Rating	Comment
2.10	Did the intervention or control comparison reflect usual Canadian practice?	+	Average fluoride level in the study ranged from 0.1 to 5.5 ppm. The upper end exceeded the MAC (1.5 ppm) in Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Cancer cases were diagnosed and registered in the Texas Cancer Registry.
3.2	Were all outcome measurements complete?	+	Only geocodable case and control records were included.
3.3	Were all important outcomes assessed?	+	Cancer cases (osteosarcoma); controls (CNS tumor and leukemia)
3.4	Were outcomes relevant?	++	Yes
3.5	Were there similar follow-up times in exposure and comparison groups?	NA	
3.6	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	Two control groups differed with each other in age, race sex and poverty index. Comparison between cases and each of the control groups was adjusted in regression analysis. However, the relationship between fluoride levels and osteosarcoma did not differ based on control group used.
4.2	Was intention to treat (ITT) analysis conducted?	NA	
4.3	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.4	Were the estimates of effect size given or calculable?	++	Odds ratio reported
4.5	Were the analytical methods appropriate?	++	Logistic regression analysis. Covariates included age, sex, race/ethnicity, poverty index.
4.6	Was the precision of intervention effects given or calculable? Were they meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	++	Unclear in some aspects due to not reporting. Adequate data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Likely generalizable to the Canadian context. The low/sub-optimal fluoridation (0.0 to 0.6 ppm) and optimal fluoridation (0.7 to 1.2 ppm), above optimal fluoridation (≥1.3 ppm)
Overall quality rating		Acceptable	

Data Extraction

GENERAL INFORMATION	
Title	Fluoride exposure in public drinking water and childhood and adolescent osteosarcoma in Texas
Author(s)	Archer et al.
Publication year	2016
Country (where the study was conducted):	USA
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To examine the association between fluoride levels in public drinking water and childhood and adolescent osteosarcoma in Texas
Study design	Population-based case-control
Study location	Texas, USA
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	0.7 to 1.2 ppm; ≥ 1.3 ppm
• Comparator	0 to 0.6 ppm
Setting	Texas Cancer Registry
Source of population	Texas children and adolescents (0 to 19 years)
Inclusion/exclusion criteria	Cases included Texas children and adolescents aged 0 to 19 years who reported to the Texas Cancer Registry and were diagnosed with primary malignant osteosarcoma between January 1, 1996 and December 31, 2006. Controls were sample from Texas children and adolescents (0 to 19 years) with either central nervous system tumours or leukemia during the same time period.
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☑ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS				
	Total	**> 1.3 ppm**	**0.7 to 1.22 ppm**	**0 to 0.6 ppm**
Number of participants enrolled	1,663	110	376	1,024
Age, mean	13.9 years	NR	NR	NR
Gender	56.4% male	NR	NR	NR
Race (%)		NR	NR	NR
White	45.2	NR	NR	NR
Black	12.8	NR	NR	NR
Hispanic	38.3	NR	NR	NR
Other/missing	3.7	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Cancer cases were diagnosed and registered in the Texas Cancer Registry.
Number of participants analysed	1,510
Number of participants excluded or missing (with reasons)	153
Imputing of missing data	NR
Statistical method of data analysis	Logistic regression analysis
Results	• Crude analysis showed no significant differences between the proportion of osteosarcoma cases and the proportion of CNS tumor and leukemia referents within each of the fluoride level categories (i.e., 0 to 0.6 ppm, 0.7 to 1.2 ppm, or ≥ 1.3 ppm) for average and highest fluoride levels, or due to the source of fluoride used (i.e., Fluorosilicic acid or natural).

Logistic regression analysis – Crude and adjusted odds ratio (OR) for osteosarcoma

Fluoride level	OR (95% CI)	
	Unadjusted	Adjusted[a]
All		
0 to 0.6 ppm	1.00 (Ref)	1.00 (Ref)
0.7 to 1.2 ppm	0.86 (0.63 to 1.16)	0.85 (0.62 to 1.16)
≥ 1.3 ppm	0.94 (0.57 to 1.53)	0.96 (0.58 to 1.58)
Male		
0 to 0.6 ppm	--	1.00 (Ref)
0.7 to 1.2 ppm	--	1.03 (0.68 to 1.55)
≥ 1.3 ppm	--	1.31 (0.70 to 2.46)
Female		
0 to 0.6 ppm	--	1.00 (Ref)
0.7 to 1.2 ppm	--	0.68 (0.42 to 1.09)
≥ 1.3 ppm	--	0.58 (0.25 to 1.36)

[a] Adjusted for age, sex, race/ethnicity, and percent of census tract below poverty index.

- In logistic regression analysis, there was no association between public water system fluoride levels and osteosarcoma among either males or females.

CONCLUSION	
Authors' conclusion	*"No relationship was found between fluoride levels in public drinking water and childhood/adolescent osteosarcoma in Texas."* (p.863)[115]
Reviewer's note	Controls to cases were 4 to 1 ratio, which increased power to detect potential differences. Limitations: Unknown about the exposure duration of each individual before being diagnosed with cancer. No information about the type of water (tap or bottle) consumed. Potential bias in the choice of cancer referents.

Bin 2016[128]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Residents aged ≥ 40 years from four counties in Northern China divided into drinking-water-excessive fluoride (> 1.2 ppm) and control (< 1.2 ppm). Population demographics adequately described.
1.2	Is the eligible population or area representative of the source population or area?	+	Sample may represent the source population
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of selection not clearly described. Response rate was 78%. Inclusion/exclusion criteria were not described.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selection of comparison only based on water fluoride level. Numbers of participants and characteristics between groups were imbalanced. No attempt to minimize selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	-	No evidence for hypothesis for the effect of fluoride on visual impairment
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, gender, education, annual income. Not controlled for other important factors including genetics.
2.5	Is the setting applicable to Canada?	-	Study conducted in China. Not applicable to Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Refractive errors measured by ophthalmologists and optometrists whose works were piloted and standardized.
3.2	Were all outcome measurements complete?	++	Yes
3.3	Were all important outcomes assessed?	+	Refractive errors (myopia, hyperopia, astigmatism)
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	++	Yes
4.3	Were the analytical methods appropriate?	++	Multiple linear regression analysis.

Item	Question	Rating	Comment
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CI reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Potentially exist of selection bias. There are some methodological limitations.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study conducted in China. Could not be generalizable to the Canadian population.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Refractive errors in Northern China between the residents with drinking water containing excessive fluorine and normal drinking water
Author(s)	Bin et al.
Publication year	2016
Country (where the study was conducted):	China
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To evaluate the refractory errors and the demographic associations between drinking water with excessive fluoride and normal drinking water
Study design	Cross-sectional
Study location	Villages in Northern China
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	1.47 ppm
• Comparator	0.2 ppm
Setting	Rural
Source of population	Residents aged ≥40 years from four counties in Northern China divided into drinking-water-excessive fluoride (> 1.2 ppm) and control (< 1.2 ppm)
Inclusion/exclusion criteria	Exclusion: corneal disease, cataract, refractive surgery history, and any other reason that may distort the eye refraction were excluded
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention (1.47 ppm)**	**Comparator (0.2 ppm)**
Number of participants enrolled	1,415	221	1,194
Age, years (SD)	57.7 (9.4)	56.4 (9.6)	58.0 (9.3)
Gender (% male/female)	72/28	61/39	74/26
Refractive errors (diopters), mean (SD)	-0.50 (2.55)	-0.61 (2.33)	-0.48 (2.59)
Level of education, %			
Half illiteracy		14.5	56.9
Primary school		46.6	23.5
Middle school		36.7	18.6
College		2.3	1.1
Annual income (Yuan), mean (SD)			
<3000		23.1	10.8
3000 to 5,000		7.2	4.8
5,000 to 10,000		10.9	31.7
10,000 to 30,000		28.2	40.0
>30,000		30.3	12.7

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Myopia, hyperopia, astigmatism were measured by ophthalmologists and optometrists. The refractive errors were transformed into spherical equivalents (SE) calculated as the spherical value plus half of the astigmatic value. Myopia: SE worse than -0.50 diopters (D) Hyperopia: SE worse than +0.50 D Astigmatism: cylindrical error worse than 0.75D
Number of participants analysed	1,415
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Multiple linear regression analysis.
Results	**Prevalence of myopia, hyperopia, and astigmatism among individuals living in high and low water fluoridated areas.**

	Prevalence[a], % (95% CI)	
	1.47 ppm	0.2 ppm
Myopia	38.2 (35.7 to 40.8)	31.7 (29.3 to 34.2)
Hyperopia	20.6 (18.5 to 22.8)	27.2 (24.9 to 29.6)
Astigmatism	43.3 (40.7 to 45.9)	45.3 (42.7 to 48.0)

[a] Adjusted for age

- Multiple linear regression analysis showed that spherical equivalents from the right eye of the eligible individuals were associated with gender, age, annual income, but not with education (*P* = 0.378) and fluoride levels in drinking water (*P* = 0.857).

CONCLUSION	
Authors' conclusion	*"The refractive errors did not result from ingestion of mild excess amounts of fluoride in the drinking water."*(p.259)[128]
Reviewer's note	Participant characteristics were imbalanced between groups.

Fluegge 2016[130]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Fluoride data were obtained from state fluoridation reports of 22 states in the US. Participant data were obtained from the County Data Indicators profile of the Diabetes Data and statistics portal through the CDC. Population demographics not reported.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear if the eligible population or area is representative of the source population, due to limited availability of public data.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Not reported on method of selection of participants from eligible population.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Not reported on how selection bias was minimized.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	No strong evidence for hypothesis.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Confounding factors identified and adjusted for one set of regression analysis using fluoride exposure in milligrams of fluoride consumption, but not in analysis with primary exposure in ppm. Confounding factors: physical inactivity, obesity, poverty, log population per square mile, mean of years fluoridated and year. Likely miss other confounding factors.
2.5	Is the setting applicable to Canada?	+	Set in the US, with different healthcare system compared to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Diabetes incidence and prevalence were from CDC reports.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Diabetes incidence and prevalence
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	

Item	Question	Rating	Comment
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Some. Unclear if they are sufficient
4.3	Were the analytical methods appropriate?	+	GEE regression analysis controlled for confounders in one analysis (exposure in mg), not in the other analysis (exposure in ppm)
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations in data collection and data analysis. Many aspects were unclear due to not reporting. Likely miss other important confounders. Risk of selection bias.
5.2	Are the findings generalizable to the source population (i.e., externally valid)?	+	May partially be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Community water fluoridation predicts increase in age-adjusted incidence and prevalence of diabetes in 22 states from 2005 and 2010
Author(s)	Fluegge
Publication year	2016
Country (where the study was conducted):	USA
Funding sources	NHI National Heart Lung and Blood Institute grant
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To examine the associations between added and naturally present fluoride and the prevalence and incidence of diabetes.
Study design	Ecological
Study location	USA
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	0.71 ± 0.31 ppm (added fluoride)
• Comparator	0.23 ± 0.27 ppm (natural fluoride)
Setting	County level
Source of population	Participant data were obtained from the County Data Indicators profile of the Diabetes Data and statistics portal through the CDC

Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Number of participants enrolled	NR, from 925 counties	NR	NR
Age, years (SD)	NR	NR	NR
Gender	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Diabetes incidence and prevalence were from CDC reports.
Number of participants analysed	NR
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Regression analysis using generalized estimating equations (GEE) controlled for confounders in one analysis (exposure in mg), not in the other analysis (exposure in ppm)
Results	Regression with primary exposure assessed in milligrams (adjusted by county-level per capita tap water consumption) and unadjusted exposure in ppm.

Covariates	**β coefficient (SE)**			
	Adjusted^a exposure in mg		Unadjusted exposure in ppm	
	Incidence	Prevalence	Incidence	Prevalence
Added fluoride	0.23 (0.06)***	0.17 (0.05)***	0.35 (0.11)**	0.27 (0.09)***
Natural fluoride	-0.23 (0.06)***	-0.15 (0.04)***	-0.73 (0.12)	-0.55 (0.09)***

*** $P < 0.001$; ** $P < 0.01$

[a] Adjusted for physical inactivity, obesity, poverty, log population per square mile, mean of years fluoridated and year

- There was a significant positive relationship between diabetes outcomes (i.e., incidence and prevalence) and added fluoride in the drinking water, after adjustment for physical inactivity, obesity, poverty, log population per square mile, mean of years fluoridated and year. A 1 mg increase in added fluoride would result in 0.23 per 1000 person increase in diabetes incidence and 0.17% increase in the diabetes prevalence
- In the same model, there was a significant inverse relationship between diabetes outcomes (i.e., incidence and prevalence) and fluoride naturally occurring in the drinking water.
- Similar observations were obtained in unadjusted analysis with primary exposure in ppm.

CONCLUSION	
Authors' conclusion	*"Community water fluoridation is associated with epidemiological outcomes for diabetes"*(p.864) [130]
Reviewer's note	The author stated that: • "it is difficult to unequivocally state that these results are the specific consequences of water fluoridation" due to "ecological fallacy" and "fluoridation is not the only source of exposure to fluoride" • "diabetes most likely has a multifactorial etiology, even including epigenetic processes" • "the analyses presented here were limited by the availability of data"

Irigoyen-Camacho 2016[105]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Study conducted in Morelos, a central state of Mexico. Setting, location and population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	The three selected communities had low SES, heads of household had less than six years of formal education, and poor housing conditions.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Not well described on method of selection. Children aged between 8 and 12 years were invited to participate. Response rate was 96.3%.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Three wells out of 18 water sources were selected. Risk of selection bias
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Sex, number of erupted teeth, fluoride concentration in water, source of drinking water, use of fluoride toothpaste, weight-for-age, and height-for-age.
2.5	Is the setting applicable to Canada?	-	Set in Mexico. Not applicable to Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis assessment using TF index. Nutritional status was classified according to the WHO Child Growth Standards criteria. Trained examiner and standardized nutritionist.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis, body weight and height.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Likely not be sufficient

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	++	Multiple logistic regression models
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Risk of selection bias. Limitations in identifying the confounding variables.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	No. Study conducted in Mexico, where socio-economic factors, healthcare and fluoride levels in drinking water are different than those in Canada.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Nutritional status and dental fluorosis among schoolchildren in communities with different drinking water fluoride concentration in a central region in Mexico
Author(s)	Irigoyen-Camacho et al.
Publication year	2016
Country (where the study was conducted):	Mexico
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To measure the association between undernutrition and dental fluorosis in children who live in communities with different drinking water fluoride concentrations
Study design	Cross-sectional
Study location	Central Mexico
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	0.70 ppm, 1.60 ppm
• Comparator	0.56 ppm
Setting	Rural communities
Source of population	Children aged between 8 and 12 years living in three communities with different well water fluoride concentrations.
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS			
	0.56 ppm	**0.70 ppm**	**1.60 ppm**
Number of participants enrolled	350	121	263
Mean age, years (SD)	9.30 (1.15)	10.21 (1.38)	9.46 (1.83)
Gender			
Male	47.7%	48.8%	51.0%
Female	52.3%	51.2%	49.0%
Source of drinking water			
Bottle	71.5%	66.1%	79.5%
Tap	28.5%	33.9%	27.6%
Use of toothpaste			
Yes	95.1%	98.3%	81.4%
No	4.9%	1.7%	18.6%
REPORTED OUTCOMES			
Definition (with units) and method of measurement	Dental fluorosis assessment using TF index. Nutritional status was classified according to the WHO Child Growth Standards criteria. TFI=0 (no dental fluorosis) TFI=1 (white thin opaque lines running across tooth surface) TFI =2 (lines join and form clouds the teeth) TFI =3 (merging of the white opaque lines occurs and clouds observed in many areas of the tooth surface) TFI=4 (entire tooth surface showed a marked opacity or appeared chalky white) TFI=5 (loss of enamel and round pits appear) TFI=6 (small pits frequently merge in opaque enamel to form bands <2 mm in vertical height) TFI=7 (loss of the outermost enamel forming irregular areas, less than half of the surface is involved) TFI=8 (loss of the outermost enamel involves more than half of the enamel) TFI=9 (loss of the major part of the enamel results in a change of the anatomical shape of the surface/tooth) TFI < 4: absent to mild; TFI ≥ 4: moderate to severe		
Number of participants analysed	734		
Number of participants excluded or missing (with reasons)	NR		
Imputing of missing data	NR		
Statistical method of data analysis	Multiple logistic regression models Sex, number of erupted teeth, fluoride concentration in water, source of drinking water, use of fluoride toothpaste, weight-for-age, and height-for-age.		

Results

Prevalence of dental fluorosis

Water fluoride concentration	TFI < 4	TFI ≥ 4
0.56 ppm	93.7%	6.3%
0.70 ppm	90.9%	9.1%
1.60 ppm	68.1%	31.9%

Association between dental fluorosis (TFI ≥ 4) and water fluoride concentration

F level	Crude OR (95% CI)	*P* value	Adjusted 1[a] OR (95% CI)	*p* value	Adjusted 2[b] OR (95% CI)	*P* value
0.56 ppm	Ref (1)		Ref (1)		Ref (1)	
0.70 ppm	1.49 (0.70 to 3.17)	0.300[c]	1.19 (1.06 to 1.34)	0.003[c]	1.20 (1.06 to 1.35)	0.003[c]
1.60 ppm	6.99 (4.23 to 11.58)	< 0.001[c]	6.27 (5.93 to 6.63)	< 0.001[c]	5.85 (5.45 to 6.29)	< 0.001[c]

[a] Adjusted for sex, number of teeth, source of drinking water, use of fluoridated toothpaste and weight-for-age
[b] Adjusted for sex, number of teeth, source of drinking water, use of fluoridated toothpaste and height-for-age
[c] Compared to Ref

- There were significant associations between dental fluorosis (TFI ≥ 4) and tap water fluoride concentrations of 0.70 ppm and 1.60 ppm in both adjusted models, using 0.56 ppm as reference.

CONCLUSION

Authors' conclusion	*"Children with low height-for-age were more likely to have dental fluorosis in the TFI categories that affect the entire tooth surface."*(p.513) [105]
Reviewer's note	Fluoridated salt was available in the studied communities. Children were likely exposed to multiple sources of fluoride (e.g., fluoridate salt), which were not controlled.

Mahantesha 2016[98]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Survey was carried out in three villages in India with three water fluoride levels. Population demographics were not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Children aged 9 to 15 years who were lifetime residents of the respective villages.
1.3	Do the selected participants or areas represent the eligible population or area?	NR	
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selection of exposure was based on water fluoride levels of three villages (0.136, 0.381, 1.36 ppm). Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Water fluoride level, tea consumption, type of diet, nutritional status, breastfeeding duration, water consumption. Likely miss other confounding factors.
2.5	Is the setting applicable to Canada?	-	Set in India. Not applicable to Canada due to different in socio-economic factors and healthcare.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis using Dean’s index according to the WHO criteria was examined by a single examiner and recorded by a trained assistant.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Prevalence and severity of dental fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Not included age and gender

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	++	Multiple logistic regression analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	Actual p values and SE were reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Risk of selection bias. Not all important confounders were identified and adjusted.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study was conducted in India. Low generalizability to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Prevalence of dental fluorosis and associated risk factors in Bagalkot district, India
Author(s)	Mahantesha et al.
Publication year	2016
Country (where the study was conducted):	India
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To investigate the risk factors of dental fluorosis in permanent teeth in the villages of northern Karnataka, India
Study design	Cross-sectional
Study location	Three villages in northern Karnataka, India, with three water fluoride levels.
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	0.136 ppm; 0.381 ppm; 1.36 ppm
Setting	Rural
Source of population	Children aged 9 to 15 years
Inclusion/exclusion criteria	Lifetime residents of the respective villages
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS			
Water fluoride concentration	**0.136 ppm**	**0.381 ppm**	**1.36 ppm**
Number of participants enrolled	100	100	96
Age, years (SE)	11.38 (0.19)	12.03 (0.12)	11.8 (0.19)
Gender	NR	NR	NR

Height, cm (SE)	134.54 (1.22)	141.29 (1.03)	133.35 (1.23)
Weight, kg (SE)	27.88 (0.84)	30.54 (0.77)	27.68 (0.71)
REPORTED OUTCOMES			
Definition (with units) and method of measurement	Dental fluorosis was assessed using Dean's index 0: Normal 1: Questionable 2: Very mild 3: Mild 4: Moderate 5: Severe		
Number of participants analysed	289		
Number of participants excluded or missing (with reasons)	7 (not continuous residents)		
Imputing of missing data	NR		
Statistical method of data analysis	Multiple logistic regression analysis		
Results	**Prevalence and severity of dental fluorosis**		

Fluoride level	Prevalence, %			Dean's index, mean (SE)
	Normal	Mild	Moderate to severe	
0.136 ppm (n = 97)	92.7	7.3	0	0.12 (0.047)[a]
0.381 ppm (n = 99)	42.4	49.5	8.1	1.42 (0.15)[b]
1.36 ppm (n = 93)	0	0	100	4.71 (0.047)

[a] $P < 0.001$ compared to 0.381 ppm and 1.36 ppm

[b] $P < 0.001$ compared to 1.36 ppm

- All children living in 1.36 ppm area had moderate to severe dental fluorosis (i.e., Dean's score ≥ 4)
- There was a significant positive relationship between prevalence of dental fluorosis (Dean's index > 1) and water fluoride concentration (β coefficient: 3.33; $P = 0.00001$), after adjustment for tea consumption, nutritional status and water consumption.
- There was a non-significant relationship between dental fluorosis severity (Dean's index: 4, 5) and water fluoride concentration (β coefficient: 22.90; $P = 0.81$), after adjustment for diet and nutritional status. Nutritional status was a significant risk factor for severity of dental fluorosis (β coefficient: 1.73; $P = 0.038$)

CONCLUSION	
Authors' conclusion	*"Presence or absence of dental fluorosis in permanent teeth was significantly associated with fluoride concentration in drinking water. Once present, its severity was determined by nutritional status of the children – malnourished children exhibiting severe form of fluorosis."*(p.256) [98]
Reviewer's note	

Nasman 2016[131]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Several nationwide registers were used. Population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Large cohort (n=455,619), born between January 1, 1900 and December 31, 1919, alive and living in municipalities of birth at the time of start of follow-up.
1.3	Do the selected participants or areas represent the eligible population or area?	++	The method of selection was well described. 96% individuals were selected from the eligible population. Inclusion and exclusion criteria were explicit.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Exposure was based on fluoride level detected in the municipalities. Potential risk of selection bias due to misclassification.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Based on the facts that trace elements in drinking water have been implicated in the pathogenesis of coronary heart disease.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Gender, age, calendar period for study entry, geographical area of residence and water hardness. Other important confounders related to heart disease were not identified and adjusted (SES, smoking, obesity, cholesterol levels, diabetes, blood pressure, antihypertensive therapy).
2.5	Is the setting applicable to Canada?	+	The setting was in Sweden. May be applicable to Canada due to similar in fluoride exposure at very low (< 0.3 ppm), low (0.3 to < 0.7 ppm) and medium (0.7 to < 1.5 ppm)
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Diagnosed myocardial infarction according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Myocardial infarction
3.4	Was there a similar follow-up time in exposure and comparison groups?	NR	Did not report if the groups had similar follow-up time.
3.5	Was follow-up time meaningful?	++	Median duration of follow-up was 15.7 years.
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Models adjusted for some confounding factors

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	++	Cox proportional hazard regression model.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good participant recruitments, adequate data collection methods, good statistical analysis, limited in the identification of confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study conducted in Sweden. Could be generalizable to the Canadian context due to similarity in water fluoride levels and other socio-economic aspects.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Natural fluoride in drinking water and myocardial infarction: A cohort study in Sweden
Author(s)	Nasman et al.
Publication year	2016
Country (where the study was conducted):	Sweden
Funding sources	Grant from Karolinska Institutet and the Swedish Patient Revenue Fund for Research in Preventive Odontology
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To assess the association between drinking water fluoride exposure and incidence of myocardial infarction in Sweden using nationwide registers
Study design	Ecological
Study location	Sweden
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Natural fluoride: < 0.3 ppm; 0.3 to < 0.7 ppm; 0.7 to < 1.5 ppm; ≥ 1.5 ppm
Setting	Nationwide registers
Source of population	Large cohort (n = 474,217), born between January 1, 1900 and December 31, 1919, alive and living in municipalities of birth at the time of start of follow-up
Inclusion/exclusion criteria	Diagnosis of myocardial infarction prior to the time of start of follow-up.
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS				
Water fluoride concentration	**< 0.3 ppm**	**0.3 to < 0.7 ppm**	**0.7 to < 1.5 ppm**	**≥ 1.5 ppm**
Number of participants enrolled	251,046	136,686	54,219	13,669
Person-years	3,982,462	2,409,539	1,028,416	174,162
Median Age, years (range 44 to 87)	63.9	61.2	59.4	68.3
Gender	54.1% male	30.5% male	12.3% male	3.1% male

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Diagnosed myocardial infarction according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)
Number of participants analysed	455,619
Number of participants excluded or missing (with reasons)	18,599 (Diagnosis of myocardial infarction prior to the time of start of follow-up and missing fluoride exposure data)
Imputing of missing data	NA
Statistical method of data analysis	Cox proportional hazard regression model.
Results	See below

Results

Risk of myocardial infarction

Fluoride level	Crude[a] HR (95% CI)[a]	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)
<0.3 ppm	Ref (1)	Ref (1)	Ref (1)
0.3 to <0.7 ppm	1.05 (1.04 to 1.06)	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.02)
0.7 to <1.5 ppm	1.07 (1.05 to 1.08)	1.01 (0.99 to 1.03)	1.02 (0.99 to 1.04)
≥1.5 ppm	1.07 (1.04 to 1.10)	0.98 (0.96 to 1.01)	1.01 (0.98 to 1.04)

CI = confidence interval; HR = hazard ratio

[a] Adjusted for sex and age.

[b] Adjusted for sex, age, calendar period for study entry and geographical area of residence.

[c] Adjusted for sex, age, calendar period for study entry, geographical area of residence and water hardness.

- There was no significant difference in the risk of myocardial infarction among different water fluoride concentrations, after adjustment for sex, age, calendar period for study entry, geographical area of residence and water hardness.

Risk of myocardial infarction among subgroup individuals

Subgroup	n	< 0.3 ppm	0.3 to < 0.7 ppm	0.7 to < 1.5 ppm	≥ 1.5 ppm
		HR (95% CI)[a]			
Gender					
Male	241,423	Ref (1)	1.00 (0.98 to 1.02)	1.01 (0.99 (1.04)	1.00 (0.96 to 1.04)
Female	214,196	Ref (1)	0.99 (0.97 to 1.02)	1.03 (1.00 to 1.06)	1.02 (0.98 to 1.07)
Age					
< 65	274,174	Ref (1)	0.98 (0.93 to 1.04)	1.03 (0.96 to 1.10)	0.94 (0.81 to 1.10)
≥ 65	423,894	Ref (1)	1.00 (0.99 to 1.02)	1.02 (1.00 to 1.04)	1.01 (0.98 to 1.04)

	• There was no significant difference in the risk of myocardial infarction in men or women among different water fluoride concentrations. • There was no significant difference in the risk of myocardial infarction in individuals aged < 65 years or ≥ 65 years among different water fluoride concentrations.
CONCLUSION	
Authors' conclusion	*"The investigated levels of natural drinking water fluoride content do not appear to be associated with myocardial infarction, nor related to the geographic myocardial infarction risk variation in Sweden."* (p.305) [131]
Reviewer's note	Other important confounders related to heart disease were not identified and adjusted (e.g., SES, smoking, obesity, cholesterol levels, diabetes, blood pressure, antihypertensive therapy)

Pretty 2016[93]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	A surveillance approach was adopted across four English cities. Two cities were served with CWF of 1 ppm and two other cities had only naturally-occurring low levels water fluoride. Population demographics not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	++	Survey of school-based children aged 11 to 14 years who self-reported life time residency in the city. Schools were selected based on prior participation in dental survey.
1.3	Do the selected participants or areas represent the eligible population or area?	++	Method of selection and inclusion criteria were appropriate and well described.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Two cities with CWF of 1 ppm vs two cities with low levels of naturally-occurring fluoride. Risk of recalling bias due to self-reporting of lifetime residency in the fluoridated and non-fluoridated areas.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Dental fluorosis caused by fluoride exposure.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors were identified and controlled
2.5	Is the setting applicable to Canada?	+	Set in England. May be applicable to Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Photographic method with TF index reporting. Images were assessed by trained and calibrated examiner.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Prevalence and severity of dental fluorosis Self-perceived aesthetic score

Item	Question	Rating	Comment
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	Yes
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Risk of selection and recalling bias due to self-reporting. Poor statistical analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Four cities in England. May partially be generalizable to Canadian context due to similar in socio-economic factors, healthcare systems and water fluoride levels.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Prevalence and severity of dental fluorosis in four English cities
Author(s)	Pretty et al.
Publication year	2016
Country (where the study was conducted):	UK
Funding sources	Public Health England
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To assess the prevalence and severity of dental fluorosis in four city-based populations and to record the aesthetic satisfaction scores of children in all four cities.
Study design	Cross-sectional
Study location	Four cities in England
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	Fluoridated (1 ppm)
• Comparator	Non-fluoridated (low fluoride levels naturally present; concentrations not reported)
Setting	School-based
Source of population	Children aged 11 to 14 years
Inclusion/exclusion criteria	Lifetime residency in the cities
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS			
Water fluoride concentration	**Total**	**Fluoridated (1.0 ppm)**	**Non fluoridated**
Number of participants enrolled	1,904	963	941
Age, years	11 to 14	NR	NR
Gender	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis was assessed using TF index using a photographic method
Number of participants analysed	Varied depending on the outcomes
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Chi-square test
Results	See below

Results

Prevalence of dental fluorosis based on TF index score

TF index	Total	Fluoridated	Non fluoridated
0	50.6%	38.5%	62.8%
1 to 2	43.1%	51.1%	35.0%
3 to 4	6.1%	9.9%	2.2%
>5	0.2%	0.5%	0%

Prevalence of dental fluorosis based on Dean’s index score

Dean’s index	Total	Fluoridated	Non fluoridated
Normal (0)	50.5%	36.0%	65.2%
Questionable to very mild (1/2 to 1)	44.3%	55.7%	32.7%
Mild to moderate (2 to 3)	5.1%	8.2%	1.9%
Severe (4)	0.1%	0.1%	0.1%

- Compared with non-fluoridated cities, fluoridated cities had significantly higher prevalence of dental fluorosis at TF>0 (61.5% vs 37.2%; *P* < 0.0001) and at TF>2 (10.4% vs 2.2%; *P* < 0.0001)

Response rate to self-perceived aesthetic score

Aesthetic score	Response rate, %	
	Fluoridated	Non fluoridated
0 (none)	6.7	6.2
1	23.0	21.9
2	30.8	33.4
3	28.8	23.0
4	5.7	7.8
5 (greatest)	4.9	6.8

- There was no significant difference in the response rate among aesthetic score between fluoridated and non-fluoridated cities.

CONCLUSION	
Authors’ conclusion	*“The proportion of children expressing dissatisfaction with the appearance of their teeth is the same in fluoridated and non-fluoridated communities… The levels of fluorosis that might be considered of aesthetic concern are low and stable.”*(p.292)[93]
Reviewer’s note	No adjustment for confounders.

Ramadan 2016[110]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Residents in two communities in Sudan. Population demographics were partially described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear
1.3	Do the selected participants or areas represent the eligible population or area?	+	A systematic random sampling technique was used. Not reported on % of selected individuals agreed to participate. Inclusion: born and bred in their communities, have at least 50% of the crowns of their permanent teeth erupted.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Two villages with different fluoride levels in well water. Systematic random sample technique was applied.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Dental fluorosis caused by fluoride exposure.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors were identified and controlled.
2.5	Is the setting applicable to Canada?	-	Set in Sudan. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Dental fluorosis was assessed according to Dean's index. Reliability and validity of outcome measures were not reported.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Prevalence and severity of dental fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No

Item	Question	Rating	Comment
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p-values reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations in population recruitment, in method of selection, in outcome measures and in data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Two villages in Sudan. Could not be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION			
Title	Dental fluorosis in two communities in Khartoum state, Sudan, with potable water fluoride levels of 1.36 and 0.45 mg/L		
Author(s)	Ramadan and Ghandour		
Publication year	2016		
Country (where the study was conducted):	Sudan		
Funding sources	NR		
Reported conflict of interest	☐ Yes ☑ No		
STUDY CHARACTERISTICS			
Objectives	To assess the prevalence and severity of dental fluorosis among residents in two communities in Sudan.		
Study design	Cross-sectional		
Study location	Tiraat El-Bijah and Um Duwanban, Sudan		
Study duration	NA		
Exposure duration	Lifetime		
Fluoride levels or Exposures:	Well water		
• Intervention	1.36 ± 0.08 ppm (range 1.29 to 1.43 ppm)		
• Comparator	0.45 ± 0.39 ppm (range 0.24 to 1.31 ppm)		
Setting	Community-level		
Source of population	Residents in two communities, mean age 17.43 years and 16.9 years, range 6 to 63 years.		
Inclusion/exclusion criteria	Inclusion: born and bred in their communities, have at least 50% of the crowns of their permanent teeth erupted.		
Recruitment or sampling procedure	A systematic random sampling technique was used.		
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited		
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention (1.36 ppm)**	**Comparator (0.45 ppm)**
Number of participants enrolled	800	400	400
Mean age, years	NR	17.43	16.9
Gender	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis was assessed according to Dean’s index.
Number of participants analysed	800
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Chi-square test
Results	**Prevalence of dental fluorosis in two communities of 1.36 ppm and 0.45 ppm**

Fluorosis severity	Prevalence, n (%)	
	1.36 ppm (N = 400)	0.45 ppm (N = 400)
Normal	120 (30.0)	230 (57.5)*
With fluorosis	280 (70.0)	170 (42.5)*
Among those with fluorosis	N = 280	N = 170
Very mild	89 (31.8)	78 (45.9)*
Mild	126 (45.0)	55 (32.4)*
Moderate	57 (20.4)	36 (21.2)*
Severe	8 (2.9)	1 (0.6)*

*$P < 0.001$

- Dental fluorosis at various degree of severity was significantly higher in community with high drinking fluoride (1.36 ppm) level compared to community with low fluoride level (0.45 ppm).
- Within each community, there was no significant difference in dental fluorosis prevalence between males and females.
- Between communities, males and females living in the 1.36 ppm drinking water fluoride area had significantly higher dental fluorosis at various degree of severity than their counterparts in the 0.45 ppm drinking water fluoride area

Prevalence of dental fluorosis stratified by age group

Age group (year)	Prevalence, n (%)	
	1.36 ppm (N = 280)	0.45 ppm (N = 170)
6 to 8	46 (16.4)	18 (10.6)
10 to 12	77 (27.5)	30 (17.8)
15 to 20	82 (29.3)	56 (32.9)
≥ 25	75 (26.8)	66 (38.8)

- Prevalence of dental fluorosis increased with age in both communities, except the age group ≥25 years in 1.36 ppm community.
- Prevalence of dental fluorosis of age groups 6 to 8 years and 10 to 12 years was higher in the 1.36 ppm area compared to the corresponding age groups in the 0. 45 ppm area.

CONCLUSION	
Authors’ conclusion	*“Significantly more dental fluorosis was found in Um Duwanban (mean potable water F 1.36 ± 0.08 mg/L) than in Tiraat El-Bijah (mean potable water F 0.45 ± 0.39 mg/L) (P < 0.001).”*(p.509) [110]
Reviewer’s note	No adjustment for confounders.

Sebastian 2016[99]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Primary school children born and raised in three villages in India. Population demographics were not described.
1.2	Is the eligible population or area representative of the source population or area?	++	Children 10-12 years of age from 3 randomly selected villages
1.3	Do the selected participants or areas represent the eligible population or area?	+	Three villages were randomly selected based on fluoride level in the water. Children aged 10 to 12 years. Inclusion/exclusion criteria were described. Percent of selected individuals agreed to participate was not reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Children were excluded if they were not permanent residents of that particular area. Unclear how the villages were selected. Potential bias in the selection of the villages.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Excessive intake of fluoride can cause dental fluorosis.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounders controlled.
2.5	Is the setting applicable to Canada?	-	Set in India. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis was assessed by a trained examiner using Dean's fluorosis index.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Prevalence and severity of dental fluorosis.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	+	Not provided additional details.
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported.

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations in population recruitment and selection, controlling for confounders, and data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study conducted in India, which has different socio-economic factors, healthcare systems and water quality standard compared to Canada.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Prevalence of dental fluorosis among primary school children in assocaition with different water fluoride levels in Mysore district, Karnataka
Author(s)	Sebastian et al.
Publication year	2016
Country (where the study was conducted):	India
Funding sources	Grant of Rs 14000/- from JSS University, Mysore
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To assess the prevalence and severity of dental fluorosis in primary school children born and raised in three villages of Mysore district.
Study design	Cross-sectional
Study location	three villages of Mysore district, Karnataka, India
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	0.4 ppm, 1.2 ppm and 2.0 ppm
Setting	School-based
Source of population	Children aged 10 to 12 years
Inclusion/exclusion criteria	Exclusion: not permanent residents, those with orthodontic brackets, those with dentofacial abnormalities, medically and physically compromised
Recruitment or sampling procedure	Three villages were randomly selected based on fluoride level in the water. Each school was considered as a cluster.
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS				
	Total	**0.4 ppm**	**1.2 ppm**	**2.0 ppm**
Number of participants enrolled	405	135	135	135
Age, years	10 to 12	10 to 12	10 to 12	10 to 12
Gender	50.4% male	56.3% male	43.0% male	51.9% male

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis was assessed according to Dean's index.
Number of participants analysed	405
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Spearman's rank correlation coefficient
Results	**Prevalence of dental fluorosis** (see table below)

Fluorosis severity	**Prevalence, n (%)**		
	0.4 ppm (N=135)	1.2 ppm (N=135)	2.0 ppm (N=135)
Normal	121 (89.6)	98 (72.6)	17 (12.6)
With fluorosis	14 (10.3)	37 (27.4)*	118 (87.4)*
Questionable	3 (2.2)	10 (7.4)	18 (13.3)
Very mild	7 (5.1)	14 (10.4)	24 (17.8)
Mild	3 (2.2)	5 (3.7)	25 (18.5)
Moderate	0	7 (5.1)	13 (9.6)
Severe	1 (0.74)	1 (0.74)	38 (28.1)

*P = 0.03

- The prevalence of dental fluorosis as a whole or at various degree of severity increased with increasing drinking water fluoride level.
- The community fluoridation index (CFI) increased with increasing drinking water fluoride level. The (CFI) was 0.14, 0.4 and 2.03 for 0.4 ppm, 1.2 ppm and 2.0 ppm, respectively.
- There was a significantly positive correlation between CFI and drinking water fluoride level (correlation coefficient r = 0.92; *P* = 0.04).

CONCLUSION	
Authors' conclusion	*"A significantly positive correlation was found between CFI and water fluoride concentration in drinking water."*(p.151)[99]
Reviewer's note	No adjustment for confounders.

Shruthi 2016[118]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Adults aged 20 to 90 years living in three villages in India. Population demographics were not described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Three villages were randomly selected based on fluoride level in the water. Method of selection of participants was not clearly described. Inclusion/exclusion criteria were described. Percent of selected individuals agreed to participate was not reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selection of exposure and comparison groups was based on fluoride level in water. One group (three villages) with fluoride level > 1.5 ppm and one group (one village) with fluoride level < 1.0 ppm. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Excessive intake of fluoride can cause skeletal fluorosis.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounders controlled.
2.5	Is the setting applicable to Canada?	-	Set in India. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Skeletal fluorosis was assessed by physical test (touching) and radiological evaluation. Inter-examiner reliability was not reported.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Prevalence skeletal fluorosis.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No

Item	Question	Rating	Comment
4.3	Were the analytical methods appropriate?	-	No
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations in population recruitment and selection, controlling for confounders, and data analysis.
5.2	Are the findings generalizable to the source Canadian population (i.e., externally valid)?	-	Study conducted in India, which has different socio-economic factors, healthcare systems and water quality standard compared to Canada.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION			
Title	A comparative study of skeletal fluorosis among adults in two study areas of Bangarpet Taluk, Kolar		
Author(s)	Shruthi et al.		
Publication year	2016		
Country (where the study was conducted):	India		
Funding sources	Nil		
Reported conflict of interest	☑ Yes ☐ No		
STUDY CHARACTERISTICS			
Objectives	To assess the prevalence of skeletal fluorosis, and to compare various epidemiological factors influencing the occurrence of skeletal fluorosis among the two groups with differential water fluoride levels in all the sources of drinking water in the study areas.		
Study design	Cross-sectional		
Study location	Bangarpet Taluk, Kolar, India		
Study duration	NA		
Exposure duration	Lifetime		
Fluoride levels or Exposures:	Three villages with fluoride concentrations of 4.13 ppm, 2.59 ppm and 0.61 ppm were divided into two groups:		
• Intervention	> 1.5 ppm		
• Comparator	< 1.0 ppm		
Setting	Rural		
Source of population	Adults aged 20 to 90 years living in three villages in India.		
Inclusion/exclusion criteria	Exclusion: pregnant women, bedridden, and persons who were not available even after two visits.		
Recruitment or sampling procedure	Random selection		
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited		
PARTICIPANT CHARACTERISTICS			
	Total	**Intervention (>1.5 ppm)**	**Comparator (<1.0 ppm)**
Number of participants	680	358	322
Age, years	20 to 90 year	NR	NR
Gender	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Skeletal fluorosis was assessed by physical test (touching) and radiological evaluation.
Number of participants analysed	680
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Chi-square test
Results	• The prevalence of skeletal fluorosis was 5.0% in both high (> 1.5 ppm) and normal drinking water fluoride level (< 1.0 ppm). • Within each group, there was no difference in skeletal fluorosis prevalence between males and females. • Between groups, there was no difference in skeletal fluorosis prevalence in males or females.
CONCLUSION	
Authors' conclusion	*"The prevalence of skeletal fluorosis at both high and normal fluoride groups was 5%."*(p.203)[118]
Reviewer's note	No adjustment for confounders

Aghaei 2015a[119]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Thirty-five rural and urban areas in the Zarand district in Iran. Ground water is the major source of drinking water. Population demographics were not described.
1.2	Is the eligible population or area representative of the source population or area?	++	35 villages and towns in the Zarand district with differing concentrations of Fluoride
1.3	Do the selected participants or areas represent the eligible population or area?	++	Random selection of 492 babies born in 2013 , exclusion criteria provided
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on fluoride levels in the ground water. Mothers were long-life residents in the study areas and lived there during their pregnancies. Potential risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Based on potential association between premature births and CWF from previous studies.
2.3	Was the contamination acceptably low?	NA	
2.4	How well were likely confounding factors identified and controlled?	-	Confounding factors not identified and controlled.
2.5	Is the setting applicable to Canada?	-	Set in Iran. Not applicable to Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	The height and birthweight data were from hospital records.

Item	Question	Rating	Comment
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Height and birthweight
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No multivariable analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Risk of selection bias, no adjustment for confounders, poor data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	The study was conducted in Iran with different socio-economic factors, healthcare system, and water quality compared to Canada. The findings could not be generalizable to the Canadian population.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Effect of fluoride in drinking water on birth height and weight: An ecological study in Kerman province, Zarand county, Iran
Author(s)	Aghaei et al.
Publication year	2015
Country (where the study was conducted):	Iran
Funding sources	NR
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To evaluate the association between maternal exposures to drinking water fluoride and birth height and weight in 35 villages and towns
Study design	Cross-sectional
Study location	35 villages and towns in Zarand county, Iran.
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	< 0.7 ppm, 0.7 to 1.5 ppm and > 1.5 ppm from ground water

Setting	Rural communities			
Source of population	Babies born during 2013 from 35 villages			
Inclusion/exclusion criteria	Inclusion: babies without complicating conditions. Mothers were life-long residents in the villages, and without history of previous illness.			
Recruitment or sampling procedure	Using random sampling proportional to the size of the population.			
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited			
	Total	**< 0.7 ppm**	**0.7 to 1.5 ppm**	**> 1.5 ppm**
Number of participants	492 babies	98	96	298
Age, years	NR	NR	NR	NR
Gender	NR	NR	NR	NR

REPORTED OUTCOMES

Definition (with units) and method of measurement	The height and birthweight data were from hospital records.
Number of participants analysed	492
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Chi-square test, Pearson's correlation

Results

Mean height and weight, and correlation between height or weight and fluoride level in drinking water

Fluoride level, ppm	Height, cm (SD)	Weight, g (SD)
< 0.7	47.7 (0.7)	2,728.8 (233.7)
0.7 to 1.5	49.1 (0.3)	2,808.3 (175.5)
> 1.5	51.2 (1.4)	3,201.4 (146.0)
Correlation coefficient		
r	0.69	0.44
P value	< 0.001	< 0.001

- Babies' height and weight increased with increasing fluoride concentration in drinking water.
- There was a positive correlation between babies' height and drinking water fluoride (r = 0.69; *P* < 0.001), and a positive correlation between babies' weight and drinking water fluoride (r = 0.44; *P* < 0.001)

CONCLUSION

Authors' conclusion	*"We found that exposure to fluoride at concentrations higher than the WHO drinking water guideline of a "desirable" upper limit of 1.5 mg/L was not associated with lower birth height and weight and that lower birth height and weight were observed with lower drinking water fluoride concentrations."*(p.160)[119]
Reviewer's note	No adjustment for confounding factors

Aghaei 2015b[114]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Two areas in West Azerbaijan in Iran with different natural concentrations of fluoride in drinking water. Population demographics were not described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear
1.3	Do the selected participants or areas represent the eligible population or area?	+	Not reported on method of selection and percent of selected participants agreed to participate. Exclusion criteria were reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on fluoride levels from well and spring water. Potential risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Based on potential toxicity of fluoride effect to the cardiovascular system.
2.3	Was the contamination acceptably low?	NA	
2.4	How well were likely confounding factors identified and controlled?	+	Age and sex. Other important confounding factors were not controlled, although individuals who had etiological factors known to contribute to hypertension were excluded.
2.5	Is the setting applicable to Canada?	-	Set in Iran. Not applicable to Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	The prevalence of hypertension data were from health records.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Prevalence of hypertension
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Age and sex.
4.3	Were the analytical methods appropriate?	++	Logistic regression analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Risk of selection and reporting bias, no adjustment for important confounders, potential flaw in study design.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	The study was conducted in Iran with different socio-economic factors, healthcare system, and water quality compared to Canada. The findings could not be generalizable to the Canadian population.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION			
Title	Hypertension and fluoride in drinking water: case study from west Azerbaijan, Iran		
Author(s)	Aghaei et al.		
Publication year	2015		
Country (where the study was conducted):	Iran		
Funding sources	NR		
Reported conflict of interest	☐ Yes ☑ No		
STUDY CHARACTERISTICS			
Objectives	To evaluate the association between drinking water fluoride and hypertension		
Study design	Cross-sectional		
Study location	Two areas in West Azerbaijan, Iran		
Study duration	NA		
Exposure duration	Lifetime		
Fluoride levels or Exposures:	Naturally occurring fluoride		
• Intervention	3.94 ppm		
• Comparator	0.25 ppm		
Setting	Rural communities		
Source of population	Adults aged 20 to 65 years living in high and low fluoride areas.		
Inclusion/exclusion criteria	Exclusion: smoking, >65 years old, family history of hypertension, lack of mobility, cardiovascular disease, and obesity.		
Recruitment or sampling procedure	Data derived from the health records both the areas		
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited		
PARTICIPANT CHARACTERISTICS			
	Total	**3.94 ppm**	**0.25 ppm**
Number of participants	2,878	897	1,981
Age, years	20 to 65	20 to 65	20 to 65
Gender	48.6% male	50.5% male	47.7% male
REPORTED OUTCOMES			
Definition (with units) and method of measurement	The prevalence of hypertension data were from health records.		
Number of participants analysed	2,878		

<table>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>NA</td></tr>
<tr><td>Imputing of missing data</td><td>NA</td></tr>
<tr><td>Statistical method of data analysis</td><td>Chi-square test, logistic regression analysis</td></tr>
<tr><td>Results</td><td>Prevalence of hypertension
<table>
<tr><th rowspan="2"></th><th>3.94 ppm</th><th>0.25 ppm</th></tr>
<tr><th colspan="2">n (%)</th></tr>
<tr><td>Total</td><td>78 (100)</td><td>162 (100)</td></tr>
<tr><td>Known etiology</td><td>45 (57.7)</td><td>102 (63.0)</td></tr>
<tr><td>Unknown etiology</td><td>33 (42.3)</td><td>60 (37.0)</td></tr>
<tr><td>Male</td><td>6 (18.2)</td><td>15 (25.0)</td></tr>
<tr><td>Female</td><td>27 (81.8)</td><td>45 (75.0)</td></tr>
<tr><td>Male and Female</td><td>33</td><td>60</td></tr>
</table>

The prevalence of hypertension of unknown etiology was 37.0% in 0.25 ppm area and 42.3% in 3.94 ppm area.
The prevalence of hypertension of unknown etiology was higher in female than in male.
Female aged 50 to 59 years living in high fluoride area had significant higher rate of hypertension than those living in low fluoride area (19.3% vs 7.7%; <i>P</i> = 0.011).
There was no significant difference in hypertension prevalence between high and low fluoride areas for different other age groups of both male and female.
Adjustment for age and sex based on logistic regression revealed no significant difference in the prevalence of hypertension of unknown etiology between high and low fluoride areas (<i>P</i> = 0.556)
</td></tr>
<tr><td colspan="2">CONCLUSION</td></tr>
<tr><td>Authors’ conclusion</td><td>No concrete conclusion provided.</td></tr>
<tr><td>Reviewer’s note</td><td>No adjustment for other confounding factors
No precise and clear evidence that fluoride exposure increases hypertension.</td></tr>
</table>

Bal 2015[92]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Primary school children aged 7 to 11 years in the Blue Mountains and Hawkesbury local government area of New South Wales, Australia. Population demographics not described.
1.2	Is the eligible population or area representative of the source population or area?	++	Survey was conducted in 18 schools with additional some smaller schools to have a geographic spread across the local government area.
1.3	Do the selected participants or areas represent the eligible population or area?	++	The schools were selected randomly using comparative size as the main criteria. All selected schools agreed to participate. Information packages were distributed to parents/guardians of the children. Response rate was 63%. Only children born after 1992 (based on 7 to 11 years old criteria) and whose parents/guardians gave consent were examined and included.

Item	Question	Rating	Comment
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Questionnaire was used to survey demographic information including exposure to fluoridated water and use of other fluoride sources. Some rural households did not received community water supply, instead their main water sources came from springs or rain. Exposures to fluoridated water were classified as percentage lifetime exposure.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes – 58 potential variables were explored in a series of bivariate analyses.
2.3	Was the contamination acceptably low?	NA	Exposure to fluoridated water was classified as percentage of lifetime exposure.
2.4	How well were likely confounding factors identified and controlled?	+	Of the 58 potential explanatory variables, five were included (frequency of toothbrushing, rinsing habit after brushing, eating or licking toothpaste, exposure to fluoridated water, and type of water used to reconstitute infant milk). SES and foods were not included.
2.5	Is the setting applicable to Canada?	+	May be applicable.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis was assessed according to the Community Index of Dental Fluorosis criteria, as recommended by WHO (Dean's index). Oral examinations were carried out by examiners, who had been calibrated before the survey. Weighed kappa scores were used to monitor the reliability of the assessment.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis. No benefits assessed
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Missing important variables such as foods and SES.
4.3	Were the analytical methods appropriate?	++	Logistic regression analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Good data collection, outcome assessment and data analysis. Some confounders not included in the analysis.

Item	Question	Rating	Comment
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Unclear if the findings are generalizable to the Canadian context. The fluoride level in the study (1 ppm) was higher than the optimal level of fluoride recommended in Canada (0.7 ppm), but still falling below the MAC (1.5 ppm).
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Dental fluorosis in the Blue Mountains and Hawkesbury, New South Wales, Australia: policy implications
Author(s)	Bal et al.
Publication year	2015
Country (where the study was conducted):	Australia
Funding sources	Centre for Oral Health Strategy, New South Wales Health.
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To determine whether the adjustment of the fluoride concentration to 1 ppm in the drinking water in 1992 was associated with fluorosis incidence in Blue Mountains, Australia.
Study design	Cross-sectional
Study location	Blue Mountains, New South Wales, Australia
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Blue Mountains was fluoridated in 1992 Hawkesbury was fluoridated in 1969 Lifetime fluoride exposure was stratified as 0%, 1 to 99%, 100%
Setting	School-based
Source of population	Primary school children aged 7 to 11 years in the Blue Mountains and Hawkesbury local government area of New South Wales, Australia.
Inclusion/exclusion criteria	Only children born after 1992 (based on 7 to 11 years old criteria) and whose parents/guardians gave consent were examined and included.
Recruitment or sampling procedure	Schools were selected randomly using comparative size as the main criteria.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS				
	Total	**0% exposure**	**1 to 99%**	**100%**
Number of participants	1,326	145	263	730
Age, years	7 to 11	NR	NR	NR
Gender	NR	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis was assessed using Dean's index 0: Normal 1: Questionable 2: Very mild 3: Mild 4: Moderate 5: Severe

Number of participants analysed	1,326 for prevalence of dental fluorosis 1,138 in logistic regression analysis
Number of participants excluded or missing (with reasons)	NR
Imputing of missing data	NR
Statistical method of data analysis	Logistic regression analysis

Results

- The prevalence of dental fluorosis in schoolchildren aged 7 to 11 years living in both Blue Mountains and Hawkesbury where fluoridation was implemented in 1992 and 1967 at 1.0 ppm was 39%, 1.5% was moderate to severe.

Logistic regression analysis of exposure to fluoridated water for very mild or more severe fluorosis on maxillary central incisors.

Exposure to fluoridated water	n	Unadjusted	Adjusted[a]
		OR (95% CI)	
0%	145	Ref (1)	Ref (1)
1 to 99%	263	1.44 (0.94 to 2.22)	1.46 (0.98 to 2.18)
100%	730	1.50 (1.07 to 2.09)	1.55 (1.21 to 2.13)
Reconstituting agent of infant formula			
Spring/rain water	145	Ref (1)	Ref (1)
Fluoridated water	611	1.64 (1.14 to 2.37)	1.69 (1.21 to 2.37)
No formula/not reported	382	1.28 (0.89 to 1.84)	1.30 (0.91 to 1.87)

[a] Adjusted for frequency of tooth brushing, rinsing habit after tooth brushing, licked or ate toothpaste.

- Compared to no exposure (0%), lifelong exposure (100%) to fluoridated water had significant higher risk of very mild or more severe dental fluorosis in both unadjusted (OR = 1.50; 95% CI, 1.07 to 2.09) or adjusted model (OR = 1.55, 95% CI, 1.21 to 2.13).
- Compared to spring or rain water, reconstituting infant formula with fluoridated water had significant higher risk of very mild or more severe dental fluorosis in both unadjusted (OR = 1.64; 95% CI, 1.14 to 2.37) or adjusted model (OR = 1.69; 95% CI 1.21 to 2.37).
- Swallowing after tooth brushing (OR = 2.30) or eating toothpaste (OR = 1.81) in early childhood was associated with significant higher risk of dental fluorosis.

CONCLUSION

Authors' conclusion	*"For the group as a whole, we concluded that: (a) fluorosis prevalence (0.39) in both regions was similar; and (b) the higher-than-expected prevalence and severity of fluorosis was due to mainly to two factors: (a) the higher-than-optimal fluoride level in drinking water; and (b) swallowing of fluoride toothpaste in early childhood."*(p.45) [92]
Reviewer's note	

Balmer 2015[94]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	The study population comprised children of 12 years participating in the 2008-2009 National Dental Epidemiological Programme in five regions in Northern England.
1.2	Is the eligible population or area representative of the source population or area?	++	12 year old children participating in the 2008-2009 National Dental Epidemiological Programme.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of sample selection was described in the previous study. 4,795 out of 21,986 12 years old children were invited to participate in the survey. 3,233 (67.4%) agreed to be examined. Inclusion/exclusion criteria were not reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Selection based in fluoridation and non-fluoridation areas. Potentially risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Based on the findings of previous studies.
2.3	Was the contamination acceptably low?	NA	
2.4	How well were likely confounding factors identified and controlled?	+	Gender and index of multiple deprivation. Other important confounders were likely missed.
2.5	Is the setting applicable to Canada?	+	Set in England. May partially be applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Molar incisor hypomineralization was assessed by trained and calibrated examiners using clinical photographs.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Prevalence of molar incisor hypomineralization
3.4	Was there a similar follow-up time in exposure and comparison groups	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Gender and index of multiple deprivation.
4.3	Were the analytical methods appropriate?	++	Binary logistic regression model.

Item	Question	Rating	Comment
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Potentially risk of selection bias and other important confounders were not adjusted.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study was conducted in England. May partially be applicable to the Canadian population.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION			
Title	A comparison of the presentation of molar incisor hypomineralization in two communities with different fluoride exposure		
Author(s)	Balmer et al.		
Publication year	2015		
Country (where the study was conducted):	UK		
Funding sources	NR		
Reported conflict of interest	☑ Yes ☐ No		
STUDY CHARACTERISTICS			
Objectives	To compare the clinical presentation of two cohorts of children with molar incisor hypomineralization (MIH) and living in areas of low and high background fluoridation.		
Study design	Cross-sectional		
Study location	Five regions in Northern England		
Study duration	NA		
Exposure duration	Lifetime		
Fluoride levels or Exposures:			
• Intervention	Fluoridation (F level not reported)		
• Comparator	Non-fluoridation (F level not reported)		
Setting	School-based		
Source of population	Children of 12 years participating in the 2008-2009 National Dental Epidemiological Programme in five regions in Northern England.		
Inclusion/exclusion criteria	NR		
Recruitment or sampling procedure	Described in the previous study.		
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited		
PARTICIPANT CHARACTERISTICS			
	Total	**Fluoridation**	**Non-fluoridation**
Number of participants	3,233	726	2,507
Age, years	12	NR	
Gender	NR	NR	
REPORTED OUTCOMES			
Definition (with units) and method of measurement	MIH was assessed using clinical photographs to detect the number, type of teeth (incisors or first permanent molar) and distribution of specific defects (i.e., demarcated, diffuse, or hypoplastic)		
Number of participants analysed	3,233		

Number of participants excluded or missing (with reasons)	1,562 (825 absent on the day of examination; 636 declined examination; 74 examination not recorded)
Imputing of missing data	NR
Statistical method of data analysis	Binary logistic regression model.
Results	

Prevalence of MIH

- Fluoridated area: 11.0% (95% CI, 8.8 to 13.5)
- Non-fluoridated area: 17.5% (95% CI, 16.0 to 19.0%)

Logistic regression

	Non-fluoridated	Fluoridated
	OR (95% CI)	
MIH children	Ref (1)	1.26 (0.89 to 1.79)[a]
Demarcated defects		
Incisors	Ref (1)	1.73 (1.33 to 2.25)[b]
First permanent molars	Ref (1)	1.30 (1.07 to 1.57)[b]
	RR (95% CI)	
Diffuse defects		
Incisors	Ref (1)	2.8 (2.3 to 3.4)***
First permanent molars	Ref (1)	2.2 (1.8 to 2.8)***
Hypoplastic defects		
Incisors	Ref (1)	1.8 (0.8 to 3.4)
First permanent molars	Ref (1)	1.4 (1.03 to 1.86)**

CI = confidence interval; OR = odds ratio; RR = risk ratio

[a] Adjusted for gender and index of multiple deprivation

[b] Adjusted for index of multiple deprivation

***$P < 0.001$; **$P = 0.035$

- After adjustment for gender and index of multiple deprivation, there was no significant different for the occurrence of MIH between fluoridated and non-fluoridated areas.
- Among the MIH group, children living in the fluoridated area had significant higher risk for an incisor tooth having a demarcated defect and higher risk for a molar tooth having a demarcated defect, after adjustment for deprivation.
- Among the MIH group, children living in the fluoridated area had significant higher risk for an incisor tooth having a diffuse defect and higher risk for a molar tooth having a diffuse defect.
- Apart from first permanent molar, fluoridation had little impact on incisor having a hypoplastic defect.

CONCLUSION	
Authors' conclusion	*"Children with MIH were at increased risk of both diffuse and demarcated defects in their incisors. Children with MIH living in the fluoridated area were at increased risk of diffuse and demarcated defects relative to MIH children living in the non-fluoridated area."*(p.257)[94]
Reviewer's note	May have incomplete control from confounders

Khan 2015[122]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Children 6 to 11 years old were recruited from two rural districts (high and low fluoride areas) in India. Population demographics were not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear how the participants were recruited. The areas were selected based on the findings of the fluoride mapping survey.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Stratified random sampling. Inclusion and exclusion criteria were explicit. Unclear about the % of selected individuals agreed to participate.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Two areas having low and high fluoride levels. Did not provide any methods to minimize selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Based on other published studies
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors controlled.
2.5	Is the setting applicable to Canada?	-	Set in India. Not applicable to Canada
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis was assessed using Dean's index. IQ levels were tested by means of Raven's coloured Progressive Matrices.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis, IQ levels
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No multivariable analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations in method of selection of exposure (risk of selection bias), in data analysis (no control for confounders)

Item	Question	Rating	Comment
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	The study was conducted in India, where the socio-economic factors and healthcare were different than those in Canada. The findings could not be generalizable to the Canadian population.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Relationship between dental fluorosis and intelligence quotient of school going children in and around Lucknow district: A cross-sectional study
Author(s)	Khan et al.
Publication year	2015
Country (where the study was conducted):	India
Funding sources	NR
Reported conflict of interest	☐ Yes ☑ No

STUDY CHARACTERISTICS	
Objectives	To compare the IQ levels of school children of two different locations, having different fluoride levels in water, and to establish between fluoride levels, prevalence of fluorosis and its effect on IQ levels.
Study design	Cross-sectional
Study location	Two rural districts (high and low fluoride areas) in India.
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	2.41 ppm
• Comparator	0.19 ppm
Setting	School-based
Source of population	Children aged 6 to 11 years from areas in and around Lucknow district
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	Unclear
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS

	Total	**Intervention (Unnao, 2.41 ppm)**	**Comparator (Tiwariganj, 0.19 ppm)**
Number of participants	429	215	214
Mean age, years (SD)	9.06 (1.31)	8.97 (1.33)	9.15 (1.29)
Gender	52.9% male	46.5% male	59.3% male

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis was assessed using Dean’s index. Normal (0); questionable (0.5); very mild (1.0); mild (2.0); moderate (3.0); severe (4.0) IQ levels were tested by means of Raven’s coloured Progressive Matrices. Grade 1: Intellectually superior Grade 2: Definitely above the average in intellectual capacity Grade 3: Intellectual average Grade 4: Definitely below the average in intellectual capacity Grade 5: Intellectually impaired

<table>
<tr><td>Number of participants analysed</td><td>429</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>NA</td></tr>
<tr><td>Imputing of missing data</td><td>NA</td></tr>
<tr><td>Statistical method of data analysis</td><td>Chi-square test; Spearman’s rank correlation</td></tr>
<tr><td>Results</td><td>Prevalence of different IQ grades at two areas
<table>
<tr><th>IQ Grade</th><th>Tiwariganj (0.19 ppm); N=214</th><th>Unnao (2.41 ppm); N=215</th></tr>
<tr><td>1</td><td>6 (2.8%)</td><td>0 (0.0%)***</td></tr>
<tr><td>2</td><td>160 (74.8%)</td><td>36 (16.7%)***</td></tr>
<tr><td>3</td><td>48 (22.4%)</td><td>125 (58.1%)***</td></tr>
<tr><td>4</td><td>0</td><td>30 (14.0%)***</td></tr>
<tr><td>5</td><td>0</td><td>24 (11.2%)***</td></tr>
</table>
***<i>P</i> < 0.001

The majority of children living in the 0.19 ppm water fluoride area had IQ grade of 2 (74.8% definitely above the average).
Significantly higher proportion of children living in the 2.41 ppm water fluoride area had IQ grade of 3 (58.1% average), 4 (14.0% below average) and 5 (11.2% intellectually impaired) compared to those living in the 0.19 ppm water fluoride area (22.4%, 0%, 0%, respectively).
</td></tr>
<tr><th colspan="2">CONCLUSION</th></tr>
<tr><td>Authors’ conclusion</td><td><i>“Findings of this study suggest that the overall IQ of the children exposed to high fluoride levels in drinking water and hence suffering from dental fluorosis were significantly lower than those of the low fluoride area.”</i>(p.10)[122]</td></tr>
<tr><td>Reviewer’s note</td><td>No adjustment for confounding factors.
Other neurotoxic elements (e.g., arsenic, lead, iodine…) were not taken into consideration.</td></tr>
</table>

Moimaz 2015[106]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	The study population consisted of all 12-year-old children registered in public schools of Birigui, Sao Paulo, Brazil. Population demographics were not described.
1.2	Is the eligible population or area representative of the source population or area?	+	All 12-year old children registered in public schools; approximately 83% of the population.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Method of selection not described. Percent of selected individuals agreed to participate not reported. No inclusion or exclusion criteria listed.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on children lived in the areas with different fluoride concentrations. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Based on previous published studies.
2.3	Was the contamination acceptably low?	+	Children were included if they always consumed water from public water supply, as opposed to bottled mineral water. Unclear if that could reduce contamination.
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors controlled
2.5	Is the setting applicable to Canada?	-	Set in Brazil. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis was assessed using modified Dean’s index by trained and calibrated examiners.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	

Item	Question	Rating	Comment
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No multivariable analysis
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p-value reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations in method of recruitment, in method of selection of exposure, and in data analysis. High risk of bias.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study was conducted in Brazil. Different healthcare system and sociodemographic characteristics to Canada.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Dental fluorosis and its influence on children's life
Author(s)	Moimaz et al.
Publication year	2015
Country (where the study was conducted):	Brazil
Funding sources	NR
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To verify the prevalence of dental fluorosis in 12-year-old children ant its association with different fluoride levels in the public water supply, and evaluate the level of perception of dental fluorosis by the studied children.
Study design	Cross-sectional
Study location	Birigui, Sao Paulo, Brazil
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Well water
• Intervention	1.2 ppm
• Comparator	0.7 ppm
Setting	School-based
Source of population	12-year-old children registered in public schools of Birigui, Sao Paulo, Brazil.
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS			
	Total	Intervention (1.2 ppm)	Comparator (0.7 ppm)
Number of participants	496	206	290
Age, years	12	12	12
Gender	47.8% male	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis was assessed using modified Dean's index.
Number of participants analysed	496
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Fisher's test
Results	**Prevalence of dental fluorosis**

	1.2 ppm (N=206)	0.7 ppm (N=290)
	n (%)	
No fluorosis	**65 (31.6)**	**139 (47.9)**
Normal	55 (26.7)	121 (41.7)
Questionable	10 (4.9)	18 (6.2)
With fluorosis	**141 (68.4)**	**151 (52.1)**
Very mild	112 (54.3)	108 (37.2)
Mild	22 (10.7)	37 (12.8)
Moderate	7 (3.4)	5 (1.8)
Severe	0 (0.0)	1 (0.3)

- The prevalence of dental fluorosis was slightly higher in 1.2 ppm area compared to 0.7 ppm area.
- However, there was no significant difference in the prevalence of dental fluorosis of various degrees between 1.2 ppm and 0.7 ppm areas.
  - Very mild to mild: 65.0% (134/206) vs 50.0% (145/290); *P* = 0.0781
  - Moderate to severe: 3.4% (7/206) vs 2.1% (6/290); *P* = 0.4615
- Among total children in both areas with dental fluorosis (n=292), 98.3% had no knowledge about fluorosis.

CONCLUSION	
Authors' conclusion	*"The prevalence of fluorosis was slightly high, and the mildest levels were the most frequently observed."* (p.1)[106] *"The majority of children did not perceive fluorosis spots, demonstrating that fluorosis did not affect their quality of life."*(p.6)[106]
Reviewer's note	No adjustment for confounders.

Peckham 2015[125]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Secondary data from the National General Practice Profiles in England.
1.2	Is the eligible population or area representative of the source population or area?	++	Practices for inclusion in the National General Practice Profiles , inclusion/exclusion criteria for practice provided
1.3	Do the selected participants or areas represent the eligible population or area?	++	7,935 out of 8,020 practices met the inclusion criteria (98.9%)
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on fluoridated and non-fluoridated areas. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Prior hypothesis for the association between fluoridation and hypothyroidism
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Proportion of women registered with the practice, proportion of patients over 40 years old registered with the practice, Index of Multiple Deprivation. Did not include confounders such as other sources of fluoride, iodine consumption, lifestyle, age, sex, and others.
2.5	Is the setting applicable to Canada?	+	Set in UK. May partially applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	+	Hypothyroidism prevalence was obtained from all GP practices in England. Hypothyroidism diagnosis from clinical practice – unclear if it is based on lab diagnosis or clinical diagnosis Fluoride measurements should be more accurate. 0.7mg/L within the acceptable range
3.2	Were all outcome measurements complete?	NA	Based on data on diagnosed hypothyroidism from the GP practices.
3.3	Were all important outcomes assessed?	+	Hypothyroidism
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Important confounders not adjusted for – medications that affect thyroid function, family history, smoking
4.3	Were the analytical methods appropriate?	++	Binary logistic regression models.

Item	Question	Rating	Comment
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Limitations in selection of exposure (potential contamination due to incorrect information). Risk of selection bias. Likely miss other important confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	+	Study was conducted in UK. Similar in healthcare system and sociodemographic characteristics to Canada. May partially be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water
Author(s)	Peckham et al.
Publication year	2015
Country (where the study was conducted):	UK
Funding sources	NR
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To examine the association between levels of fluoride in water supplies with practice level hypothyroidism prevalence
Study design	Cross-sectional
Study location	West Midlands (fluoridated) and Greater Manchester (non-fluoridated) of England
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Low (≤ 0.3 ppm); medium (> 0.3 to ≤ 0.7 ppm); high (> 0.7 ppm)
Setting	General practice
Source of population	Individuals aged 40 years and over from two areas in England.
Inclusion/exclusion criteria	Criteria used by Public Health England
Recruitment or sampling procedure	Only data from two areas were selected, instead of the whole country.
Applicability to Canadian context	☐ High ☑ Partial ☐ Limited

PARTICIPANT CHARACTERISTICS				
	Total	≤ 0.3 ppm	> 0.3 to ≤ 0.7 ppm	> 0.7 ppm
Number of GP practices	7,935	NR	NR	NR
Age, years	≥40	NR	NR	NR
Gender	49.9% females	NR	NR	NR

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Hypothyroidism prevalence was obtained from all GP practices in England.
Number of participants analysed	7,935 GP practices
Number of participants excluded or missing (with reasons)	85
Imputing of missing data	NA
Statistical method of data analysis	Binary logistic regression models
Results	

Odds ratios of upper tertile (high level) hypothyroidism prevalence according to drinking water fluoride levels

Maximum fluoride level	Unadjusted	Adjusted[a]
	OR (95% CI)	
≤ 0.3 ppm	Ref (1)	Ref (1)
> 0.3 to ≤ 0.7 ppm	1.71 (1.44 to 2.03)	1.37 (1.12 to 1.68)
> 0.7 ppm	1.45 (1.27 to 1.66)	1.62 (1.38 to 1.90)

[a] Adjusted for proportion of women registered with the practice, proportion of patients over 40 years old registered with the practice, Index of Multiple Deprivation.

- After adjustment for proportion of women registered with the practice, proportion of patients over 40 years old registered with the practice and Index of Multiple Deprivation, the odds of practice recording high levels of hypothyroidism was 1.62 times higher in > 0.7 ppm area and 1.37 times higher in > 0.3 to ≤ 0.7 ppm area compared to ≤ 0.3 ppm area.

Odds ratios of upper tertile (high level) hypothyroidism prevalence according to areas

Maximum fluoride level	Unadjusted	Adjusted[a]
	OR (95% CI)	
No fluoridation (≤ 0.3 ppm)	Ref (1)	Ref (1)
With fluoridation (> 0.3 ppm)	1.54 (1.16 to 2.04)	1.94 (1.39 to 2.70)

[a] Adjusted for proportion of women registered with the practice, proportion of patients over 40 years old registered with the practice, Index of Multiple Deprivation.

- After adjustment for covariates, the odds of recording a high level of hypothyroidism was 1.94 times higher in > 0.3 ppm area compared to ≤ 0.3 ppm area.

CONCLUSION	
Authors' conclusion	*"The findings of the study raise particular concerns about the availability of community fluoridation as a safe public health measure."* (p.619)[125]
Reviewer's note	Did not adjust for other sources of fluoride, iodine consumption, lifestyle, age, sex, and other. Upper tertile, i.e., high hypothyroidism prevalence was used instead of actual prevalence. Two of the tertiles of deprivation were combined.

Sebastian 2015[100]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	School children aged 10 to 12 years from three villages in India were included. Population demographics were not reported.
1.2	Is the eligible population or area representative of the source population or area?	++	Each School was considered as a cluster. All schoolchildren who fulfilled the criteria were included. Informed consent was obtained from parents.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Three villages in India were randomly selected based on water fluoride level. Inclusion/exclusion criteria were described. Percent of selected individuals agreed to participate was not reported. Risk of selection bias.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on fluoridated and non-fluoridated areas.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	+	Evidence for hypothesis based on the neurotoxicant effect of fluoride.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, gender, parental education, family income. Did not control for other confounders such as other fluoride sources and environmental contaminants.
2.5	Is the setting applicable to Canada?	-	Set in India. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis was assessed using Dean's index. IQ was evaluated using Raven's Coloured Progressive Matrices. Intra-rater score was reported for dental fluorosis assessment, but not for ID evaluation.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis, IQ
3.4	Was there a similar follow-up time in exposure and comparison groups	NA	
3.5	Was follow-up time meaningful	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	

Item	Question	Rating	Comment
4.2	Were multiple explanatory variables considered in the analyses?	+	All confounders not accounted for.
4.3	Were the analytical methods appropriate?	++	Binary logistic regression models.
4.4	Was the precision of association given or calculable? Is association meaningful?	++	95% CIs reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations in selection of exposure. Risk of selection bias and bias in outcome measures. Likely miss other confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study was conducted in India with difference in fluoride level, healthcare system and sociodemographic characteristics to Canada. Could not be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	A cross-sectional study to assess the intelligence quotient (IQ) of school going children aged 10 to 12 years in villages of Mysore district, India with different fluoride levels
Author(s)	Sebastian and Sunitha
Publication year	2015
Country (where the study was conducted):	India
Funding sources	NR
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To assess the intelligence quotient (IQ) of school going children aged 10 to 12 years in villages of Mysore district with different fluoride levels.
Study design	Cross-sectional
Study location	Villages of Mysore district, India
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	0.4 ppm; 1.2 ppm; 2.0 ppm
Setting	School-based
Source of population	School going children aged 10 to 12 years in villages of Mysore district.
Inclusion/exclusion criteria	Children were long-life residents of the villages, and their mothers lived in the areas during pregnancy.
Recruitment or sampling procedure	Each school was considered as a cluster. All schoolchildren who fulfilled the criteria were included
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS				
	Total	**0.4 ppm**	**1.2 ppm**	**2.0 ppm**
Number of participants	405	135	135	135
Age, years	10 to 12	NR	NR	NR
Gender	NR	NR	NR	NR
REPORTED OUTCOMES				
Definition (with units) and method of measurement	Dental fluorosis was assessed using Dean's index. IQ was evaluated using Raven's Coloured Progressive Matrices.			
Number of participants analysed	405			
Number of participants excluded or missing (with reasons)	NA			
Imputing of missing data	NA			
Statistical method of data analysis	Binary logistic regression models			
Results	**Prevalence of dental fluorosis**			

	2.0 ppm (N = 135)	1.2 ppm (N = 135)	0.4 ppm (N = 135)
	n (%)		
No fluorosis	**35 (25.9)**	**108 (80.0)**	**124 (91.9)**
Normal	17 (12.6)	98 (72.6)	121 (89.6)
Questionable	18 (13.3)	10 (7.4)	3 (2.2)
With fluorosis	**100 (74.1)**	**27 (20.0)**	**11 (8.1)**
Very mild	24 (17.8)	14 (10.4)	7 (5.2)
Mild	25 (18.5)	5 (3.7)	3 (2.2)
Moderate	13 (9.6)	7 (5.2)	0 (0.0)
Severe	38 (28.1)	1 (0.7)	1 (0.7)

- The prevalence of dental fluorosis at the 2.0 ppm area was 74% compared to 20% and 8% in 1.2 ppm and 0.4 ppm, respectively.
- Severe dental fluorosis prevalence at the 2.0 ppm area was 28% compared to 0.7% in the other two areas.

IQ score and IQ prevalence distribution

	2.0 ppm (N = 135)	1.2 ppm (N = 135)	0.4 ppm (N = 135)
Mean IQ (SD)	80.49 (12.67)$^{a, b}$	88.60 (14.01)^{c}	86.37 (13.58)
IQ category, n (%)			
Superior	5 (3.7)	3 (2.2)	4 (3.0)
Above average	1 (0.7)	7 (5.2)	4 (3.0)
Average	30 (22.2)	52 (38.5)	42 (31.1)
Below average	13 (9.6)	16 (11.9)	22 (16.3)
Border line	86 (63.7)	57 (42.2)	63 (46.7)

[a] *P* = 0.007 compared to 1.2 ppm
[b] *P* = 0.03 compared to 0.4 ppm
[c] *P* = 0.361 compared to 0.4 ppm

- Significantly lower mean IQ of children in the 2.0 ppm water fluoride area compared to 1.2 ppm and 0.4 ppm areas.
- Higher proportion of children in the 2.0 ppm water fluoride area had below average or border line (73.3%) compared to 1.2 ppm (54.1%) and 0.4 ppm (63.0%) areas.

Binary regression analysis on IQ scores and water fluoride levels

	2.0 ppm (N=135)	1.2 ppm (N=135)	0.4 ppm (N=135)
OR[a] (95% CI)	0.59 (0.29 to 1.19)[b]	1.74 (1.02 to 2.98)[c]	Ref (1)

[a] Adjusted for age, gender, parental education and family income.
[b] *P* = 0.140 compared to 0.4 ppm
[c] *P* = 0.044 compared to 0.4 ppm

- Compared to 0.4 ppm, children in 2.0 ppm fluoride area showed no significant difference, while those living in 1.2 ppm fluoride area had significant higher IQ scores, after adjustment for age, gender, parental education and family income.

CONCLUSION	
Authors' conclusion	*"School children residing in areas with higher than normal water fluoride level demonstrated more impaired development of intelligence when compared to school children residing in areas with normal and low water fluoride levels. Thus, children's intelligence can be affected by high water fluoride levels."* (p.307)[100]
Reviewer's note	The authors' conclusion did not reflect the findings.

Punitha 2014[101]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	All schoolchildren from five of 140 villages in India were included. Population demographics were not described
1.2	Is the eligible population or area representative of the source population or area?	-	Unclear
1.3	Do the selected participants or areas represent the eligible population or area?	+	Informed consent was obtained from the head of schools in five villages. Inclusion/exclusion criteria were not reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	-	Unclear how the villages were selected. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis based on previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors controlled.
2.5	Is the setting applicable to Canada?	-	Set in India. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis was assessed using Dean's index by trained dentist.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	

Item	Question	Rating	Comment
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported.
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitations in population recruitment, selection of exposure and data analysis. Risk of selection bias and bias in outcome measures.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study was conducted in India with difference in fluoride level, healthcare system and sociodemographic characteristics compared to Canada. Could not be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Prevalence of dental fluorosis in a non-endemic district of Tamil Nadu, India
Author(s)	Punitha et al.
Publication year	2014
Country (where the study was conducted):	India
Funding sources	NR
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To describe the prevalence of dental fluorosis among children aged 7 to 15 years. To assess fluoride levels in drinking water supply in the study villages. To assess knowledge and attitude regarding fluorosis among children affected with fluorosis.
Study design	Cross-sectional
Study location	Five villages in India
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	
• Intervention	2.05 ppm
• Comparator	0.47 ppm
Setting	School-based
Source of population	Children aged 7 to 15 years attended schools in five villages in India
Inclusion/exclusion criteria	NR
Recruitment or sampling procedure	NR
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS			
	Total	Intervention (2.05 ppm)	Comparator (0.47 ppm)
Number of participants	348	141	207
Age, years	7 to 15	NR	NR
Gender	52.9% male	NR	NR

<table>
<tr><th colspan="2">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td>Dental fluorosis was assessed using Dean's index
0: Normal
1: Questionable
2: Very mild
3: Mild
4: Moderate
5: Severe</td></tr>
<tr><td>Number of participants analysed</td><td>348</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>NA</td></tr>
<tr><td>Imputing of missing data</td><td>NA</td></tr>
<tr><td>Statistical method of data analysis</td><td>NR</td></tr>
<tr><td>Results</td><td>Prevalence of dental fluorosis
<table>
<tr><th></th><th>2.05 ppm (N=141)</th><th>0.47 ppm (N=207)</th></tr>
<tr><th></th><th colspan="2"><i>n (%)</i></th></tr>
<tr><td>No fluorosis</td><td>79 (56.0)</td><td>202 (97.6)</td></tr>
<tr><td>With fluorosis</td><td>62 (44.0)</td><td>5 (2.4)</td></tr>
</table>

The prevalence of dental fluorosis was 44% in villages with mean fluoride level of 2.05 ppm compared to 2.4% in villages with mean fluoride level of 0.47 ppm
There was a positive correlation between severity of fluorosis and levels of fluoride (r = 0.457; <i>P</i> < 0.0001)
</td></tr>
</table>

CONCLUSION	
Authors' conclusion	*"Significant correlation between high fluoride levels and occurrence of fluorosis found."* (p.159)[101]
Reviewer's note	Limitations in research methodology

Rango 2014[108]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	++	Children aged 10 to 15 years from 33 rural communities (out of 94) where ground water was the main source of drinking water. Population demographics were adequately described.
1.2	Is the eligible population or area representative of the source population or area?	+	Recruitment was made through volunteer with parent consent.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Children were selected if they volunteered by coming to the local clinics, schools or other village-level meeting sites. Percent of selected individuals agreed to participate and inclusion/exclusion criteria were not described.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on level of fluoride in well's water and urine fluoride levels.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Yes
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	+	Age, sex, BMI and breast feeding duration.
2.5	Is the setting applicable to Canada?	-	Set in Ethiopia. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis was assessed using TF index by trained and calibrated dental examiners.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	+	Not all confounders adjusted.
4.3	Were the analytical methods appropriate?	++	Multivariable regression analysis.
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported.

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	+	Unclear in population recruitment. Good in outcome measure and data analysis.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study was conducted in Ethiopia with difference in fluoride level, healthcare system and sociodemographic characteristics compared to Canada. Could not be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Fluoride exposure from groundwater as reflected by urine fluoride and children's dental fluorosis in the Main Ethiopian Rift Valley
Author(s)	Rango et al.
Publication year	2014
Country (where the study was conducted):	Ethiopia
Funding sources	Duke Global Health Institute, Nicholas Institute for Environmental Policy Solutions, and Duke University Procost's PFIRST
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To explore the relationship between children's fluoride exposure from drinking groundwater and urinary fluoride concentrations combined with dental fluorosis in the main Ethiopian Rift Valley.
Study design	Cross-sectional
Study location	Ethiopian Rift Valley
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	Groundwater fluoride: 1.06 to 18.0 ppm
Setting	Rural
Source of population	33 rural communities (out of 94) where ground water was the main source of drinking water.
Inclusion/exclusion criteria	Children aged 10 to 15 years, who were lifelong residents drinking from community wells that were constructed before their birth.
Recruitment or sampling procedure	Recruitment was made through volunteers with parental consent.
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited
PARTICIPANT CHARACTERISTICS	
	Total
Number of participants	491
Mean age, years (SD)	12.1 (1.6)
Gender	47.7% male
Mean BMI, kg/m^2 (SD)	16.4 (2.2)

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis was assessed using TF index TFI = 0 (no dental fluorosis) TFI = 1 (white thin opaque lines running across tooth surface) TFI = 2 (lines join and form clouds the teeth) TFI = 3 (merging of the white opaque lines occurs and clouds observed in many areas of the tooth surface) TFI = 4 (entire tooth surface showed a marked opacity or appeared chalky white) TFI = 5 (loss of enamel and round pits appear) TFI = 6 (small pits frequently merge in opaque enamel to form bands < 2 mm in vertical height) TFI = 7 (loss of the outermost enamel forming irregular areas, less than half of the surface is involved) TFI = 8 (loss of the outermost enamel involves more than half of the enamel) TFI = 9 (loss of the major part of the enamel results in a change of the anatomical shape of the surface/tooth) TFI<4: absent to mild; TFI≥4: moderate to severe
Number of participants analysed	491
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Multivariable regression analysis
Results	**Prevalence of dental fluorosis (multivariable analyses controlling for age, sex, BMI, and breast feeding duration)** • 100% dental fluorosis prevalence (TF scores ≥ 1) for children drinking groundwater fluoride levels of 1.06 to 18.0 ppm • At fluoride levels ≥ 6 ppm, most of the TF scores were of 5 and 6 (i.e., moderate to severe). • At fluoride levels < 1.6 ppm, most children had normal teeth (TF scores of 0). • At 1.5 ppm (WHO standard), the prevalence of mild and moderate dental fluorosis was 53% and 5%, respectively. • At 2.0 ppm (US EPA’s SMLC standard), the prevalence of moderate and severe dental fluorosis was 14.7% and 2.8%, respectively. • At 4.0 ppm (US EPA’s MCLG standard), the prevalence of mild, moderate and severe dental fluorosis was 28.5%, 28% and 26%, respectively. • The prevalence of moderate and severe dental fluorosis approached zero at fluoride levels below 1.2 ppm and 1.8 ppm, respectively.
CONCLUSION	
Authors’ conclusion	*“A significant proportion of the children examined in this study drinks water from sources with high levels of F^-, excretes urine with high levels of F^-, and suffers from dental health damage in the form of severe DF.”* (p.195)[108]
Reviewer’s note	

Sukhabogi 2014[102]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Schoolchildren aged 12 to 15 years from one district in India. The district has 59 mandals and divided into four zones. Population demographics were not adequately described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear since only one school from each mandal was selected.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Two stage cluster sampling was used for selection. One school from each of the 20 mandals was selected using lottery method of simple random sampling. Inclusion/exclusion criteria were explicit. Percent of individuals agreed to participate was not reported.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on level of fluoride in areas. Risk of selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Effect of high fluoride level on dental fluorosis.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors controlled.
2.5	Is the setting applicable to Canada?	-	Set in India. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Dental fluorosis was assessed using Dean's index by a single trained and calibrated dental examiner. Intra-rater reliability was reported.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	Yes
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No multivariable regression analysis conducted.
4.4	Was the precision of association given or calculable? Is association meaningful?	+	p values and 95% CIs reported.

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitation in population recruitment, method of selection of exposure, and data analysis. No attempt to minimize selection bias and control for confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study was conducted in India with difference in fluoride level, healthcare system and sociodemographic characteristics compared to Canada. Could not be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Dental fluorosis and dental caries prevalence among 12 and 15-year-old school children in Nalgonda district, Andhra Pradesh, India
Author(s)	Sukhabogi et al.
Publication year	2014
Country (where the study was conducted):	India
Funding sources	Nil
Reported conflict of interest	☑ Yes ☐ No
STUDY CHARACTERISTICS	
Objectives	To assess dental caries and dental fluorosis prevalence among 12 and 15-year-old school children in Nalgonda district, Andhra Pradesh, India
Study design	Cross-sectional
Study location	Nalgonda district, Andhra Pradesh, India
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	< 0.7 ppm; 0.7 to < 1.2 ppm; 1.2 to < 4.0 ppm; 4.0 to 6.28 ppm
Setting	School-based
Source of population	One school of each of the 59 mandals Nalgonda district was selected.
Inclusion/exclusion criteria	Inclusion: 12 and 15-year-old school children, lifelong residents, used one source of drinking water since birth for to least 10 years, permanent teeth with at least 50% of the crown erupted.
Recruitment or sampling procedure	Unclear
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS					
	Total	**<0.7 ppm**	**0.7 to <1.2 ppm**	**1.2 to <4.0 ppm**	**4.0 to 6.28 ppm**
Number of participants	1,875	496	108	904	367
Age, years	12 and 15	12 and 15	12 and 15	12 and 15	12 and 15
Gender	47.9% male	46.0% male	53.7% male	47.1% male	50.7% male

REPORTED OUTCOMES	
Definition (with units) and method of measurement	Dental fluorosis was assessed using Dean's index 0: Normal 1: Questionable 2: Very mild 3: Mild 4: Moderate 5: Severe
Number of participants analysed	1,875
Number of participants excluded or missing (with reasons)	NA
Imputing of missing data	NA
Statistical method of data analysis	Chi-square test; Spearman's correlation
Results	See below

Prevalence of dental fluorosis among 12 years old children

Fluoride level	Total	Male	Female
	%		
< 0.7 ppm (N = 238)	31.1	38.2	26.7
0.7 to < 1.2 ppm (N = 59)	47.5	53.1	40.7
1.2 to <4.0 ppm (N = 458)	95.9	96.7	95.1
4.0 to 6.28 ppm (N = 169)	100.0	100.0	100.0

Prevalence of dental fluorosis among 15 years old children

Fluoride level	Total	Male	Female
	%		
< 0.7 ppm (N = 258)	28.7	28.6	28.8
0.7 to < 1.2 ppm (N = 49)	46.9	46.1	47.8
1.2 to < 4.0 ppm (N = 446)	97.3	96.7	97.9
4.0 to 6.28 ppm (N = 198)	100.0	100.0	100.0

- The prevalence of dental fluorosis increased with increasing fluoride concentration among 12 and 15 years old children. The prevalence was 29.8%, 47.2%, 96.6% and 100% in areas with fluoride level of < 0.7 ppm, 0.7 to < 1.2 ppm, 1.2 to < 4.0 ppm and 4.0 to 6.28 ppm, respectively.
- There was no difference in the prevalence of dental fluorosis between 12 and 15 years old children or between males and females.
- Dental fluorosis index score was positively correlated with fluoride concentration (*rho* = 0.92)

CONCLUSION	
Authors' conclusion	*"The fluorosis prevalence increased with increasing fluoride concentration with no difference in gender and age distribution."* (p.1) [102]
Reviewer's note	No adjustment for confounders.

Wong 2014[111]

Quality Assessment

Item	Question	Rating	Comment
SECTION 1: POPULATION			
1.1	Is the source population or source area well described?	+	Data from the photographic slides of 12-year old children were taken from the four previous epidemiological surveys in Hong Kong (1983, 1991, 2002 and 2010). Population demographics were not described.
1.2	Is the eligible population or area representative of the source population or area?	+	Unclear how recruitment was conducted.
1.3	Do the selected participants or areas represent the eligible population or area?	+	Children were randomly selected. Not reported on percent of individuals agreed to participate and inclusion/exclusion criteria. Children born in 1970, 1978, 1988 and 1997.
SECTION 2: METHOD OF SELECTION OF EXPOSURE (OR COMPARISON) GROUP			
2.1	Selection of exposure (and comparison) group. How was selection bias minimised?	+	Based on level of fluoride in different periods of survey. Not reported on attempt to minimize selection bias.
2.2	Was the selection of explanatory variables based on a sound theoretical basis?	++	Evidence for hypothesis derived from previous studies.
2.3	Was the contamination acceptably low?	NR	
2.4	How well were likely confounding factors identified and controlled?	-	No confounding factors controlled.
2.5	Is the setting applicable to Canada?	-	Set in Hong Kong. Not applicable to Canada.
SECTION 3: OUTCOMES			
3.1	Were outcome measures reliable?	++	Diffuse opacities were assessed by single calibrated and blinded examiner based on the modified FDI (DDE) index.
3.2	Were all outcome measurements complete?	NR	
3.3	Were all important outcomes assessed?	+	Dental fluorosis.
3.4	Was there a similar follow-up time in exposure and comparison groups?	NA	
3.5	Was follow-up time meaningful?	NA	
SECTION 4: ANALYSES			
4.1	Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.2	Were multiple explanatory variables considered in the analyses?	-	No
4.3	Were the analytical methods appropriate?	-	No multivariable regression analysis conducted.
4.4	Was the precision of association given or calculable? Is association meaningful?	+	Only p values reported.

Item	Question	Rating	Comment
SECTION 5: SUMMARY			
5.1	Are the study results internally valid (i.e., unbiased)?	-	Limitation in population recruitment, method of selection of exposure, and data analysis. No attempt to minimize selection bias and control for confounders.
5.2	Are the findings generalizable to the Canadian population (i.e., externally valid)?	-	Study was conducted in Hong Kong with difference healthcare system and sociodemographic characteristics compared to Canada. Could not be generalizable to the Canadian context.
Overall quality rating		Low	

Data Extraction

GENERAL INFORMATION	
Title	Diffusion opacities in 12-year-old Hong Kong children – four cross-sectional surveys
Author(s)	Wong et al.
Publication year	2014
Country (where the study was conducted):	China
Funding sources	Research Grants council of the Hong Kong Special Administrative Region, China
Reported conflict of interest	☐ Yes ☑ No
STUDY CHARACTERISTICS	
Objectives	To compare the prevalence and severity of diffuse opacities among 12-year-old children whose maxillary incisors developed during periods with different concentrations of fluoride in Hong Kong public water system.
Study design	Cross-sectional
Study location	Hong Kong
Study duration	NA
Exposure duration	Lifetime
Fluoride levels or Exposures:	1.0 ppm, 0.7 ppm, 0.5 ppm and 0.5 ppm in 1983, 1991, 2001 and 2010, respectively
Setting	School-based
Source of population	Data from the photographic slides of 12-year old children were taken from the four previous epidemiological surveys in Hong Kong (1983, 1991, 2002 and 2010).
Inclusion/exclusion criteria	Children born in 1970, 1978, 1988 and 1997.
Recruitment or sampling procedure	Children were randomly selected.
Applicability to Canadian context	☐ High ☐ Partial ☑ Limited

PARTICIPANT CHARACTERISTICS					
	Total	**1.0 ppm (1983)**	**0.7 ppm (1991)**	**0.5 ppm (2001)**	**0.5 ppm (2010)**
Number of participants	2,658	700	670	620	668
Age, years	12	12	12	12	12
Gender	NR	NR	NR	NR	NR

<table>
<tr><th colspan="2">REPORTED OUTCOMES</th></tr>
<tr><td>Definition (with units) and method of measurement</td><td>Diffuse opacities were assessed using the modified FDI (DDE) index.
Diffuse opacities = abnormality involving an alteration in the translucency of the enamel, and there is no clear boundary between the adjacent normal enamel.</td></tr>
<tr><td>Number of participants analysed</td><td>2,658 photographic slides</td></tr>
<tr><td>Number of participants excluded or missing (with reasons)</td><td>NA</td></tr>
<tr><td>Imputing of missing data</td><td>NA</td></tr>
<tr><td>Statistical method of data analysis</td><td>Chi-square test</td></tr>
<tr><td>Results</td><td>
Prevalence of diffuse opacities at mouth level
<table>
<tr><th>1983; N = 700</th><th>1991; N = 670</th><th>2001; N = 620</th><th>2010; N = 668</th></tr>
<tr><td>1.0 ppm</td><td>0.7 ppm</td><td>0.5 ppm</td><td>0.5 ppm</td></tr>
<tr><td>89.3%[a]</td><td>48.5%[b]</td><td>32.4%</td><td>42.1%[c]</td></tr>
</table>
[a] <i>P</i> < 0.0001 for 1983 vs 1991, 2001 and 2010
[b] <i>P</i> <0.0001 for 1991 vs 2001
[c] <i>P</i> < 0.0001 for 2010 vs 2001
The prevalence of diffuse opacities decreased from 89.3% in 1983 to 48.5% in 1991 and to 32.4% in 2001, and then increased to 42.1 % in 2010.
Prevalence of diffuse opacities at tooth level
<table>
<tr><th>1983; N = 2,667</th><th>1991; N = 2,569</th><th>2001; N = 2,398</th><th>2010; N = 2,573</th></tr>
<tr><td>1.0 ppm</td><td>0.7 ppm</td><td>0.5 ppm</td><td>0.5 ppm</td></tr>
<tr><td>81.7%[a]</td><td>44.9%[b]</td><td>26.1%</td><td>37.3%[c]</td></tr>
</table>
[a] <i>P</i> < 0.0001 for 1983 > 1991, 2001 and 2010
[b] <i>P</i> < 0.0001 for 1991 > 2001 and 2010
[c] <i>P</i> < 0.0001 for 2010 > 2001
The prevalence of diffuse opacities decreased over the years 1983, 1991, 2001, and then increased in 2010.
Severity of diffuse opacities
The proportion of children who had more severe subtype (diffuse confluent) decreased over the years: 1983 > 1991 > 2010 > 2001 (<i>P</i> < 0.0001).
</td></tr>
<tr><th colspan="2">CONCLUSION</th></tr>
<tr><td>Authors' conclusion</td><td><i>"The prevalence and severity of diffuse opacities among maxillary incisor teeth of Hong Kong children decreased from 1983 and then increased in 2010; however, this change did not fully correspond to the concentration of fluoride in the drinking water during the time of enamel development."</i> (p.61)[111]</td></tr>
<tr><td>Reviewer's note</td><td>No attempt to minimize selection bias and control for confounders.</td></tr>
</table>

Appendix 10: Studies Identified From Alerts (Updated Searches)

Citation	Authors' Conclusions
Crnosija N, Choi M, Meliker JR. Fluoridation and county-level secondary bone cancer among cancer patients 18 years or older in New York State. *Environ Geochem Health.* 2018.	*"We found no evidence of an association between community water fluoridation category and secondary bone cancer from 2008 to 2010 at the county level in New York State."*[156]
Cruz M, Narvai PC. Caries and fluoridated water in two Brazilian municipalities with low prevalence of the disease. *Rev Saude Publica.* 2018; 52: 28.	*"Exposure to fluoridated water implied lower mean values for the DMFT ans SiC indexes, even in the presence of the concomitant exposure to fluoridated toothpaste, in a scenario of low prevalence of the disease, and with a similar pattern of caries distribution in the populations analyzed."*[151]
Firmino RT, Bueno, A.X., Martins, C.C. et al. . Dental caries and dental fluorosis according to water fluoridation among 12-year-old Brazilian schoolchildren: a nation-wide study comparing different municipalities. *J Public Health: From Theory to Practice.* 2018; 26: 501-507.	*"Lower prevalence of dental caries was found with the increasing percentage of municipalities with optimal fluoridated water and with the increasing prevalence of dental fluorosis."*[152]
Macey R, Tickle M, MacKay L, McGrady M, Pretty IA. A comparison of dental fluorosis in adult populations with and without lifetime exposure to water fluoridation. *Community Dent Oral Epidemiol.* 2018	*"Although fluorosis is more common in adults with lifetime exposure to water fluoridation than those with no exposure, the aesthetic impact of fluorosis seems to diminish with age."*[155]
Sezgin BI, Onur SG, Mentes A, Okutan AE, Haznedaroglu E, Vieira AR. Two-fold excess of fluoride in the drinking water has no obvious health effects other than dental fluorosis. *J Trace Elem Med Biol.* 2018; 50: 216-222.	*"Exposure to levels of fluoride twice as high than the optimum in the drinking water increases the prevalence of fluorosis, dramatically decreases dental caries, and does not increase the risk of cancer, cardiovascular events, and asthma."*[157]
Slade GD, Grider WB, Maas WR, Sanders AE. Water Fluoridation and Dental Caries in U.S. Children and Adolescents. *J Dent Res.* 2018; 97(10): 1122-1128.	*"These findings confirm a substantial caries-preventive benefit of CWF for U.S. children and that the benefit is most pronounced in primary teeth."*[153]
Spencer AJ, Do LG, Ha DH. Contemporary evidence on the effectiveness of water fluoridation in the prevention of childhood caries. *Community Dent Oral Epidemiol.* 2018; 46(4): 407-415.	*"Analysis of contemporary data representative of the Australian child population found consistent associations between %LEFW and childhood caries, which persisted when socioeconomic differences were adjusted across exposure, supporting the continued effectiveness of water fluoridation."*[154]