



Te Kāwanatanga o Aotearoa
New Zealand Government



Community Water Fluoridation: An evidence review

2024

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1. Executive summary

The 2014 report from the Royal Society of New Zealand (RSNZ) and the 2021 report from the Office of the Prime Minister's Chief Science Advisor (OPMCSA) on the risks and benefits of community water fluoridation (CWF) concluded that CWF is a safe and effective public health intervention to prevent dental caries.

This current review updates the evidence regarding CWF published since the OPMCSA report of 2021.

- The current review supports that conclusion on the basis that;
 - the evidence that has been published since 2021 indicates ongoing clear benefits from CWF even during the period when alternative forms of fluoride (such as fluoride toothpaste) are available and
 - CWF promotes equity by decreasing the incidence and severity of dental caries in individuals in areas of high socioeconomic deprivation as much as, or more than individuals in areas of less deprivation and
 - there has been no high-quality evidence published since those 2014 and 2021 reports to suggest a causal link between fluoride exposure at the levels used in Aotearoa New Zealand for CWF and significant harm to health.
- Individuals living in countries with high naturally occurring fluoride in drinking water, are at greater risk of dental fluorosis. However, the risk and severity of this complication in the setting of CWF is very low. Aotearoa New Zealand does not have high naturally occurring fluoride levels in drinking water.

2. Background

In June 2023, New Health New Zealand Inc (NHNZ) filed legal proceedings challenging the Director-General of Health's 2022 directions to 14 local authorities to add fluoride to one or more of their drinking water supplies. That challenge has two components: (i) a "procedural" aspect, that the Director-General should have explicitly considered the New Zealand Bill of Rights Act (NZBORA) in making a decision on each direction; and (ii) a "substantive" challenge to the directions, alleging that the scientific evidence on CWF does not support its safety or efficacy. Only the first component has been heard to date.

In November 2023, the High Court ruled, on the first component, that the Director-General should have explicitly considered the NZBORA in the decision to make the directions. In February 2024, the High Court Judge kept the 14 directions in place and directed the Director-General to carry out a NZBORA analysis. The Judge also directed the Director-General to consider the views of NHNZ as part of the analysis. As part of its submission to the Court, NHNZ referred to several scientific studies, which have been included in this review, if not already referenced in the earlier reviews by OPMCSA and RSNZ. The studies referred to by NHNZ are listed in Appendix 8.

The Royal Society of New Zealand (RSNZ) and Office of the Prime Minister's Chief Science Advisor (OPMSCA) have published reports on the risks and benefits of water fluoridation, in 2014 and 2021 respectively. The 2014 report recommended a review of the evidence be repeated every 10 years. However, given the outcome of the judicial review, the Public Health Agency (PHA) Ope Aorangi team requested that an update of the evidence be carried out now in order to inform the NZBORA analysis. A review of the evidence of the safety and effectiveness of CWF was undertaken by the Office of the Chief Science Advisor (OCSA) in collaboration with the PHA Intelligence, Surveillance and Knowledge Group (ISK). The document produced was peer reviewed by subject matter experts external to the Ministry of Health.

3. Conclusions from the review by the OPMCSA (2021)

The review of the risks of fluoridation undertaken by the OPMCSA in 2021 supported the conclusions of the report undertaken by RSNZ published in 2014.

The key points from the 2021 OPMCSA report are as follows:

- The low levels of fluoride that occur naturally in Aotearoa New Zealand's water do not contribute to better dental health.
- How much fluoride a person is exposed to depends on their diet, how much water they drink, the level of fluoride in the water supply, and their oral hygiene routines.
- Adding fluoride to water helps reduce the incidence of dental caries in Aotearoa New Zealand and is particularly important in reducing socioeconomic inequities in health.
- Excessive fluoride intake can cause dental fluorosis (a tooth enamel defect resulting in opaque white spots on the teeth). However, at the levels used for water fluoridation in Aotearoa New Zealand, this is generally mild (i.e., of no health concern and little-to-no cosmetic concern) and the incidence of dental fluorosis is generally similar between fluoridated and non-fluoridated areas.
- Some groups may be exposed to higher levels of fluoride than what is necessary to gain oral health benefits, in particular formula-fed infants living in areas with fluoridated water supplies. This may put them at higher risk of experiencing mild dental fluorosis, but no other health concerns are expected.
- Recent studies suggest that at very high levels and with chronic exposure, fluoride could have negative neurodevelopmental and cognitive impacts. However, this is not a concern at levels used in fluoridation of water supplies in Aotearoa New Zealand.

Reports outlining the risks and benefits of CWF from Australia, Europe, Canada, the United States, and the World Health Organisation (WHO) were included in the OPMCSA 2021 review.

4. Scope of current review

The scope of the current review was to assess whether or not the evidence regarding CWF published since the 2021 OPMCSA report significantly shifts the overall balance of evidence to suggest that CWF is no longer a safe and effective public health measure.

5. Limitations of this evidence review

There is always a risk that not all studies have been identified and included in this report. However, collating published studies from systematic reviews and regularly supplementing this information with newly published data from original studies using robust search criteria provides an effective mechanism for ensuring inclusion of relevant studies. In addition, the use of systematic reviews is a way of identifying and synthesising a body of evidence, that is, it looks at the overall evidence, identifies sources of bias and makes conclusions about that body of evidence. In this situation, it is very unlikely that a single study published after the search date for this report (or not identified in the search) would alter the conclusions based on the body of evidence.

6. Methods

a. Study design

Systematic reviews¹ and meta-analyses² were given priority in synthesising the evidence. Evidence from randomised trials and observational trials was also assessed for completeness and to ensure that evidence presented by NHNZ was addressed as requested by the Court. Publications that were not peer reviewed, editorials, opinion pieces and review articles which did not use a systematic methodology (that is, narrative reviews) were not incorporated into this review.

b. Identification of Evidence

The review was performed by undertaking a systematic review of the evidence regarding the risks and benefits of CWF published between January 2019 and April 2024. Search criteria are provided in Appendix 7. The start date was extended earlier than the 2021 publication date of the OPMCSA report to ensure all the relevant literature was identified.

The categorisation of evidence covered the following issues:

1. Benefits of fluoridation
 - a) Prevention of dental caries
 - b) Equity
2. Risks of fluoridation
 - a) Neurodevelopmental delay
 - b) Dental fluorosis
 - c) Hypothyroidism

Skeletal fluorosis and cancer were not assessed in detail. Economic analyses of CWF were also not considered in this evidence review.

Skeletal fluorosis, a summary of which was published in the 2021 OPMCSA report, occurs only after many years of exposure to very high levels of fluoride. The OPMCSA report stated that skeletal fluorosis does not occur in the setting of CWF and has not been reported to occur in New Zealand.

A single study assessing the risks of bone diseases (hip fracture, osteoporosis, and bone cancer) in an area in which CWF had been implemented from 1982 to 2004,

¹ an objective, reproducible method to find answers to a certain research question, by collecting all available studies related to that question and reviewing and analysing their result

² the statistical process of analysing and combining results from several similar studies

compared to a non-fluoridated adjacent region, did not identify any association between hip fracture or bone cancer. (Lee et al., 2020)

The role of fluoride in skeletal physiology is complex and dose-dependent. At low dose, fluoride has been demonstrated to improve bone mineral density. (Skalny et al., 2023)

c. Exclusions and Inclusions

Evidence of the risks and benefits of CWF was assessed. Systematic reviews of water supplies with naturally occurring fluoride were included where appropriate. However, as many naturally occurring water sources contain concentrations of fluoride above that used for CWF and the concentrations of fluoride vary over time, the relevance of individual studies reporting naturally fluoridated water is limited. Papers which were referenced in the OPMCSA report of 2021 were excluded from this report as they informed the existing evidence base. Non-English language publications were excluded³.

d. Risk of Bias

Bias is an important concept to understand when it comes to evaluating the quality of research. Bias is a systematic mistake in the planning, execution, or analysis of a study that results in inaccurate conclusions. This makes the assessment of the risk of bias important when interpreting research findings. One important source of bias is confounding factors. Confounding factors are associated with both the exposure and the outcome and, if not accounted for, can cause spurious results in a study.⁴ Systematic reviews aim to minimize bias by using explicit, systematic methods documented in advance with a protocol for inclusion and exclusion.

Confounders and the risk of bias were identified in publications where possible. Confounders related to the outcomes of dental caries, dental fluorosis, and neurodevelopmental delay/IQ are as follows;

1) Dental caries

The caries-preventive benefits of fluoride may be obtained from multiple other sources including fluoride toothpaste, gels, mouthwash and foods which contain fluoride. The risks of tooth decay are influenced by a wide range of behaviours and dietary factors, along with structural and contextual factors as with any non-communicable disease (NCD). Where possible these confounders were identified.

³ Only one study was excluded on this basis

⁴ For example, intelligence is known to be sensitive to a range of demographic variables which can interact. If an unmeasured variable, such as alcohol use in pregnancy (a known neurotoxin) is associated with both the exposure location (a city with CWF) and the outcome measure (neurodevelopmental delay) a false association will be identified between the exposure and the outcome.

2) Dental fluorosis

The risks of dental fluorosis can be influenced by sources of fluoride products other than CWF, including fluoride toothpaste, tablets and varnish.

3) Neurodevelopmental delay/IQ

The risks of neurodevelopmental delay, including low IQ, are influenced by a wide range of factors such as established neurotoxins, including alcohol (Giordano & Costa, 2012), congenital disorders, complications of pregnancy and the newborn period, nutritional status, residence and sociodemographic variables such as parental educational levels.

7. Results

Studies of the risks and benefits of CWF are presented as summaries of systematic reviews followed by summaries of trials and studies.

a. Dental caries

Dental caries is determined by systematically examining the dentition and noting the presence of cavities and restorations (along with missing teeth). The usual practice in dental epidemiological studies is to determine the status of the tooth surfaces and to record the number of decayed, missing or filled surfaces (DMFS for permanent dentition or dmfs for deciduous dentition) or teeth (DMFT / dmft). This report has attempted to accurately refer to dental experience as the relevant DMFT indices and caries prevalence as the percentage of individuals who experience any caries, which can be expressed as DMFT >0.

1) Systematic reviews and meta-analyses

Twenty-six systematic reviews and meta-analyses were identified in the search. Twenty publications were excluded for the following reasons: did not assess CWF (n=13); were not systematic reviews (n=9); and did not assess dental caries as an outcome (n=4). Some publications were excluded for more than one reason. Of the six publications remaining, three undertook a meta-analysis. Two publications identified original studies published after 2020 and both were identified in the search of observational and randomised controlled trials. A table of the systematic reviews not included is provided in Appendix 1.

A summary of the publications included is provided in Table 1.

Table 1: List of systematic reviews included in this review

No	Study	Number of included studies	Years of included studies	Author's Summary	Reviewer's Comment
1	(Al Rasheed & Jones, 2024)	9 studies	1956 - 1998	Water fluoridation was effective in improving dental caries among the Scottish child population.	Similar results to the 2015 Cochrane review demonstrating the effectiveness of fluoridation prior to widespread introduction of fluoridated toothpaste.
2	(Belotti & Frazao, 2022)	10 studies	1998 - 2018	Fluoridated areas exhibited lower mean dmft/DMFT than non-fluoridated areas.	CWF remains effective in preventing dental caries in children younger than 13 years, even with the

No	Study	Number of included studies	Years of included studies	Author's Summary	Reviewer's Comment
				The caries prevalence was 1.4 times and 57% lower, respectively, in primary and permanent dentitions in fluoridated areas	widespread use of fluoride toothpaste.
3	(Moynihan et al., 2019).	32 studies	1965 - 1997	Meta-analysis of data on the impact on ECC ⁵ from living in a fluoridated area showed a significant effect (mean difference, -1.25; 95% CI, -1.24 to -0.36). Providing access to fluoridated water and raising awareness among caregivers are justified approaches to ECC prevention.	CWF remains effective in preventing dental caries in a metanalysis pooled from four studies.
4	(Senevirathna et al., 2023)	24 studies	1960 - 2022	Studies report that water fluoridation has reduced dental caries by 26-44% in children, teenagers, and adults, benefiting everyone regardless of age, income, or access to dental care. CWF is a cost-effective intervention to prevent dental caries, especially in rural and low-income areas.	CWF remains effective in preventing dental caries and decreases inequality.
5	(Sharma et al., 2024)	31 studies	Up to June 2022	Dental caries in children has consistently declined in the Republic of Ireland in the last seven decades. Since the introduction of CWF, a greater reduction in dental caries has been reported among children living in areas with CWF than among those without CWF.	CWF remains effective in preventing dental caries in the presence of declines in the prevalence of dental caries.
6	(Shen et al., 2021)	4 studies	2007 - 2020	The quality of included papers was moderate. The overall findings suggest that whole population interventions such as water fluoridation are more likely to reduce inequalities in children's caries than target population and individual interventions.	CWF remains effective as a public health intervention to decrease dental caries even in the presence of other existing individually focussed interventions.

⁵ early childhood caries

i. Outcomes

All six systematic reviews reported a lower rate of dental caries associated with CWF. Five of the six studies (all except Al Rasheed et al) (Al Rasheed & Jones, 2024) analysed data published during a period when additional vehicles for fluoride application such as fluoride toothpaste were widely available. Benefits were observed for both the primary (or deciduous) and permanent teeth but were more pronounced for primary dentitions.

ii. Equity

Two systematic reviews reported the effect of CWF in the context of greater equity in outcomes. (Senevirathna et al., 2023; Shen et al., 2021) One review reported that CWF was associated with a lower rate of dental caries in all groups irrespective of age, income and access to dental care, consistent with greater equity for oral health outcomes. (Senevirathna et al., 2023) The second study reported that CWF resulted in less inequality for children's oral health than targeted approaches. (Shen et al., 2021)

2) Observational Studies⁶

i. Study selection

Fifty-nine studies were identified in the search and reviewed by title and abstract to identify those assessing the benefits of CWF. A full review was undertaken of all studies relating to CWF or when a title and abstract did not provide sufficient information to determine inclusion.

Thirty-one studies assessing CWF published since 2018 which were not included in the OPMCSA 2021 report were identified from the search. Of these 31 papers, three did not have sufficient information in the abstract to classify and the originals could not be sourced. (Pollick, 2019a, 2019b; Sanders et al., 2019) A further six studies were excluded after a full review. One paper was in Portuguese without an available English translation, (Corrêa et al., 2020) one paper combined results from both naturally occurring and actively fluoridated groups, (Moore et al., 2024) one paper did not provide sufficient information regarding fluoridation status of the comparison groups, (Dixit et al., 2024) two papers were duplications of the same data (McLaren et al., 2022b; Meyer et al., 2018) and one paper was an economic analysis of CWF without associated clinical data. (Cronin et al., 2021)

A table of the observational studies not included is provided in Appendix 2.

ii. Types of studies

Of the remaining 22 papers, three were prospective observational studies, three retrospective observational studies and 16 were cross-sectional studies. A summary of the studies is included in Table 2.

⁶ An observational study is a type of investigation used in clinical research to simply observe a group of people or study participants without intervening or influencing them, for example, by allocating a treatment

Table 2: List of observational studies included in this review

No	Study / Country	Type of study	Author's Summary	Reviewer's Comment
1	(Batsos et al., 2021) Canada	Cross-sectional	Residence in a municipality with water fluoridation was associated with a lower caries experience in a national sample of newly enrolled Canadian Armed Forces members. The benefits of water fluoridation were uniform across neighbourhood income and military rank classes.	The socioeconomic class of recruits was relatively uniform.
2	(Brito et al., 2020) Brazil	Cross-sectional	Water fluoridation was associated with a lower DMFT index ($OR_p^7 = 0.766$). Dental caries experience is still associated with social inequalities at different levels.	CWF is effective in a modern setting. CWF addresses inequities in oral health
3	(Cruz & Narvai, 2018) Brazil	Cross-sectional	Exposure to fluoridated water is associated with lower mean values for the DMFT and SiC ⁸ indices, 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 analysed.	CWF is effective in a modern environment and low prevalence of tooth decay.
4	(Dalla Nora et al., 2020) Brazil	Cross-sectional	In conclusion, this cross-sectional study found that urban schoolchildren showed greater caries experience than rural students, and that this increment was related to active non-cavitated lesions.	No difference between groups using WHO criteria for DMFT. No adjustment for variables known to influence the incidence of dental caries.
5	(Do et al., 2018) Australia	Cross-sectional	Caries experience was higher in non-fluoride (NF) than fluoride (F) strata. Race- and income-related gradients in caries experience were observed in both F and NF areas. All indices of inequality indicated that caries experience was concentrated among lower income groups. Absolute inequalities were consistently lower in F than in NF areas.	CWF effective in a modern setting. CWF reduces inequities in oral health

⁷ OR_p = Odds ratio using Poisson regression analysis.

⁸ the Mean DMFT of the one third of the study group with the highest caries score

No	Study / Country	Type of study	Author's Summary	Reviewer's Comment
6	(Foley et al., 2022) Australia	Cross-sectional	Longer lifetime exposure to fluoridated drinking water is causally associated with a lower childhood dental caries prevalence and more positive parental ratings of child oral health. The associations are stronger for younger children.	CWF is effective in a modern setting. The associations are stronger for younger children.
7	(Gnanapragasam et al., 2024) Malaysia	Retrospective longitudinal	After controlling for confounders, partial exposure to CWF remained a strong predictor for mean caries increment over a five-year study period. This study showed greater mean caries increment in permanent dentition among schoolchildren in Pahang after CWF ceased.	CWF is effective in a modern setting and has a positive impact on permanent dentition.
8	(Goodwin et al., 2022) United Kingdom	Prospective longitudinal	The evidence, after adjusting for deprivation, age and sex, with an adjusted odds ratio of 0.74 (95% confidence interval 0.56 to 0.98), suggested that water fluoridation was likely to have a modest beneficial effect.	CWF is effective in a modern setting. The authors state that the low response rate to the questionnaires limited the power of this study
9	(Gussy et al., 2020) Australia	Prospective longitudinal	Independent protectors of surface cavitation included water fluoridation, and older age of mothers.	Well-conducted multi-year prospective study identified risk factors at a population, household and individual level.
10	(Kim et al., 2019) South Korea	Prospective observational ⁹	The caries-reducing effect was so high that health policy makers should consider CWF as a priority policy for caries-reducing in Korean children and adolescents.	CWF was effective in a modern setting in deciduous and permanent dentition.
11	(Kroon et al., 2019) Australia	Cross-sectional	Between the pre- & post-CWF surveys age-weighted mean dmft decreased by 37.7% & DMFT decreased by 35%. Between the 1- & 4-year post-CWF surveys DMFT/dmft increased by 25% & 7.7%, respectively.	CWF is effective in a modern setting.
12	(Levy et al., 2023) Israel	Cross-sectional	The findings indicated that subjects exposed to fluoridated water during their childhood had significantly lower rates of caries-related treatment, regardless of access to free dental care.	CWF is effective in a modern setting and is more effective than free oral care.

⁹ Data from Korean National Health and Nutrition Examination Survey. (KNHANES)

No	Study / Country	Type of study	Author's Summary	Reviewer's Comment
13	(Matsuo et al., 2020) United States	Cross-sectional	Among the children without any CWF lifetime exposure, statistically significant caries disparities by parental educational attainment were observed. Socioeconomic disparities in dental caries were not observed among 10-19-year-old schoolchildren with lifetime CWF exposure. CWF seemed to reduce dental caries disparities.	CWF is effective in a modern setting. CWF decreases inequities in oral health.
14	(McLaren et al., 2022a) Canada	Cross-sectional	Social inequities in dental caries were present in both Calgary and Edmonton. Those inequities tended to be worse in Calgary where fluoridation was ceased.	CWF is beneficial in a modern setting. CWF decreases inequities in oral health.
15	(Melough et al., 2023) United States	Cross-sectional	Free sugars intake, especially in the form of added sugars and specifically in sweetened beverages, was associated with higher dental caries. Water fluoride exposures modify these associations, reducing caries risk in the primary dentition of children whose home water meets recommended fluoride levels.,	CWF is effective in a modern setting and can ameliorate risks from sugar-sweetened beverages.
16	(Meyer et al., 2022). United States	Cross-sectional	The results are consistent with previous research that has demonstrated a significant protective effect of CWF against dental caries.	CWF is effective in a modern setting
17	(Silva et al., 2021) Brazil	Cross-sectional	Children and adolescents who consumed fluoridated water had lower dental caries prevalence and severity than those who used only fluoridated toothpaste as the source of fluoride. There is an association between water fluoridation and very mild/mild and moderate fluorosis in adolescents.	CWF is effective in a modern setting for both deciduous and permanent dentition
18	(Silveira Schuch et al., 2021) Brazil	Cross-sectional	In crude analysis, children who consumed bottled water ¹⁰ had a lower risk of decayed teeth, lower experience of dental caries and less severe disease. No associations were observed after adjustments for socioeconomic conditions. Drinking fluoridated tap water is as effective in dental caries prevention as	CWF is effective in a modern setting. CWF decreases inequities in oral health.

¹⁰ In this study, bottled water contained a variable amount of fluoride which was generally within therapeutic range for prevention of dental caries.

No	Study / Country	Type of study	Author's Summary	Reviewer's Comment
			bottled water with acceptable levels of fluoride, with the advantage of being accessible to all.	
19	(Slade et al., 2018) United States	Cross-sectional	Statistically significant associations were seen when % CWF was modelled as a continuum, and differences tended to be greater in covariate-adjusted analysis and in sensitivity analysis. These findings confirm a substantial caries-preventive benefit of CWF for U.S. children and that the benefit is most pronounced in primary teeth.	CWF is effective in a modern setting
20	(Tobias et al., 2024) Israel	Cross-sectional	Based on DMFT, the caries experience was significantly higher in non-fluoridated cities (1.38 vs 0.98 in fluoridated cities) and there were more caries-free children in fluoridated cities (56.4% vs 40.6% in non-fluoridated).	CWF is effective in a modern setting. CWF decreases inequities in oral health.
21	(Tuan et al., 2023) United States	Retrospective	Children living in rural and non-fluoridated water communities had 1.7 to 1.8 times greater rates of developing early childhood caries.	CWF is effective in a modern setting. CWF decreases inequities in oral health.
22	(Yazdanbakhsh et al., 2024) Canada	Retrospective	Discontinuing water fluoridation appears to negatively affect young children's oral health, potentially leading to a significant increase in caries-related dental treatments under general anaesthesia and oral health disparities in this paediatric population.	CWF is effective in a modern setting. CWF decreases inequities in oral health.

iii. Location of Studies

The location of studies was as follows; Brazil (n = 5), United States (n=5), Australia (n=4), Canada (n = 3), Israel (n = 2) and one study each in Malaysia, South Korea and the United Kingdom.

iv. Study periods

The study periods for data collection ranged from the 1999 through to 2021. Data collection often spanned many years. All but three studies collected data in the decade from 2000 to 2009 (8 studies) or from 2010 to 2019 (21 studies).

v. Outcomes

Dental Caries

Twenty-one of the 22 observational studies of CWF reported that CWF was associated with a lower dental caries experience in groups studied. The CWF exposure in all studies occurred during the last 25 years, when fluoridated toothpaste was widely available¹¹. One study identified a positive association between CWF and a greater dental caries experience using a modification of the WHO criteria for dental caries when comparing an urban (CWF) and rural (non-CWF) samples. No association was identified using the standard WHO criteria¹². However, that study did not adjust for socioeconomic variables (known to be associated with dental caries) or diet. In addition, the water fluoride concentration in some locations without CWF was within the therapeutic range (range: 0.17 – 0.52 ppm), which would have provided some oral health benefits to individuals living in non-CWF areas. (Dalla Nora et al., 2020)

Equity

Of the 22 included studies, 17 collected some sociodemographic data. Dental caries in children was positively associated with socioeconomic deprivation or lower socioeconomic status in the majority of studies. (Brito et al., 2020; Do et al., 2018; Hobbs et al., 2020; Matsuo et al., 2020; McLaren et al., 2022a; Silveira Schuch et al., 2021; Tobias et al., 2024; Tuan et al., 2023; Yazdanbakhsh et al., 2024)

CWF was associated with better oral health in children with greater levels of socioeconomic deprivation in 7 studies (Do et al., 2018; Hobbs et al., 2020; Levy et al., 2023; Matsuo et al., 2020; Tobias et al., 2024; Tuan et al., 2023; Yazdanbakhsh et al., 2024) but not in one study (Goodwin et al., 2022).

b. Risks of CWF

1) Neurodevelopment

The effect of CWF on neurodevelopment and cognition (including IQ) was specifically investigated.

A search for relevant research identified 43 publications of which 10 met the inclusion criteria for this review. Of the ten publications, six were systematic reviews and four were primary studies not included in any of the other reviews.

Thirty-three publications were excluded. Nineteen were already included in a systematic review (including the OPMCSA (2021) review), nine were of the wrong study/publication type (including editorials, letter, and conference proceedings) and five were of an outcome other than neurodevelopmental or cognitive outcomes. A list of the excluded publications is provided in Appendix 3.

¹¹<https://www.cdc.gov/fluoridation/basics/timeline.html#:~:text=1956,over%20the%20next%20few%20decades.>

¹² <https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3812>

An evidence table with more details of the publications included is provided in Appendix 4.

i. Systematic reviews and meta-analyses

Two systematic reviews investigated ADHD as an outcome (Fiore et al., 2023; Taher et al., 2024) and found no association with fluoride levels in drinking water.

Five systematic reviews provided evidence relating to IQ as an outcome. (Gopu et al., 2022; Kumar et al., 2023; Miranda et al., 2021; Taher et al., 2024; Veneri et al., 2023) Three of those concluded there was no association between lower IQ and fluoride in drinking water at levels comparable to that used in Aotearoa New Zealand for CWF. (Gopu et al., 2022; Kumar et al., 2023; Miranda et al., 2021) The other two reviews reported a negative association between water fluoride concentration and IQ. (Taher et al., 2024; Veneri et al., 2023) However, there are significant limitations and concerns about the methodological quality and robustness of results of these two reviews. Many of the included studies had exposures to fluoride of levels well above that used for CWF and are not relevant to a review of the risks of CWF. There are serious concerns regarding the risk of bias assessment in the review by Taher et al. (Taher et al., 2024) where most studies have been assessed as being of 'high quality' using a modified assessment tool of uncertain validity. This is at odds to other risk of bias assessments of the same studies by different authors. Moreover, they have mis-attributed an association at low fluoride levels (as used in CWF) with lower IQ where, in fact, the association is with much higher levels of fluoride than those used in CWF. There are similar issues with the publication by Veneri et al. (Veneri et al., 2023) However, the authors were more cautious in their conclusions, stating that the limitations of most of the primary studies (particularly residual confounding) raises uncertainties about the causal nature of the findings and the exact thresholds of exposure involved.

A brief summary of the findings from the systematic reviews is provided in Table 3.

Table 3: Summary of the systematic reviews investigating neurodevelopmental outcomes

Study/country Outcomes	Results	Conclusions by the authors
(Fiore et al., 2023) Italy/USA ADHD spectrum disorder	3/7 studies suggest an association 4/7 found no association	"...heterogeneity in study designs and results from human studies did not allow us to reliably identify fluoride exposure as a risk factor for ADHD development. "
(Gopu et al., 2022) UK Cognitive outcomes ¹³	25/31 studies found mean IQ lower for exposure to ≥ 2 mg/l compared to < 2 mg/l	"...many low quality studies and the lack of robust estimates of fluoride exposure from all sources make it difficult to provide definitive conclusions."

¹³ including IQ

Study/country Outcomes	Results	Conclusions by the authors
(Kumar et al., 2023) USA IQ scores	2 studies found no association between IQ and community fluoridation 8 studies in non-endemic areas (mean fluoride 0.90 vs. 0.30 mg/l) found no association	“These meta-analyses show that fluoride exposure relevant to community water fluoridation is not associated with lower IQ scores in children. ”
(Miranda et al., 2021) Brazil/Canada Neurological disorders ¹⁴	Odds of “low IQ” significantly greater in high fluoride area (>2mg/l) compared to low fluoride area (0.5-1.0 mg/ml)	“...showed IQ impairment only for individuals under high fluoride exposure considering the World Health Organization criteria, without evidence of association between low levels and any neurological disorder. ”
(Taher et al., 2024) Canada Health effects ¹⁵	16/21 studies found an association between fluoride levels in water and reduced IQ Insufficient evidence for any association between water fluoride and ADHD	“The evidence supports a conclusion that fluoride exposure reduces IQ levels in children at concentrations close to those seen in North American drinking water, although there is some uncertainty in the weight of evidence for causality and considerable uncertainty in the point of departure. ”
(Veneri et al., 2023) USA/Italy IQ scores	Mean difference in IQ score (highest vs. lowest fluoride level in each included study) for water fluoride level -5.60 (95% CI: -7.76 to -3.44) $I^2 = 91.69\%$	“...we found an overall indication of dose-dependent adverse effects of fluoride on children’s cognitive neurodevelopment, starting at rather low exposure. However, the limitations of most studies included in this meta-analysis, with particular reference to the risk of residual confounding, raise uncertainties about both the causal nature of such relation and the exact thresholds of exposure involved. ”

ii. Additional primary studies¹⁶

Four additional studies were identified that were not included in the systematic reviews above. (Dewey et al., 2023; Do et al., 2023; Ibarluzea et al., 2023; Krzeczowski et al., 2024) Three used data from longitudinal cohort studies and

¹⁴ all IQ except one study

¹⁵ including ADHD and IQ

¹⁶ One additional publication was identified after the completion of this review and is discussed in Appendix 9.

considered a number of confounding factors. A summary of additional studies is presented in Table 4.

An evidence table of the included additional primary publications is provided in Appendix 5.

Table 4: Summary of the additional studies of neurodevelopmental outcomes

Study/country Outcomes	Results	Conclusions by the authors
(Dewey et al., 2023) Ecological study Canada IQ and executive function	No association between exposure to CWF during pregnancy and IQ Exposure to CWF was associated with poorer inhibitory control and cognitive flexibility.	No associations were found between exposure to drinking water from a community water supply fluoridated at 0.7 mg/L throughout pregnancy and measures of intelligence at 3–5 years of age. Maternal exposure to drinking water throughout pregnancy fluoridated at the level of 0.7 mg/L was associated with poorer inhibitory control and cognitive flexibility, particularly in girls, suggesting a possible need to reduce maternal fluoride exposure during pregnancy
(Do et al., 2023) Cohort Australia/UK Emotional, behavioural development, and executive functioning	Comparable scores for those fully exposed and never exposed to CWF	Exposure to fluoridated water by young children was not negatively associated with child emotional, behavioural development, and executive functioning in their adolescent years
(Ibarluzea et al., 2023) Cohort Spain/UK Probable cognitive problems/inattention, hyperactivity/impulsivity, & ADHD	Non-significant associations were observed between MUFcr ¹⁷ levels and cognitive outcomes at age 8 years. Significant reduction in risk of probable cognitive problems/inattention scores at 11 years of age for maternal urinary fluoride levels at 32 weeks gestation and all of pregnancy.	Higher levels of maternal urinary fluoride levels in pregnant women were associated with a lower risk of cognitive problems/inattention at 11 years.

¹⁷ maternal urinary fluoride concentration (adjusted for creatinine)

Study/country Outcomes	Results	Conclusions by the authors
	All other associations non-significant.	
(Krzeczkowski et al., 2024) Cohort Canada Visual acuity & heart rate variability	Poorer visual acuity and one measure of heart rate variability at 6 months associated with water fluoride levels and maternal fluoride intake	Fluoride in drinking water was associated with poorer visual acuity and differences in cardiac autonomic function in infancy , adding to the growing body of evidence suggesting fluoride’s developmental neurotoxicity.

One study found no association between CWF exposure during pregnancy and the infants’ IQ at 3-5 years of age. (Dewey et al., 2023) The same study found an association between CWF and poorer inhibitory control (using some assessment tools) and cognitive flexibility in girls only. The clinical significance of the observed differences was not placed in a clinical context, so are not clear.

An Australian study found no effect of CWF on the emotional and behavioural development and executive functioning of adolescents. (Do et al., 2023) This was a nationwide population-based follow-up study with relevant and valid outcome and exposure measurement.

A Spanish study found no association between maternal urinary fluoride levels and ADHD. (Ibarluzea et al., 2023) Interestingly, the study did find an association between maternal urinary fluoride levels and lower risk of cognitive problems/inattention at 11 years. This result should not be interpreted as suggesting that antenatal exposure to fluoride decreases the risk of ADHD, but that maternal urinary fluoride is an unreliable measure of antenatal exposure and that neurodevelopmental outcomes are primarily determined by factors other than fluoride.

The final study, also using the MIREC dataset, used three different methods to estimate maternal fluoride intake and found an association between both water fluoride levels and estimated fluoride consumption, but not maternal urinary fluoride concentration and lower visual acuity and heart rate variability. (Krzeczkowski et al., 2024)

The use of the MIREC dataset for multiple analyses in multiple subgroups raises concerns regarding the reliability of the findings and the relevance of the results to other populations. Repeated analysis of a single dataset will result in the identification of associations by chance. It is also possible that within the MIREC dataset, fluoride is a marker for a range of known causes of neurotoxicity, such as alcohol, pregnancy complications and sociodemographic variables. The over-reliance on a single dataset will provide a distorted view of the strength of possible associations.

2) Thyroid function

A recent systematic review and meta-analysis was identified that investigated the effect of fluoride exposure on thyroid function. (Iamandii et al., 2024) This review included 33 studies of variable quality (risk of bias) and compared measures of thyroid function at the highest fluoride concentration with those at the lowest concentration. With regards to fluoride sourced from drinking water, there was some difference in thyroid function but whether this was significant clinically is very uncertain. No test of statistical significance was conducted and levels of statistical heterogeneity¹⁸ were all very high. This is extremely concerning because it is an indication that the studies in the meta-analysis are not comparable. In addition, there was no exploration of the reasons for this high heterogeneity. It is very likely that the source is the variation in the populations, exposures and outcomes of the included studies. It is certainly clear that the fluoride concentrations were not comparable as the authors used the highest fluoride concentration in any single study and compared it to the lowest fluoride concentration. This makes the generalisability and applicability of these findings to CWF in Aotearoa New Zealand weak. An evidence table with more details of the publications included is provided in Appendix 6.

A dose-response meta-analysis was also conducted in this systematic review which is more applicable and generalisable to CWF in Aotearoa New Zealand as it covers all water fluoride concentrations in the included studies. The results of these dose-response meta-analyses show that at levels comparable to CWF, there is no effect on thyroid function; any effect on thyroid-stimulating hormone (TSH) levels occurred only above 2ppm (or 2.5 ppm when the highest quality studies are considered).

3) Dental fluorosis

Dental fluorosis is an abnormality of the tooth enamel due to fluoride. The severity of fluorosis is assessed by a range of methods. (Mohd Nor, 2017) Mild degrees of fluorosis may cause cosmetic concern but are of no functional significance. Mild degrees of dental fluorosis often resolve with time due to surface abrasion and ongoing mineralisation. (Do et al., 2016)

i. Systematic reviews and meta-analyses

Three systematic reviews assessing the relationship between fluoride in drinking water and dental fluorosis were identified. (Akuno et al., 2019) (Taher et al., 2024) (Umer, 2023). All three studies reported findings primarily from naturally occurring fluoride at different concentrations and were not relevant to CWF in Aotearoa New Zealand. Analyses were not undertaken based on the severity of fluorosis.

ii. Observational studies

Ten studies were identified which analysed the risk of fluorosis associated with fluoride in drinking water. Only two of these studies were undertaken in the presence of CWF.

¹⁸ Heterogeneity refers to any kind of variability among studies in a systematic review including variability in the participants, interventions, outcomes, study design, risk of bias, and intervention effects. Statistical heterogeneity is where the observed intervention effects being more different from each other than one would expect due to chance alone.

A study in Brazil, reported that the prevalence of fluorosis in 12-year-olds was higher in those groups who were provided with CWF. (Silva et al., 2021) Very mild/mild and moderate fluorosis increased from 15.2 % and 3.3% in the group without fluoridated water, to 41.6% and 18.0% with fluoridated water respectively. The concentration of fluoride in CWF samples was reported to be between 0.5 and 0.6 mg/l.

The second study (undertaken in Israel) reported the prevalence of fluorosis in adolescents as 10.3%, of which 9.3% were classified as questionable or mild fluorosis. (Tobias et al., 2024)

One further study, the United States National Health and Nutrition Survey (NHANES), which included both CWF and non-CWF sources is included in the review. (Hung et al., 2023) NHANES recorded the concentration of fluoride in the drinking water, the fluoride concentration in serum and the use of fluoride supplementation.

The most recent data from the 2015/16 NHANES survey reported an adjusted¹⁹ odds ratio (OR) for dental fluorosis for increasing concentrations of fluoride using a concentration of less than 0.30 mg/l as the reference value. For a water fluoride concentration of 0.31 to 0.50, the OR (95% CI)²⁰ was 1.105 (0.377 – 3.469), at a concentration of 0.51 to 0.70 mg/l, OR = 1.828 (0.735 to 4.909) and for a concentration of greater than 0.70 mg/l, OR = 2.378 (1.218 – 5.249) (Hung et al., 2023). These data suggest that CWF at a concentration of less than 0.7 mg/l is not associated with a significantly greater risk of fluorosis compared to non-fluoridated water. The severity of fluorosis, which was identified by a visual inspection, was collected in the NHANES data in a four-point scale from 0 = no fluorosis to 4 = severe fluorosis. However, the study reported fluorosis as yes or no and will include mild and transitory degrees of dental fluorosis.

¹⁹ Adjusted for age, sex, race, ethnicity, family educational level, ratio of family income to area poverty level and period of survey.

²⁰ 95% CI = 95% confidence interval.

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Taher, M. K., Momoli, F., Go, J., Hagiwara, S., Ramoju, S., Hu, X., Jensen, N., Terrell, R., Hemmerich, A., & Krewski, D. (2024). Systematic review of epidemiological and toxicological evidence on health effects of fluoride in drinking water. *Critical Reviews in Toxicology*, 54(1), 2-34.

<https://doi.org/https://dx.doi.org/10.1080/10408444.2023.2295338>

Tobias, G., Khaimov, A., Zini, A., Sgan-Cohen, H. D., Mann, J., Chotiner Bar-Yehuda, Y., Aflalo, E., & Vered, Y. (2024). Caries prevalence and water fluoridation in Israel: a cross-sectional study. *Quintessence International*, 55(2), 166-172.

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Tuan, W. J., Leinbach, L. I., & Gill, S. A. (2023). Assessing risks of early childhood caries in primary care practice using electronic health records and neighborhood data [Article]. *Journal of Public Health Management and Practice*, 29(2), 178-185.

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Umer, M. F. (2023). A Systematic Review on Water Fluoride Levels Causing Dental Fluorosis [Review]. *Sustainability (Switzerland)*, 15(16), Article 12227.

<https://doi.org/10.3390/su151612227>

Veneri, F., Vinceti, M., Generali, L., Giannone, M. E., Mazzoleni, E., Birnbaum, L. S., Consolo, U., & Filippini, T. (2023). Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis. *Environmental Research*, 221, 115239. <https://doi.org/10.1016/j.envres.2023.115239>

Yazdanbakhsh, E., Bohlouli, B., Patterson, S., & Amin, M. (2024). Community water fluoride cessation and rate of caries-related pediatric dental treatments under general anesthesia in Alberta, Canada. *Canadian Journal of Public Health*, 115(2), 305-314.

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Appendix 1: Table of systematic reviews not used in this review

Reference	Summary
Akuno, M. H., et al. (2019). "Factors influencing the relationship between fluoride in drinking water and dental fluorosis: a ten-year systematic review and meta-analysis." <i>Journal of water and health</i> 17 (6): 845-862.	Studies were of naturally occurring fluoridation in Asia and Africa, not CWF. Publication bias identified.
Anopa, Y., et al. (2020). "Systematic Review of Economic Evaluations of Primary Caries Prevention in 2- to 5-Year-Old Preschool Children." <i>Value in health</i> , 23 (8): 1109-1118.	Did not include studies on CWF
Chou, R., et al. (2023). "Screening, Referral, Behavioral Counseling, and Preventive Interventions for Oral Health in Children and Adolescents Ages 5 to 17 Years: A Systematic Review for the U.S. Preventive Services Task Force."	Did not include studies on CWF
Chou, R., et al. (2021). "Screening and Interventions to Prevent Dental Caries in Children Younger Than Age Five Years: A Systematic Review for the U.S. Preventive Services Task Force."	Did not include studies on CWF
Davidson, K. W., et al. (2021). "Screening and Interventions to Prevent Dental Caries in Children Younger Than 5 Years: US Preventive Services Task Force Recommendation Statement." <i>JAMA</i> 326 (21): 2172-2178.	Did not include studies on CWF
Ivančáková, R. K. et al. Exogenous Intake of Fluorides in Caries Prevention: Benefits and Risks. <i>Acta Medica</i> 2021 Vol. 64 Issue 2 Pages 71-76	Not a systematic review.
Kathuria, N. S., et al. (2022). "Patterns and Distribution of Dental Caries and Dental Fluorosis in Areas with Varying Degrees of Fluoride Ion Concentration in Drinking Water: A Systemic Review and Meta analysis." <i>International Journal of Toxicological and Pharmacological Research</i> 12 (4): 201-205.	Did not include studies on CWF. Did not assess benefits, only risks

Reference	Summary
Koberova Ivancakova, R., et al. (2021). "Exogenous Intake of Fluorides in Caries Prevention: Benefits and Risks." <i>Acta medica (Hradec Kralove)</i> 64(2): 71-76.	Not a systematic review. Only briefly mentions CWF. Duplicate of Ivancakova et al.
Skeie, M. S. and K. S. Klock (2018). "Dental caries prevention strategies among children and adolescents with immigrant - or low socioeconomic backgrounds- do they work? A systematic review." <i>BMC oral health</i> 18(1): 20.	Did not include studies on CWF
Peng, S.-M. and C. McGrath (2020). "What can we do to prevent small children from suffering from tooth decay?" <i>Evidence-based dentistry</i> 21(3): 90-91.	A review of Moynihan, P., et al. (2019). "Systematic Review of Evidence Pertaining to Factors That Modify Risk of Early Childhood Caries." <i>JDR clinical and translational research</i> 4(3): 202-216.
Taher, M. K., et al. (2024). "Systematic review of epidemiological and toxicological evidence on health effects of fluoride in drinking water." <i>Critical reviews in toxicology</i> 54(1): 2-34.	Did not include studies on CWF. Did not assess benefits.
Takahashi, R., et al. (2017). "Fluoride supplementation (with tablets, drops, lozenges or chewing gum) in pregnant women for preventing dental caries in the primary teeth of their children." <i>Cochrane Database Syst Rev</i> 10(10): Cd011850.	Did not include studies on CWF
Toumba, K. J., et al. (2019). "Guidelines on the use of fluoride for caries prevention in children: an updated EAPD policy document." <i>European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry</i> 20(6): 507-516.	Did not include studies on CWF
Umer, M. F. (2023). "A Systematic Review on Water Fluoride Levels Causing Dental Fluorosis." <i>Sustainability (Switzerland)</i> 15(16).	Not CWF. Did not include studies on CWF. Studies from endemic fluorosis areas.
Valkenburg, C., et al. (2019). "Is plaque regrowth inhibited by dentifrice?: A systematic review and meta-analysis with trial sequential analysis." <i>International journal of dental hygiene</i> 17(1): 27-38.	Did not include studies on CWF
Veneri, F., et al. (2024). "Fluoride and caries prevention: a scoping review of public health policies." <i>Annali di igiene: medicina preventiva e di comunita</i> 36(3): 270-280.	Did not include studies on CWF Scoping review of public policies, not evidence
Zanatta, R. F., et al. (2020). "Protective effect of fluorides on erosion and erosion/abrasion in enamel: a systematic review and meta-analysis of randomized in situ trials." <i>Archives of oral biology</i> 120: 104945.	Did not include studies on CWF

Appendix 2: Table of observational studies not included in this review

Reference	Exclusion indication
<p>Ambarkova, V. et al 2022</p> <p>The Correlation Between the DMFT of the 15-year-old Children and the Concentration of Fluoride in Drinking Water from the East Region of the Republic of Macedonia.</p> <p>Open Access Macedonian Journal of Medical Sciences,10 260-266</p>	Not CWF
<p>Anisha, M, et al, 2020</p> <p>The effect of fluoride in the prevention of dental caries and prevalence of dental fluorosis among high and low fluoridated areas of Tamil Nadu - a cross-sectional survey</p> <p>Indian Journal of Public Health Research and Development 2020 Vol. 11 Issue 7 Pages 62-67</p>	<p>Not CWF</p> <p>Fluoride concentrations above CWF</p>
<p>Arheiam et al, 2020</p> <p>Changes in dental caries and sugar intake before and during the conflict in Libya: A natural experiment. Community dentistry and oral epidemiology 2020 Vol. 48 Issue 3 Pages 201-207</p>	Not CWF
<p>Arheiam et al 2022</p> <p>Dental Fluorosis and Its Associated Factors Amongst Libyan Schoolchildren.</p> <p>International dental journal 2022 Vol. 72 Issue 6 Pages 853-858</p>	<p>Not CWF</p> <p>Fluorosis, not caries</p>
<p>Corrêa, et al 2020</p> <p>Factors associated with dental caries in adolescents: A cross-sectional study, São Paulo State, Brazil, Epidemiologia e Servicos de Saude 2020 Vol. 29 Issue 5</p>	In Portuguese
<p>Garcia-Perez, et al.</p> <p>Impact of diseases of the hard tissues of teeth on oral health-related quality of life of schoolchildren in area with a high concentration of fluoride in drinking water. Community dental health 2022 Vol. 39 Issue 4 Pages 240-246</p>	<p>Not CWF.</p> <p>Assessed QOL not dental caries.</p>
<p>Gousalya et al 2023</p> <p>Effect of Fluoride on Oral Health Status Among General Population Residing in High- and Low-Level Fluoride Blocks in Erode District, Tamil Nadu, India: A Cross-Sectional Study.</p> <p>Journal of pharmacy & bioallied sciences 2023 Vol. 15 Issue Suppl 1 Pages S752-S755</p>	<p>Not CWF</p> <p>High natural fluoride levels</p>

Reference	Exclusion indication
<p>Hearnshaw et al. 2023</p> <p>Comments on recent community water fluoridation studies.</p> <p>British dental journal 2023 Vol. 235 Issue 8 Pages 639-641</p>	<p>Not primary study</p> <p>Commentary on CATFISH study</p>
<p>Hobbs et al 2020.</p> <p>Area-level deprivation, childhood dental ambulatory sensitive hospitalizations and community water fluoridation: evidence from New Zealand</p> <p>International journal of epidemiology 2020 Vol. 49 Issue 3 Pages 908-916</p>	<p>Included in OPMCSA 2021report</p>
<p>Lee et al 2020</p> <p>The Association between Community Water Fluoridation and Bone Diseases: A Natural Experiment in Cheongju, Korea.</p> <p>International journal of environmental research and public health 2020 Vol. 17 Issue 24</p>	<p>Assessed risk of cancer and bone disease.</p> <p>Did not assess caries.</p>
<p>Matsuyama et al,</p> <p>Tap water natural fluoride and parent-reported experience of child dental caries in Japan: Evidence from a nationwide birth cohort survey</p> <p>Community dentistry and oral epidemiology 2023 Vol. 51 Issue 6 Pages 1141-1149</p>	<p>Not CWF</p>
<p>Miranda-Rius, et al 2020</p> <p>Periodontal and dental conditions of a school population in a volcanic region of Tanzania with highly fluoridated community drinking water</p> <p>African health sciences 2020 Vol. 20 Issue 1 Pages 476-487</p>	<p>Assessed fluorosis.</p> <p>Did not assess caries.</p>
<p>Montanha-Andrade et al, 2019</p> <p>Dental health status and its indicators in adult Brazilian Indians without exposition to drinking water fluoridation: a cross-sectional study.</p> <p>Environmental science and pollution research international 2019 Vol. 26 Issue 33 Pages 34440-34447</p>	<p>Not CWF</p>
<p>Moore, D., et al. 2024</p> <p>How effective and cost-effective is water fluoridation for adults and adolescents? The LOTUS 10-year retrospective cohort study.</p> <p>Community Dentistry and Oral Epidemiology. https://onlinelibrary.wiley.com/doi/abs/10.1111/cdoe.12930</p>	<p>Not CWF.</p>
<p>Munoz-Milan et al 2018.</p> <p>Effectiveness of fluoride varnish in preventing early childhood caries in rural areas without access to fluoridated drinking water: A randomized control trial.</p> <p>Community dentistry and oral epidemiology 2018 Vol. 46 Issue 1 Pages 63-69</p>	<p>Not CWF</p> <p>Assessed benefits of fluoride varnish</p>

Reference	Exclusion indication
<p>Nguyen, T. M., et al. (2023).</p> <p>Economic Evaluations of Preventive Interventions for Dental Caries and Periodontitis: A Systematic Review.</p> <p>Applied health economics and health policy 21(1): 53-70.</p>	Economic Evaluation
<p>Perez et al 2020.</p> <p>Marginalization and fluorosis its relationship with dental caries in rural children in Mexico: A cross-sectional study</p> <p>Community Dental Health 2020 Vol. 37 Issue 3 Pages 216-222</p>	Not CWF
<p>Ramesh et al.</p> <p>A cross-sectional study to find the correlation between the level of fluoride in drinking water, dental fluorosis and associated risk factors</p> <p>Journal of Pharmacy and Bioallied Sciences 2023 Vol. 15 Issue 5 Pages 651-655</p>	Not CWF.
<p>Rani et al 2022</p> <p>Prevalence of dental fluorosis and dental caries in fluoride endemic areas of Rohtak district, Haryana</p> <p>Journal of the Indian Society of Pedodontics and Preventive Dentistry 2022 Vol. 40 Issue 2 Pages 140-145</p>	Not CWF High levels of fluoride
<p>Rezki et al 2023</p> <p>Effect of Drinking Water Fluoride on Gingivitis and Caries: A Study in Peat and Non-Peat Land: A Comparative Cross-Sectional Study</p> <p>Journal of International Society of Preventive & Community Dentistry 2023 Vol. 13 Issue 6 Pages 509-515</p>	Not CWF
<p>Saunders et al 2018</p> <p>Blood Lead Levels and Dental Caries in U.S. Children Who Do Not Drink Tap Water.</p> <p>American journal of preventive medicine 2018 Vol. 54 Issue 2 Pages 157-163</p>	Not CWF Tested lead levels in drinking water
<p>Schluter et al 2020</p> <p>Association Between Community Water Fluoridation and Severe Dental Caries Experience in 4-Year-Old New Zealand Children</p> <p>JAMA pediatrics 2020 Vol. 174 Issue 10 Pages 969-976</p>	Included in OPMCSA 2021 report.
<p>Whittaker et al 2024</p> <p>Economic evaluation of a water fluoridation scheme in Cumbria, UK</p> <p>Community dentistry and oral epidemiology 2024</p>	Economic analysis

Appendix 3: Exclusion table for neurodevelopmental outcomes

Reference	Reason for exclusion
Bashash, M., et al., Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6-12 years of age in Mexico City. <i>Environ Int</i> , 2018. 121(Pt 1): p. 658-666 DOI:10.1016/j.envint.2018.09.017.	ELEMENT project Included in the Fiore et al 2023 and Gopu et al 2022 systematic reviews
Bashash, M., et al., Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6-12 Years of Age in Mexico. <i>Environ Health Perspect</i> , 2017. 125(9): p. 097017 DOI:10.1289/ehp655.	ELEMENT project Included in the PMCSA update
Broadbent, J.M., et al., Community Water Fluoridation and Intelligence: Prospective Study in New Zealand. <i>Am J Public Health</i> , 2015. 105(1): p. 72-76 DOI:10.2105/ajph.2013.301857.	Dunedin Multidisciplinary Health and Development study Included in the PMCSA update and the Gopu et al 2022 systematic review
Canadian Agency for Drugs and Technologies in Health. Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects – A 2020 Update. CADTH Rapid Response Report: Summary with Critical Appraisal 2020; Available from: https://www.ncbi.nlm.nih.gov/books/NBK567579/ .	HTA update Included in the OPMCSA update
Canadian Agency for Drugs and Technologies in Health. Community Water Fluoridation: A Review of Neurological and Cognitive Effects. CADTH rapid response report: summary with critical appraisal 2019; Available from: https://americanfluoridationsociety.org/wp-content/uploads/2019/12/cadth-evaluation-of-green-till-study.pdf .	HTA Included in the OPMCSA update
Cantoral, A., et al., Dietary fluoride intake during pregnancy and neurodevelopment in toddlers: A prospective study in the progress cohort. <i>Neurotoxicology</i> , 2021. 87: p. 86-93 DOI:10.1016/j.neuro.2021.08.015.	PROGRESS cohort Included in Kumar et al 2023
Choi, A.L., et al., Association of lifetime exposure to fluoride and cognitive functions in Chinese children: a pilot study. <i>Neurotoxicol Teratol</i> , 2015. 47: p. 96-101 DOI:10.1016/j.ntt.2014.11.001.	Pilot study Included in Gopu et al 2022 systematic review
Duan, Q., et al., Association between water fluoride and the level of children's intelligence: a dose-response meta-analysis.	Meta-analysis Included in the OPMCSA update

Public Health, 2018. 154: p. 87-97 DOI:10.1016/j.puhe.2017.08.013.	
Farmus, L., et al., Critical windows of fluoride neurotoxicity in Canadian children. <i>Environ Res</i> , 2021. 200: p. 111315 DOI:10.1016/j.envres.2021.111315.	MIREC cohort Included in the Veneri et al 2023, Kumar et al 2023, and Taher et al 2024 systematic reviews
Goodman, C.V., et al., Domain-specific effects of prenatal fluoride exposure on child IQ at 4, 5, and 6-12 years in the ELEMENT cohort. <i>Environ Res</i> , 2022. 211: p. 112993 DOI:10.1016/j.envres.2022.112993.	ELEMENT project Included in the Veneri et al 2023, , and Taher et al 2024 systematic reviews
Grandjean, P., Developmental fluoride neurotoxicity: an updated review. <i>Environ Health</i> , 2019. 18(1): p. 110 DOI:10.1186/s12940-019-0551-x.	Integrated literature review Included in the OPMCSA update
Grandjean, P., Updated review by Grandjean of developmental fluoride neurotoxicity. <i>Fluoride</i> , 2020. 53	Editorial Wrong study design
Grandjean, P., et al., A Benchmark Dose Analysis for Maternal Pregnancy Urine-Fluoride and IQ in Children. <i>Risk Anal</i> , 2022. 42(3): p. 439-449 DOI:10.1111/risa.13767.	ELEMENT and MIREC cohort data Wrong outcome (benchmark dose analysis) Both primary studies used for this paper already included
Grandjean, P. and P.J. Landrigan, Neurobehavioural effects of developmental toxicity. <i>The Lancet Neurology</i> , 2014. 13(3): p. 330-338 DOI:10.1016/S1474-4422(13)70278-3.	Narrative review Wrong study design
Grandjean, P., et al., Dose dependence of prenatal fluoride exposure associations with cognitive performance at school age in three prospective studies. <i>Eur J Public Health</i> , 2024. 34(1): p. 143-149 DOI:10.1093/eurpub/ckad170.	Added Odense Child Cohort to ELEMENT and MIREC cohort data Wrong outcome (benchmark dose analysis)
Green, R., et al. Effects of Trimester-Specific Prenatal Fluoride Exposure and Childhood IQ in a Canadian Birth Cohort. in <i>BIRTH DEFECTS RESEARCH</i> . 2019. WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.	Wrong article type (Conference proceedings)
Green, R., et al., Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada. <i>JAMA Pediatr</i> , 2019. 173(10): p. 940-948 DOI:10.1001/jamapediatrics.2019.1729.	MIREC cohort Included in the PMCSA update and Gopu et al 2022 systematic review
Green, R., et al., Sex-specific neurotoxic effects of early-life exposure to fluoride: A review of the epidemiologic and animal literature. <i>Curr Epidemiol Rep</i> , 2020. 7(4): p. 263-273 DOI:10.1007/s40471-020-00246-1.	Wrong study design i.e., not a systematic review Wrong outcome (difference in mean IQ between boys and girls)
Guth, S., et al., Contribution to the ongoing discussion on fluoride toxicity. <i>Arch Toxicol</i> , 2021. 95(7): p. 2571-2587 DOI:10.1007/s00204-021-03072-6.	Reply Wrong study type
Hirzy, J.H., et al., Developmental Neurotoxicity of Fluoride: A Quantitative Risk Analysis Toward Establishing a Safe Dose for Children. <i>Fluoride</i> , 2016. 49(4): p. 379-400 DOI:10.5772/intechopen.70852.	Wrong outcome (benchmark dose analysis)

Ibarluzea, J., et al., Prenatal exposure to fluoride and neuropsychological development in early childhood: 1-to 4 years old children. <i>Environ Res</i> , 2022. 207: p. 112181 DOI:10.1016/j.envres.2021.112181.	"Infancia y Medio Ambiente" (INMA) birth cohort Included in the Kumar 2023 systematic review
Khairkar, P., et al., Outcome of Systemic Fluoride Effects on Developmental Neurocognitions and Psychopathology in Adolescent Children. <i>Indian J Pediatr</i> , 2021. 88(12): p. 1264 DOI:10.1007/s12098-021-03903-5.	Case-control Included in the Fiore et al 2023 systematic review
Kjelleveid, M. and M. Kippler, Fluoride - a scoping review for Nordic Nutrition Recommendations 2023. <i>Food Nutr Res</i> , 2023. 67 DOI:10.29219/fnr.v67.10327.	Scoping review Wrong study design and outcome
Mustafa, D.E.Y., U.M. and S.A. Elhaga, The relationship between the fluoride levels in drinking water and the schooling performance of children in rural areas of Khartoum state, Sudan. <i>Fluoride</i> , 2018. 51(2): p. 102-113	Included in Taher et al 2024 systematic review
National Academies of Sciences, E., et al. Review of the Draft NTP Monograph: Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects. 2020; Available from: https://nap.nationalacademies.org/catalog/25715/review-of-the-draft-ntp-monograph-systematic-review-of-fluoride .	Review of systematic review Included in the PMCSA update
Riddell, J.K., et al., Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth. <i>Environ Int</i> , 2019. 133(Pt B): p. 105190 DOI:10.1016/j.envint.2019.105190.	Canadian Health Measures Survey Included in the Fiore et al 2023 systematic review
Saeed, M., et al. (2021). "WITHDRAWN: Co-exposure effects of arsenic and fluoride on intelligence and oxidative stress in school-aged children: A cohort study." <i>Environmental research</i> 196: 110168 DOI: https://dx.doi.org/10.1016/j.envres.2020.110168	Withdrawn Included in the Gopu et al 2022 systematic review
Spittle, B., Fluoride, IQ, and advice on type I and II errors. <i>Fluoride</i> , 2014. 47(3): p. 188-190	Wrong article type (Editorial)
Spittle, B., Development of fluoride toxicity including cognitive impairment with reduced IQ: Pathophysiology, interactions with other elements, and predisposing and protective factors. <i>Fluoride</i> , 2016. 49(3): p. 189-193	Wrong article type (Editorial)
Spittle, B., Reviews of developmental fluoride neurotoxicity by Grandjean and Guth et al. <i>Fluoride</i> , 2020. 53(2): p. 204-219	Wrong article type (Editorial)
Thomas, D.B., et al., Urinary and plasma fluoride levels in pregnant women from Mexico City. <i>Environ Res</i> , 2016. 150: p. 489-495 DOI:10.1016/j.envres.2016.06.046.	ELEMENT Wrong outcome (fluoride levels in urine and plasma)
Till, C., et al., Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. <i>Environ Int</i> , 2020. 134: p. 105315 DOI:10.1016/j.envint.2019.105315.	MIREC Included in the Gopu et al 2022 systematic review

Appendix 4: Evidence table of included systematic reviews for neurodevelopmental outcomes

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
<p>(Fiore et al., 2023) Systematic review Italy/USA</p> <p>Journal Medicina</p> <p><u>Funding:</u> This study was supported by the grant "Dipartimenti di Eccellenza 2018–2022" to the UNIMORE Department of Biomedical, Metabolic and Neural Sciences from the Italian Ministry of Education, University and Research. T.F. was also supported by the grants "UNIMORE FAR 2021 and 2022, FOMO Line" by University of Modena and</p>	<p><u>Search:</u> PubMed, EMBASE and Web of Science on the 31st March 2023</p> <p><u>Inclusion criteria:</u> a healthy child and adolescent population (P), fluoride exposure of any type (E), comparison with low or null exposure (C), ADHD spectrum disorder (O), and ecological, cross-sectional, case-control and cohort studies (S).</p> <p>No exclusion criteria or limits on language or data [sic]</p> <p><u>Studies included:</u></p> <ul style="list-style-type: none"> • Bashash et al 2018 • Malin and Till 2015/Perrott 2018 • Riddell et al 2019 	<p><u>Exposure:</u> fluoride exposure of any type (water, toothpaste, diet)</p> <p><u>Comparator:</u> Lowest fluoride exposure in cohort or no exposure</p> <p>Each study used different methods to assess fluoride exposure and diagnose ADHD: 5 used urinary fluoride levels and 2 fluoride water levels; only 3 used validated questionnaires for ADHD</p> <p><u>Outcome:</u> ADHD</p>	<p>N=7 studies included (1 cohort, 1 case control, 5 cross-sectional)</p> <p>Two from USA and Canada, one from Mexico, China and India</p> <p><u>Findings:</u> Overall, 3 studies suggest an association between fluoride exposure and ADHD and 4 studies find no association.</p> <p>Malin and Till 2015, Riddell et al., 2019 and Khairkar et al., 2021 suggest there is a positive correlation between fluoride exposure and ADHD diagnosis.</p> <p>Bashash et al., 2018 found an association between maternal fluoride exposure and inattention,</p>	<p>Significant heterogeneity in populations, fluoride levels, and outcome assessment and small number of studies limits ability to make any general conclusions.</p> <p>Of note, it is not possible to attribute causality in studies with a cross-sectional design.</p> <p><u>Quality of this systematic review:</u> Adequate search and selection criteria, however, there has been no discussion of methodological quality of the included studies. Likely risk of misclassification and residual confounding and study design also precludes drawing of definitive conclusions.</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
<p>Reggio Emilia and Fondazione di Modena.</p> <p><u>Conflicts of Interest:</u> The authors declare no conflict of interest.</p>	<ul style="list-style-type: none"> Adkins et al 2022 Wang 2022 Barberio et al 2017 Khairkar et al 2021 <p><u>Appraisal:</u> No appraisal of quality conducted</p>		<p>whereas no association is found between maternal fluoride exposure and hyperactivity or impulse control dysfunctions.</p> <p>Conversely, Barberio et al., 2017 and Perrott 2018 observe no association between fluoride exposure and ADHD.</p> <p>Adkins and Wang note an association between fluoride exposure and the development of internalizing symptoms such as somatization, but they do not find any significant connection with ADHD.</p>	<p><u>Authors' conclusions:</u> Current epidemiological evidence indicates that fluoride exposure may have neurotoxic effects on neurodevelopment, including behavioral alterations, cognitive impairment and psychosomatic issues. However, the heterogeneity in study designs and results from human studies did not allow us to reliably identify fluoride exposure as a risk factor for ADHD development.</p>
<p>(Gopu et al., 2022) Systematic review UK</p> <p><u>Journal</u> International Journal of Environmental Research and Public Health.</p>	<p><u>Search:</u> MEDLINE, Embase, and CINHAL via EBSCO host, PubMed, Web of Science, Scopus, and PsycINFO using MeSH</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Population: pregnant women and children > 18 years 	<p><u>Exposure:</u> fluoride exposure of any type (water, toothpaste, diet)</p> <p><u>Source of fluoride:</u> coal (N=4 studies); drinking water (N=42 studies)</p> <p><u>Fluoride levels:</u></p> <ul style="list-style-type: none"> 0.13 to 9.4 mg/L in the drinking water 	<p>N=46 studies included (6 longitudinal; 40 cross-sectional)</p> <p>23 from China; 9 from India; 6 from Mexico; 3 Canadian; 2 Iranian; one each from NZ, Mongolia and Pakistan</p> <p><u>Quality of studies:</u></p> <ul style="list-style-type: none"> Excellent N=5 Good N=7 	<p>Some clinical heterogeneity in population, fluoride exposure levels, and outcomes, therefore narrative synthesis (i.e., no meta-analysis conducted)</p> <p><u>Quality of this systematic review:</u> Adequate search and selection criteria with appraisal of quality. Appropriate subgroup analysis and</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
<p><u>Funding:</u> This research was funded by Teesside University Ph.D. Studentship.</p> <p><u>Conflicts of Interest:</u> The authors have no conflicts of interest to declare.</p>	<ul style="list-style-type: none"> Exposure: fluoride through sources including groundwater, tea and milk, diet, toothpaste, mouthwash, industrial emissions, coal-burning for fuel, supplements, pesticide residues, and certain pharmaceuticals; Outcome: cognitive outcomes measured with a validated tool²¹ Study design: Longitudinal, cross-sectional, and experimental studies Only publications in the English language. <p><u>Exclusion criteria:</u> animal studies; studies in adults over 18 years; case studies; narrative reports; expert opinions; reviews; abstracts; conference proceedings</p> <p><u>Studies included:</u></p>	<ul style="list-style-type: none"> 0.03 to 2.33 mg/m³ through coal burning ≥2 mg/l in 27 studies <2 mg/l in 13 studies 6 studies did not report level <p><u>Duration of exposure:</u></p> <ul style="list-style-type: none"> from birth (N=28) not reported (N=18) <p><u>Outcomes:</u> cognitive outcomes</p>	<ul style="list-style-type: none"> Fair N=14 Poor N=20 <p><u>Findings:</u> 31 out of the 46 included studies reported mean IQ scores alone:</p> <ul style="list-style-type: none"> Of these, 25 studies found mean IQ levels of children exposed to fluoride ≥2 mg/L were significantly lower than those exposed to <2 mg/L, while the remaining 6 studies found no significant association <p>The remaining 15 studies reported on various outcomes:</p> <ul style="list-style-type: none"> 11 found a negative association between fluoride exposure and mental and psychomotor development index (N=1 study), neonatal behavioural neurological assessment scores (N=1), intelligence ranking (N=2), mean intelligence grades (N=2), and intelligence assessment scores (N=4) 	<p>narrative synthesis. Generalisability and applicability is limited due to fluoride exposures above that used for water fluoridation in Aotearoa New Zealand (0.7 – 1.0 mg/l).</p> <p>Other limitations include: preponderance of cross-sectional studies which make it difficult to attribute causality; the use of mean IQ to measure cognition ignores the complexity of cognition and the factors influencing it; risk of residual confounding by not including other factors that influence IQ such as maternal IQ, nutrition, education, maternal depression, and deficiencies in iron and iodine.</p> <p><u>Authors' conclusions:</u> The overall evidence from this systematic review suggests that exposure to fluoride at a</p>

²¹ Various tools used including Raven's Standard progressive matrices; official IQ Tests; Raymond B Cattell test; Chinese Binet IQ test etc

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<ul style="list-style-type: none"> • Chen et al 2008 • Choi et al 2015 • Chunyuan & Olsen 2011 • Cui et al 2018 • Ding et al 2011 • Guo et al 2008 • Li et al 2008 • Lou et al 202 • Lu et al 2000 • Qin et al 2008 • Ren et al 2008 • Wang et al 2020 • Wang et al 2008 • Wang et al 2019 • Wang et al 2008b • Wang et al 2007 • Wei et al 2014 • Xiang et al 2003 • Xu et al 2020 • Yang et al 2008 • Yu et al 2018 • Zhao et al 2021 • Zhao et al 1996 • Aravind et al 2016 • Eswar et al 2011 • Kumar et al 2021 		<ul style="list-style-type: none"> • 4 found no effect on self-reporting learning ability, the mean general cognitive index, the strengths and difficulty questionnaire, or intelligence deficiency <p><u>Subgroup analysis:</u></p> <ul style="list-style-type: none"> • study design: more likely to report a negative effect with cross-sectional studies • age: no difference for ≤ 8 years vs. > 8 years old • fluoride level: more likely to report negative association with fluoride ≥ 2 mg/l exposure • study quality: more likely to report a negative association with fair or poor quality study 	<p>level of more than 2 mg/L in drinking water may result in impaired cognitive outcomes among children. However, the inclusion of many low quality studies and the lack of robust estimates of fluoride exposure from all sources make it difficult to provide definitive conclusions.</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<ul style="list-style-type: none"> • Kundu et al 2015 • Razdan et al 2017 • Saxena et al 2012 • Sebastian et al 2015 • Sharma et al 2016 • Trivedi et al 2007 • Bashash et al 2018 • Jimenez et al 2017 • Martinez et al 2016 • Rocha-Amador et al 2007 • Soto-Barreras et al 2019 • Barberio et al 2017 • Green et al 2019 • Till et al 2020 • Karimzade et al 2014 • Seraj et al 2012 • Li et al 2008 • Broadbent et al 2015 • Saeed et al 2020 <p><u>Appraisal:</u> STROBE-M tool</p>			
(Kumar et al., 2023) Systematic review USA	<p><u>Search:</u></p> <ul style="list-style-type: none"> • N=26 studies from Duan et al. (2018) systematic review up to Nov 2016 	<p><u>Source of fluoride:</u> drinking water or urinary F</p> <p><u>Exposure:</u></p>	N=33 studies included overall <u>SMD meta-analysis:</u>	Well conducted systematic review overall. Small number of studies (N=8) relevant to community water fluoridation.

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
<p>Journal Public Health</p> <p><u>Funding:</u> Funding was not sought for this project.</p> <p><u>Conflicts of Interest:</u> J.V.K. is a member of the American Dental Association's National Fluoridation Advisory Committee. He was a reviewer of the National Academies of Sciences, Engineering, and Medicine report Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Letter Report (2021). S.F.-O. is a member of the American Academy of Pediatrics' Section on Oral Health. She was a co-author of 'Fluoride Use in Caries Prevention in the Primary Care Setting' and</p>	<ul style="list-style-type: none"> N=46 studies from the National Toxicology Program (NTP) (2022) review PubMed, Google Scholar, and Mendeley (May 2020-Dec 2021) <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Population: children 1-18 years Exposure: water or urinary F Outcomes: info to calculate SMD and/or regression coefficient for change in cognition and IQ scores Study design: observational (cohort and cross-sectional) Available in English <p><u>Exclusion criteria:</u> (for assessing the effect at low fluoride levels)</p> <ul style="list-style-type: none"> Exposure >1.5 mg/l (endemic fluorosis areas) 	<ul style="list-style-type: none"> Mean water fluoride 0.90 mg/l vs. 0.30 mg/l [non-endemic areas] Mean water fluoride 3.7 mg/l vs. 0.7 mg/l [endemic areas] Urinary fluoride (children and maternal) <p><u>Outcomes:</u> IQ</p>	<p>Three studies from China and one each from India, New Zealand, Mexico, Canada and Spain.</p> <p>Quality of studies:</p> <ul style="list-style-type: none"> Probably low risk N=2 Probably high risk N=3 Definitely high risk N=3 <p>Non-endemic areas (N=8 studies)</p> <ul style="list-style-type: none"> SMD=0.07 (95%CI: -0.02 to 0.17) I²=0% <p>Endemic areas (N=23 studies)²²</p> <ul style="list-style-type: none"> SMD=-0.46 (95%CI: -0.58 to -0.35) I²=81% <p><u>Regression coefficient meta-analysis:</u> Two studies from Canada, one each from Mexico, China and Spain.</p> <p>Quality of studies:</p> <ul style="list-style-type: none"> Probably low risk N=1 Probably high risk N=3 <p>[One study not appraised for RoB]</p>	<p>Overall, a preponderance of studies with high risk of bias.</p> <p>Confounding factors in primary studies for SMD meta-analysis not reported.</p> <p><u>Quality of this systematic review:</u> Adequate search and selection criteria with appraisal of quality. Appropriate meta-analyses. Sensitivity analyses conducted of random-effects SMD and regression coefficient (Beta) estimates of child's intelligence score with higher fluoride exposure. Tested for publication bias. Generalisability and applicability to Aotearoa New Zealand good with restriction to community water fluoridation levels used here.</p> <p><u>Authors' conclusions:</u> These meta-analyses show that</p>

²² NB: studies not listed here as levels in water much greater than that used for community water fluoridation in Aotearoa New Zealand (0.7 to 1.0 mg/l)

NB2: 22 studies 'definitely high risk of bias' and one 'probably high risk of bias'

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<p>'Review of Safety, Frequency and Intervals of Preventive Fluoride Varnish Application for Children.' She consults for Arcora Foundation on medical/dental integration and has research funding for medical/dental integration from Health Resources Services Administration (HRSA) D88HP37553. She serves on an independent DSMB for a study funded by Colgate.</p>	<ul style="list-style-type: none"> Source other than water or urinary fluoride Overlapping publications <p>Studies that used dental fluorosis as exposure were also excluded, as well as studies that used different IQ and dental fluorosis measurement format than other studies</p> <p><u>Studies included:</u> SMD meta-analysis (N=8)</p> <ul style="list-style-type: none"> Xu 1994 Zhang 1998 Xiang 2003 Broadbent 2015 (child) Sebastian 2015 Bashash 2017 Green 2019 Ibarluzea 2021 <p><u>Child urinary fluoride:</u></p> <ul style="list-style-type: none"> Bashash 2017 Yu 2018 Farmus 2021 		<p><i>Child urinary fluoride:</i> Non-endemic areas (N=3 studies)</p> <ul style="list-style-type: none"> $\beta=0.16$ (95%CI: -0.40 to 0.73); $p=0.57$; $I^2=0\%$ <p><i>Maternal urinary fluoride:</i> Non-endemic areas (N=3 studies)</p> <ul style="list-style-type: none"> $\beta=-0.92$ (95%CI: -3.29 to 1.46); $p=0.45$; $I^2=72\%$ <p>Community water fluoridation (N=2)</p> <ul style="list-style-type: none"> $\beta=0.12$ (95%CI: -2.45 to 2.68) $I^2=63\%$ <p>Salt fluoridation (N=1)</p> <ul style="list-style-type: none"> $\beta=-3.15$ (95%CI:-5.43 to -0.87) $I^2=\text{not applicable}$ <p>Further regression analysis by standardizing absolute mean IQ scores from lower fluoride areas did not show a relationship between F concentration and IQ scores (Model Likelihood-ratio test: P-value = 0.34.)</p>	<p>fluoride exposure relevant to community water fluoridation is not associated with lower IQ scores in children. However, the reported association observed at higher fluoride levels in endemic areas requires further investigation.</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<p><u>Maternal urinary fluoride:</u></p> <ul style="list-style-type: none"> • Green 2019 • Ibarluzea 2021 • Bashash 2017 <p><u>Appraisal:</u> Office of Health Assessment and Translation Risk of Bias rating tool</p> <ul style="list-style-type: none"> • probably low risk (+) • probably high risk (-) • definitely high risk (--) 			
<p>(Miranda et al., 2021) Systematic review and meta-analysis Brazil/Canada</p> <p><u>Journal</u> Scientific Reports</p> <p><u>Funding:</u> This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. The funder was not involved in the design of the study, data</p>	<p><u>Search:</u> PubMed, Scopus, Web of Science, Lilacs, Cochrane and Google Scholar (Jan 2021).</p> <p>No restrictions on date or language</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • observational studies in humans (P) • exposed to high concentrations of F (E) and low concentrations (C) 	<p><u>Exposure:</u> >2mg/l fluoride in drinking water ("high" level)</p> <p><u>Comparator:</u> 0.5-1.0 mg/ml fluoride in drinking water ("low" level)</p> <p><u>Outcome:</u> neurological disorders (all IQ except one study)</p> <p>Note that IQ results have been dichotomised into "low IQ" and "normal IQ" to calculate an odds ratio. There is no description of how a "low IQ" was assigned.</p>	<p>N=27 studies included (all cross-sectional)</p> <p>Eleven studies from China, 13 from India, and 3 from Iran</p> <p><u>Risk of bias:</u></p> <ul style="list-style-type: none"> • Low N=19 • High N=8 <p><u>Findings:</u> Odds of "low IQ" significantly greater in high fluoride area (>2mg/l) compared to low fluoride area (0.5-1.0 mg/ml)</p> <ul style="list-style-type: none"> • OR=3.88 (95%CI: 2.41 to 6.23); p<0.00001; I²=77% 	<p><u>Quality of this systematic review:</u> Some concerns about appropriateness of data analysis especially how "low IQ" was ascertained. Conclusions limited by methodological quality of primary studies, high statistical heterogeneity and evidence of publication bias. In addition the cross-sectional nature of the studies precludes determination of any causal relationship. Other concerns include the variety of tools used to measure IQ and residual confounding</p>

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<p>collection, analysis, and interpretation of the data and the writing of the manuscript. The APC was funded by Pró-Reitoria de Pesquisa e Pós-graduação da Universidade Federal do Pará (PROPESP-UFPA).</p> <p><u>Conflicts of interest:</u> The authors declare no competing interests.</p>	<ul style="list-style-type: none"> • in which the associations between F and neurological damage (O) were investigated. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Case reports, descriptive studies, review articles, opinion articles, technical articles, guidelines, animal and <i>in vitro</i> studies <p><u>Studies included:</u></p> <ul style="list-style-type: none"> • Aravind 2016 • Chen 1991 • Eswar 2011 • Guo 1991 • Hong 2001 • Karimzade 2014 • Khan 2015 • Kundu 2015 • Lu 2000 • Nagarajappa 2013 • Poureslami 2011 • Qin 2008 • Raxdan 2017 • Saxena 2012 		<ul style="list-style-type: none"> • N=10 studies with total of 2,839 participants • significant publication bias • GRADE Quality of evidence: very low (downgraded due to serious imprecision) 	<p>(particularly from co-contamination of water supply by other substances and nutritional status etc.</p> <p><u>Authors' conclusions:</u> Ten studies were included on the meta-analysis, which showed IQ impairment only for individuals under high fluoride exposure considering the World Health Organization criteria, without evidences of association between low levels and any neurological disorder. However, the high heterogeneity observed compromise the final conclusions obtained by the quantitative analyses regarding such high levels. Furthermore, this association was classified as very low-level evidence. At this time, the current evidence does not allow us to state that fluoride is associated with neurological damage, indicating the need for new</p>

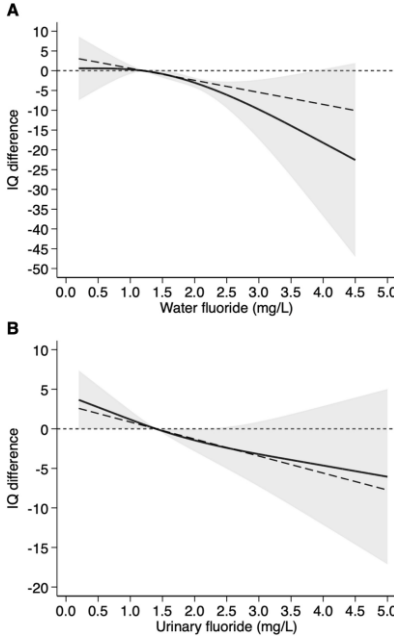
Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<ul style="list-style-type: none"> • Sebastian 2015 • Seraj 2012 • Sharma 2009 • Shivaprakash 2011 • Sudhir 2009 • Trivedi 2007 • Trived 2012 • Wang 2006, 2007, 2008 • Xiang 2003 • Yu 2018 • Zhao 1996 <p><u>Appraisal methods:</u></p> <ul style="list-style-type: none"> • Checklist of Fowkes and Fulton (low or high risk) for risk of bias • GRADE approach used for assessment of the quality of evidence overall 			<p>epidemiological studies that could provide further evidence regarding this possible association.</p>
<p>(Taher et al., 2024) Systematic review Canada Critical Reviews in Toxicology <u>Funding:</u> This work was requested by Health Canada</p>	<p><u>Search:</u> Human studies</p> <ul style="list-style-type: none"> • Updating previous SRs: Canadian Agency for Drugs and Technologies in Health (2019, 2020) and Jack B (2016) 	<p><u>Exposure:</u> fluoride at any level in drinking water (added or naturally occurring)</p> <p><u>Outcomes:</u></p> <ul style="list-style-type: none"> • Cognitive dysfunction including ADHD, dementia, Down 	<p>N=89 human studies (of which 21 concern cognitive dysfunction)</p> <p>Seven studies from China; 3 from Mexico; 2 from Canada, India, and Pakistan; one each from Indonesia, Peru, Spain, Sudan and USA.</p>	<p>Serious concerns about the conduct of this systematic review including: the validity of the risk of bias assessment using a modified tool which has likely inflated the quality assessment of studies by not taking into account the innate limitations of observational</p>

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<p>under a competitive master standing offer agreement, which includes RSI as a provider of health risk assessment services. The contract report on which this manuscript is based was completed during the period from January 2020 to March 2023.</p> <p><u>Conflicts of interest:</u> All authors who contributed to the current systematic review report no conflict of interest existed at any stage of planning or preparation for this review, as well as the drafting, critical review, and approval of the aforementioned manuscript.</p>	<ul style="list-style-type: none"> 10 bibliographic databases; 6 clinical trial registries; 18 grey literature sources and web-based materials were also examined, including relevant national and international authoritative and technical health agencies, academic dissertations, major scientific hubs, and international conference proceedings. NB: also updated systematic reviews of animal studies [NTP-National Toxicology Program (2016)] and <i>in vitro</i> studies [Health Canada (2010)] <p><u>Inclusion criteria:</u> review articles and original human studies that examined the association between exposure to fluoride in drinking water (community water fluoridation or naturally occurring) with any health risks published between 2016 and July 2021.</p>	<p>syndrome, IQ, and trouble working</p> <ul style="list-style-type: none"> Others including thyroid, kidney, and cancer 	<p><u>Cognitive dysfunction:</u></p> <ul style="list-style-type: none"> ADHD (2 studies; all high quality) Dementia (1 study; high quality) Down syndrome (no new studies) IQ reduction (17 studies; N=12 high quality; N=5 acceptable quality) trouble working (1 study; acceptable quality) <p>NB: there is a discrepancy between the number of studies stated for IQ in various places of the article</p> <p><u>Findings:</u></p> <p>ADHD</p> <ul style="list-style-type: none"> Insufficient evidence to evaluate any association <p>IQ reduction</p> <ul style="list-style-type: none"> Positive relationship <p>“Current review evidence synthesis: Based on the available literature to date, the cumulative body of evidence suggests a positive</p>	<p>studies especially cross-sectional studies. Other concerns are the external validity of the included studies especially the levels of fluoride in drinking water being above that used for water fluoridation in Aotearoa New Zealand. In addition, six IQ studies are missing from relevant tables and parts of the text. Moreover, the authors appear to be not always correctly reporting the exact nuanced findings of some studies in detail.</p> <p><u>Quality:</u> Some serious concerns regarding the conduct of this review (see above) and concerns that the aim of this review is not correctly aligned with the aim of this evidence review.</p> <p><u>Authors' conclusions:</u> The evidence supports a conclusion that fluoride exposure reduces IQ levels in children at concentrations</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<p><u>Exclusion criteria:</u> studies that examined other fluoride formulations or mixtures, assessed dental outcomes other than dental fluorosis, reported irrelevant assessments (e.g. hazard quotient), or published in a non-Latin language, as well as study types such as commentaries, editorials, case reports, case series, books and general informational materials</p> <p><u>Studies included:</u></p> <p>NB: human studies (IQ)</p> <ul style="list-style-type: none"> • Ahmad et al. (2022) • Bashash et al. (2017) • Cui et al. (2018) • Cui et al. (2020) • Farmus et al. (2021) • Feng et al. (2022) • Goodman et al. (2022) • Heck (2016) • Ibarluzea et al. (2022) • Kaur et al. (2022) • Kousik and Mondal (2016) • Mustafa et al. (2018) • Saeed et al. (2022) 		<p>association of reduced IQ scores for children and fluoride exposures relevant to current North American drinking water levels.”</p>	<p>close to those seen in North American drinking water, although there is some uncertainty in the weight of evidence for causality and considerable uncertainty in the point of departure.</p>

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	<ul style="list-style-type: none"> • Soto-Barreras et al. (2019) • Till et al. (2020) • Wang et al. (2020) • Wang et al. (2021) • Yani et al. (2021) • Yu et al. (2018) • Yu et al. (2021) • Zhao et al. (2021) <p><u>Appraisal methods:</u> risk of bias assessed with a modified OHAT risk of bias tool</p> <ul style="list-style-type: none"> • high quality (1) • acceptable quality (2) • low quality (3) 			
<p>(Veneri et al., 2023) Systematic review USA/Italy</p> <p><u>Funding:</u> This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.</p>	<p><u>Search:</u> PubMed/MEDLINE, Web of Science, and Embase (inception up to December 30, 2022)</p> <p>No language or date restrictions were applied.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • (P) children ≤18 years of age 	<p><u>Exposure:</u></p> <ul style="list-style-type: none"> • fluoride in drinking water (0.13 to 5.55 mg/l) • urinary fluoride (0.16 to 7 mg/l) • hair/nail fluoride (6.9 and 27.8 µg/g, and 8.3 and 57 µg/g respectively) • serum fluoride (0.04 to 0.18 mg/l) <p><u>Comparator:</u></p>	<p>N=33 studies (N=30 in meta-analysis)</p> <p>N=29 cross-sectional studies and N=4 cohort</p> <p>Total population of 12,263 children were enrolled in 7 countries (China N=15, India N=7, Canada N=2, Iran N=4, Mexico N=3, Pakistan N=1, New Zealand N=1).</p>	<p>Serious concerns regarding the appropriateness of conducting a meta-analysis of highly heterogeneous studies (particularly in terms of fluoride level comparisons and exposure source) and the external validity of said studies. Statistical heterogeneity was extremely high for all meta-analyses with little exploration of the reasons for this. In addition, many studies had a</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
<p><u>Conflicts of interest:</u> The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.</p>	<ul style="list-style-type: none"> • (E) early or prenatal fluoride exposure from any source (e.g. water, dietary, and supplemental intake, topical dental products) or evaluating a biomarker of exposure (e.g. urinary, bone, hair fluoride) • (C) exposure to any lower dose of fluoride • (O) neurodevelopmental function • (S) observational studies and clinical trials <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • conference proceedings, abstracts, letters to the editor, commentaries, case reports, reviews, and meta-analysis • exposure to fluoride from coal-burning or volcanic eruptions • specific populations, such as children born preterm and institutionalized children 	<ul style="list-style-type: none"> • any lower dose of fluoride <p><u>Outcome:</u></p>	<p><u>Risk of bias:</u></p> <ul style="list-style-type: none"> • High in 11 studies • Moderate in 19 studies • Low in 3 studies <p>NB: main source of high RoB was lack of adjustment for potential confounders (N=11) as well as potential selection bias (selected based on fluoride exposure N=25)</p> <p><u>Findings:</u></p> <p>Mean difference (MD) in IQ scores (highest vs. lowest F level)</p> <ul style="list-style-type: none"> • All F sources: -4.68 (95% CI: - 6.45 to - 2.92) $I^2 = 98.75\%$ • Water F: -5.60 (95% CI: -7.76 to -3.44) $I^2 = 91.69\%$ • Urinary F: -3.84 (95% CI: -7.93 to 0.24) $I^2 = 96.22\%$ 	<p>high risk of bias mainly due to lack of controlling for important confounders e.g., nutrition status (maternal and child), co-contaminants (e.g., lead, arsenic), education levels of parents, birth weight, income, presence of iron and/or iodine deficiency, alcohol and substance use, and comorbidities, among others.</p> <p>Note the dose-response curves with no effect on IQ for drinking water fluoride levels below about 1.25 mg/l and urinary fluoride levels below about 1.5mg/l.</p> <p><u>Quality:</u> Some serious concerns regarding the conduct of this review (see above), particularly the appropriateness of conducting a meta-analysis in the presence of significant statistical heterogeneity and risk of residual confounding.</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<ul style="list-style-type: none"> • specific health conditions including autism, Down's syndrome, attention-deficit/hyperactivity disorder (ADHD) or other behavioral issues, anxiety, and depression <p><u>Studies included:</u></p> <ul style="list-style-type: none"> • Ahmad et al., 2022 • Aravind et al., 2016 • Bashash et al., 2017 • Broadbent et al., 2015 • Chen et al., 2008 • Das and Mondal, 2016 • Ding et al., 2011 • Eswar et al., 2011 • Farmus et al., 2021 • Feng et al., 2022 • Goodman et al., 2022 • Hong et al., 2008 • Karimzade et al., 2014 • Li et al., 1995 • Li et al., 2008 • Lu et al., 2000 • Poureslami et al., 2011 • Rocha-Amador et al., 2007 		<p><u>Dose-response analysis:</u></p>  <p>Fig. 5. Dose-response splines of intelligence (IQ score) and exposure to fluoride from drinking water (A) and urinary fluoride (B). Spline curve (black solid line) with 95% confidence limits (grey area), linear relation (black dotted line). Median values used as reference: 1.2 mg/L for drinking</p>	<p><u>Authors' conclusions:</u> In conclusion, we found an overall indication of dose-dependent adverse effects of fluoride on children's cognitive neurodevelopment, starting at rather low exposure. However, the limitations of most studies included in this meta-analysis, with particular reference to the risk of residual confounding, raise uncertainties about both the causal nature of such relation and the exact thresholds of exposure involved.</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<ul style="list-style-type: none"> • Saxena et al., 2012 • Sebastian and Sunitha, 2015 • Seraj et al., 2012 • Seraj et al., 2007 • Shivaprakash et al., 2011 • Till et al., 2020 • Trivedi et al., 2007 • Wang et al., 2008 • Wang et al., 2021 • Wang et al., 2007 • Xiang et al., 2003 • Xiang et al., 2011 • Yu et al., 2021 • Zhang et al., 2015 • Zhao et al., 1996 <p><u>Appraisal methods:</u> ROBINS-E tool</p>		<p>water fluoride and 1.4 mg/L for urinary fluoride, respectively.</p>	

Appendix 5: Evidence table of included primary studies for neurodevelopmental outcomes

Author/year Study design/Country Funding Conflicts of interest	Participants Inclusion/exclusion criteria Characteristics	Exposure Outcome measures Confounders	Results	Comments Quality Authors' conclusions
<p>(Dewey et al., 2023) Ecological study Canada</p> <p>Journal: Science of the Total Environment</p> <p><u>Funding:</u> Dewey, Giesbrecht, Letourneau, APrON Study Team</p>	<p>n=616 maternal-child pairs enrolled in the Calgary cohort of the Alberta Pregnancy Outcomes and Nutrition (APrON) study between 2009 and 2012.</p> <p>Water fluoride level = 0.7mg/l</p> <p>On May 19, 2011, Calgary, Canada stopped fluoridating its drinking water. The background fluoride level in the Calgary water source is reported to be 0.1 – 0.4 mg/L²³</p> <p><u>Eligibility criteria:</u></p>	<p><u>Exposures:</u></p> <p>n=295 fully exposed to fluoridated drinking water throughout pregnancy²⁴</p> <p>n=220 exposed during part of pregnancy²⁵</p> <p>n=101 not exposed during pregnancy²⁶</p> <p><u>Outcome measures:</u></p> <p><u>IQ:</u></p>	<p><u>IQ:</u></p> <ul style="list-style-type: none"> no association between exposure group and full IQ for boys or girls. <p><u>Executive Function</u></p> <p><u>Working Memory</u></p> <ul style="list-style-type: none"> No associations were noted for the overall group. Sex-stratified analyses also revealed no associations. <p><u>Inhibitory Control</u></p> <ul style="list-style-type: none"> Full exposure vs. no exposure was associated with reduced Gift Delay 	<p><u>Quality:</u> innate risk of bias due to observational cross sectional study design. Adjusted for smoking but not for alcohol use, preterm birth or maternal diabetes²⁷</p> <p>Removal of children with low birthweight altered the magnitude of some associations, but no details provided.</p> <p><u>Authors' conclusions:</u> "...no associations were found between exposure to</p>

²³ The article referenced does not provide a valid link to the background fluoride concentration. Naturally occurring fluoride levels reported as 0.1 – 0.4 mg/L from the Calgary Water Supply Authority. <https://www.calgary.ca/water/drinking-water/fluoride.html#:~:text=Fluoride%20naturally%20occurs%20in%20the,0.1%20and%200.4%20mg%2FL>.

²⁴ Includes women who gave birth prior to cessation of CWF on 19 May 2011.

²⁵ Includes women who gave birth from 19th May 2011 to 13 May 2012.

²⁶ Includes women who gave birth after May 13, 2012

Author/year Study design/Country Funding Conflicts of interest	Participants Inclusion/exclusion criteria Characteristics	Exposure Outcome measures Confounders	Results	Comments Quality Authors' conclusions
<p><u>Conflicts of interest:</u> The authors have no conflicts of interest to declare.</p>	<p>Women were eligible if they could communicate in English, were <27 weeks gestational age and were ≥16 years of age.</p> <p>A subset of 616 maternal-child pairs from Calgary whose children participated in cognitive and executive function assessments at 3 to 5 years of age (M = 4.24 SD = 0.51)</p> <p><u>Characteristics:</u></p> <ul style="list-style-type: none"> • Significant differences in the rate of maternal smoking during pregnancy and the proportion of mothers born in Canada. 51.3% were boys • 71.29% not exposed born in Canada compared to 83.64% partially exposed and 84.75% fully exposed 	<p>Canadian Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV^{CDN}).</p> <p><u>Executive functions:</u> Working memory - WPPSI-IVCDN Working Memory Index.</p> <p><u>Inhibitory control</u> Gift Delay, NEPSY-II Statue subtest.</p> <p><u>Cognitive flexibility</u> Boy-Girl Stroop, Dimensional Change Card Sort (DCCS).</p>	<p>(B = 0.53, 95 % CI = 0.31, 0.93).</p> <ul style="list-style-type: none"> • Sex-stratified models showed that girls in the fully exposed group (AOR =0.30, 95 % CI = 0.13, 0.74) displayed lower odd of passing the Gift Delay compared to girls in the not exposed group. • No associations were found between exposure group and children's scores for the NEPSY-II Statue subtest. <p><u>Cognitive Flexibility</u> For the DCCS, no associations were found between fluoride exposure group and odds of passing the DCCS in the overall group or for boys. Girls in the fully (AOR = 0.34, 95 % CI = 0.14, 0.88) and partially exposed groups (AOR =0.29 95 % CI = 0.12, 0.73) were approximately one third less likely to pass the DCCS compared to girls in the not exposed group.</p>	<p>drinking water from a community water supply fluoridated at 0.7 mg/L throughout pregnancy and measures of intelligence at 3–5 years of age.”</p> <p>Maternal exposure to drinking water throughout pregnancy fluoridated at the level of 0.7 mg/L was associated with poorer inhibitory control and cognitive flexibility, particularly in girls, suggesting a possible need to reduce maternal fluoride exposure during pregnancy.</p>

Author/year Study design/Country Funding Conflicts of interest	Participants Inclusion/exclusion criteria Characteristics	Exposure Outcome measures Confounders	Results	Comments Quality Authors' conclusions
			No associations were found between fluoride exposure group and scores on Boy-Girl Stroop.	
<p>(Do et al., 2023) Cohort Australia/UK</p> <p><u>Funding:</u> The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The follow-up study was funded by a National Health and Medical Research Council Project Grant APP1161581.</p> <p><u>Conflicts of interest:</u> The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.</p>	<p>Data is from Australia's National Child Oral Health Study (NCOHS) 2012–14 (total participants with both questionnaire and oral exam data n=24,664)</p> <p>n=15,793 participants included as they were <18 years old in 2018-19</p>	<p><u>Exposure:</u> individual-level percentage of lifetime exposure to fluoridated water from birth to age 5 years (%LEFW)</p> <ul style="list-style-type: none"> • 0% LEFW • >0% to <100% LEFW • 100% LEFW <p><u>Outcome measures:</u></p> <ul style="list-style-type: none"> • Strength and Difficulties Questionnaire Total Difficulties Score (SDQ TDS) • Behavior Rating Inventory of Executive Function Global Executive Composite (BRIEF GEC) <p>Note SDQ TDS 16+ and BRIEF GEC 65+ indicate clinically significant mental health</p>	<p>n=2,682 completed the SDQ and BRIEF</p> <p>Note retention rates were higher in 100% LEFW, parents with tertiary education, and high income households</p> <p><u>Multivariable regression model results:</u></p> <ul style="list-style-type: none"> • comparable SDQ TDS and BRIEF GEC scores for 0% LEFW vs. 100% LEFW • higher prevalence rate (PR) of SDQ TDS 16+ and BRIEF GEC 65+²⁸ in the 0% LEFW compared to 100% LEFW • mean scores of SDQ TDS and BRIEF GEC were associated with household income, Indigenous identity, and neurodevelopmental diagnosis 	<p><u>Quality:</u> Probable low risk of bias due to representative sampling, and good coverage of actual and potential confounders. Good exposure and outcome measures.</p> <p><u>Authors' conclusions:</u> This nationwide population-based follow-up study has provided consistent evidence that exposure to fluoridated water by young children was not negatively associated with child emotional, behavioral development, and executive functioning in their adolescent years. Children who had been exposed to fluoridated water for their whole early childhood had their measures of emotional, behavioral development, and executive functioning at least</p>

²⁸ not statistically significant

Author/year Study design/Country Funding Conflicts of interest	Participants Inclusion/exclusion criteria Characteristics	Exposure Outcome measures Confounders	Results	Comments Quality Authors' conclusions
		<p>issues and greater level of executive dysfunction</p> <p><u>Confounders measured:</u></p> <ul style="list-style-type: none"> • child's age at follow-up • sex • Indigenous identity • household income • parental education • country of birth • area-level remoteness status • neurodevelopmental diagnosis • breastfeeding • toothbrushing with fluoride toothpaste in early childhood 	<ul style="list-style-type: none"> • prevalence of SDQ16+ and GEC65+ was also associated with those factors as well as with parental education 	<p>equivalent to that of children who had no exposure to fluoridated water.</p>
<p>(Ibarluzea et al., 2023)</p> <p>Cohort</p> <p>Spain/UK</p> <p><u>Funding:</u> This study was funded by grants from Instituto de Salud Carlos III, CIBERESP, Department of Health of the Basque, the</p>	<p>Data from the Spanish for Environment and Childhood: INfancia y Medio Ambiente (INMA) mother-infant cohort.</p> <p>n=255 and 236 mother-child pairs for 8 years and 11 years follow-up, respectively had both ADHD outcome measures and maternal urinary fluoride data</p>	<p><u>Exposures:</u></p> <ul style="list-style-type: none"> • Maternal urinary fluoride (creatinine adjusted) • Drinking water <p><u>Outcome measures:</u></p> <p>Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S).</p>	<p><u>Fluoride exposures:</u></p> <ul style="list-style-type: none"> • Mean maternal urine 0.62 and 0.64mg/g for 8 year and 11 year follow-up • similar mean values for 8 year and 11 year follow-up for each zone and type of drinking water 	<p><u>Quality:</u> Probable low risk of bias due to cohort design, extensive consideration of potential confounders (including alcohol) and sensitivity analysis. Good exposure and outcome measures.</p>

Author/year Study design/Country Funding Conflicts of interest	Participants Inclusion/exclusion criteria Characteristics	Exposure Outcome measures Confounders	Results	Comments Quality Authors' conclusions
<p>Provincial Government of Gipuzkoa and annual agreements with the municipalities of the study area</p> <p><u>Conflicts of Interest:</u> The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.</p>	<p><u>Inclusion criteria for the INMA cohort:</u></p> <ul style="list-style-type: none"> maternal age \geq 16 years old, singleton pregnancy, recruitment during the first antenatal visit, pregnancy achieved without assisted reproduction techniques, planned to give birth in the referral hospital and no communication problems in Spanish or Basque <p><u>Selection criteria for this study (subsample of INMA cohort):</u></p> <ul style="list-style-type: none"> children with data on neuropsychological assessment at 8 or 11 year of age mothers with data on maternal urinary F level adjusted for creatinine (MUFcr) at the first and third trimesters <p><u>Characteristics:</u></p> <ul style="list-style-type: none"> mean birth age: 31 years 	<p><u>Confounders measured:</u></p> <ul style="list-style-type: none"> maternal age, social class, education, BMI, birth country, smoking, alcohol, drinking water source and amount, maternal IQ, breastfeeding infant sex, birth order, premature birth, small for gestational age, daycare attendance family context: Haezi-Etxadi Scale (HES) maternal urine: arsenic, manganese umbilical blood: mercury, lead 	<p><u>Cognitive outcomes at 8 and 11 years:</u></p> <p>Probable cognitive problems/inattention</p> <ul style="list-style-type: none"> 9.8% and 6.8%, respectively <p>Probable Hyperactivity-Impulsivity</p> <ul style="list-style-type: none"> 9.8% and 8.5% <p>Probable ADHD</p> <ul style="list-style-type: none"> 6.7% and 5.5% <p><u>Association between F exposure and ADHD scores:</u></p> <p>Non-significant associations were observed between MUFcr levels and cognitive outcomes at age 8 years</p> <p>Significant reduction in risk of probable cognitive problems/inattention scores at 11 years of age for maternal urinary fluoride levels at 32 weeks gestation and all of pregnancy. All other associations non-significant.</p> <p><u>Sensitivity analysis:</u></p> <p>Analysis including neurotoxicants, family context, alcohol, and community water fluoridation did</p>	<p><u>Authors' conclusions:</u> Higher levels of MUFcr in pregnant women were associated with a lower risk of cognitive problems-inattention at 11 years. These findings are inconsistent with those from previous studies and indicate the need for other population-based studies to confirm or overturn these results.</p>

Author/year Study design/Country Funding Conflicts of interest	Participants Inclusion/exclusion criteria Characteristics	Exposure Outcome measures Confounders	Results	Comments Quality Authors' conclusions
	<ul style="list-style-type: none"> • pre-pregnancy BMI 22.8-23 kg/m² • 58.9–60.0% nulliparous • 49.3–51.7% uni degree • 59.6–59.7% non-manual social class • 9% smoked in pregnancy • infants: 49.8% and 54.2% were females, 2.7% and 2.5% were preterm and 7.8% and 8.0% were small for gestational age. <p>No significant differences between the follow-ups, with the exception to the zone of residence (fluoridated vs non-fluoridated), type of drinking water consumed, parity and order between brother/sister at the age of 8.</p>		not change the overall picture or the ORs substantially	
<p>(Krzeczkowski et al., 2024) Cohort Canada</p> <p><u>Funding:</u> This research was funded by the National Institute of Environmental Health Science, grant number R01ES030365, 2020-2025. The</p>	<p>A subsample of 525 mothers were invited to participate in the MIREC infant development (MIREC-ID) follow-up study, which involved the assessment of infant health at 6-months of age.</p> <p>90 (16.8 %) did not complete the visual assessment. Another six (1.1</p>	<p><u>Exposures:</u></p> <ul style="list-style-type: none"> • fluoride concentration in drinking water (mg/L) • maternal urinary fluoride adjusted for specific gravity (MUFSG; mg/L) and averaged across pregnancy 	<p><u>Fluoride exposure:</u></p> <ul style="list-style-type: none"> • Median water fluoride (n=337) 0.2 mg/l • Median daily fluoride intake (n=280) 4.82µg/kg/day • Median maternal urinary fluoride (n=424) 0.44 mg/l 	<p>Water fluoride and daily intake associated with reduced TAC score and RMSSD. Unclear whether these reductions are clinically relevant. Retesting at other ages would give more meaningful data i.e., whether the visual acuity changes.</p>

Author/year Study design/Country Funding Conflicts of interest	Participants Inclusion/exclusion criteria Characteristics	Exposure Outcome measures Confounders	Results	Comments Quality Authors' conclusions
<p>Maternal-Infant Research on Environmental Chemicals Study was funded by the Chemicals Management Plan at Health Canada, the Ontario Ministry of the Environment, and the Canadian Institutes for Health Research (grant MOP-81285). The funding source had no involvement in any aspect of the study.</p> <p><u>Conflicts of interest:</u> The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Disclosure: Dr. Lanphear (co-author) served as a non-retained expert witness in the federal fluoride case to describe the results of the fluoride studies using the MIREC cohort (Food & Water Watch, et al. vs. U.S. Environmental Protection</p>	<p>%) were excluded due to suspected ocular abnormality, including congenital cataract or retinoblastoma.</p> <p><u>Final sample:</u> n=429 had visual acuity data and n=390 had heart rate variability (HRV) data</p> <p><u>Eligibility criteria:</u> infant was born from a singleton pregnancy and was free of birth defects and/or neurological disorders</p> <p><u>Characteristics:</u></p> <ul style="list-style-type: none"> mothers mean age 31.6 years; 94.6% married; 66.1% bachelor's degree +; 91.3% white infants mean age 6.81 months; 48% female; 5.2% <37 weeks gestation; 6.1% low birth weight; mean TAC score 5.75 cpd; RMSSD 15.25 and SDNN 39.10 	<ul style="list-style-type: none"> maternal fluoride intake ($\mu\text{g}/\text{kg}/\text{day}$) from consumption of water, tea, and coffee, adjusted for maternal body weight (kg). <p><u>Outcome measures:</u></p> <ul style="list-style-type: none"> Teller Acuity Cards II (TAC-II) ECG: RMSSD²⁹ and SNDD³⁰ <p><u>Confounders measured:</u></p> <ul style="list-style-type: none"> infant age at testing (months), birthweight (g), sex, maternal age (years), pre-pregnancy BMI, smoking in trimester 1 (never, former, quit during pregnancy/current), education, 	<p><u>Visual acuity:</u> (adjusted)</p> <ul style="list-style-type: none"> water F $\beta = -1.51$; 95 % CI: $-2.14, -0.88$, $p < 0.001$). maternal F intake $\beta = -0.82$; 95 % CI: $-1.35, -0.29$, $p = 0.003$). maternal urinary F $\beta = 0.11$; 95 % CI: $-0.30, 0.51$, $p = 0.60$). <p><u>Heart rate variability:</u> (adjusted)</p> <p>RMSSD</p> <ul style="list-style-type: none"> water F $\beta = -1.60$; 95 % CI: $-2.74, -0.46$, $p = 0.006$). maternal F intake $\beta = -1.22$; 95 % CI: $-2.15, -0.30$, $p = 0.01$). maternal urinary F $\beta = 0.22$; 95 % CI: $-0.47, 0.92$, $p = 0.53$). <p>SNDD</p> <ul style="list-style-type: none"> water F $\beta = -1.31$, 95 % CI: $-4.70, 2.09$, $p = 0.45$ 	<p>Authors conclusions overstated.</p> <p><u>Quality:</u> Unclear risk of bias due to potential residual confounding and uncertain meaningful difference in outcome measures (visual acuity and HRV) at 6 months</p> <p><u>Authors' conclusions:</u> Fluoride in drinking water was associated with reduced visual acuity and alterations in cardiac autonomic function in infancy, adding to the growing body of evidence suggesting fluoride's developmental neurotoxicity.</p>

²⁹ root mean square of successive differences

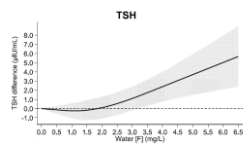
³⁰ standard deviation of N-N intervals

Author/year Study design/Country Funding Conflicts of interest	Participants Inclusion/exclusion criteria Characteristics	Exposure Outcome measures Confounders	Results	Comments Quality Authors' conclusions
<p>Agency, United States District Court for the Northern District of California at San Francisco. He received no payment for his service. All authors report no conflict of interest.].</p>	<p>Compared to full MIREC sample (n=1,983) there were some differences in the sub-sample</p> <ul style="list-style-type: none"> • less smokers, more likely white and greater gestational age in those with maternal urine fluoride, all confounders and visual acuity data • less likely income >\$100,000 in those with visual acuity data • less likely married in those with HRV data • mothers more likely married, white, higher birthweight infants in those with both infant outcomes • higher birthweight in infants born in fluoridated areas 	<ul style="list-style-type: none"> • race (white vs. other), • birth country (Canada vs elsewhere), • parity, • family income, • marital status, • self-reported ratings of warmth/affection 	<ul style="list-style-type: none"> • maternal F intake $\beta = -2.13$, 95 % CI: $-4.98, 0.72$, $p = 0.14$) • maternal urinary $\beta = 0.10$, 95 % CI: $-0.20, 2.20$, $p = 0.92$; <p>No significant interaction by sex except for water F in boys and RMSSD</p>	

Appendix 6: Evidence table for thyroid function

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
<p>(Iamandii et al., 2024) Systematic review Italy/USA/Netherlands/Denmark/Iceland</p> <p><u>Funding:</u> This study did not receive any specific funding.</p> <p><u>Conflicts of Interest:</u> The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.</p>	<p><u>Search:</u> PubMed/MEDLINE, Web of Science, and Embase from inception up to November 15, 2023</p> <p><u>Inclusion criteria:</u> (P) population of any age; (E) assessment of long-term fluoride exposure through drinking water or diet, and/or assessment of biomarkers of exposure (urinary or serum fluoride); (C) comparison of at least two categories of fluoride exposure; (O) biomarkers of thyroid function (e.g., TSH, T4, T3 hormones), thyroid disease risk (e.g., hypothyroidism, goitre) or thyroid volume as endpoints in (S) both nonexperimental (observational) or experimental (clinical trial) study design.</p> <p><u>Exclusion criteria:</u> studies that did not present original data</p>	<p><u>Exposure:</u> Highest fluoride exposure of any type (water, toothpaste, diet and/or urinary or serum fluoride)</p> <p><u>Comparator:</u> Lowest fluoride exposure in cohort or no exposure</p> <p><u>Outcome:</u> thyroid function (e.g., TSH, T4, T3 hormones), thyroid disease risk (e.g., hypothyroidism, goitre) or thyroid volume</p>	<p>N=33 studies included (1 cohort, 5 case control, 27 cross-sectional)</p> <p>Three studies from Europe, 3 in Africa, 2 in Canada, 25 from Asia (including 8 in China and 10 in India)</p> <p><u>Risk of bias of studies:</u> Very high N=5 High N=10 Some concerns N=17 Low N=1</p> <p><u>Findings:</u> Thyroid function: TSH (thyroid stimulating hormone) Mean difference (MD) in TSH for highest fluoride level compared to lowest level in children (6-18 years)</p>	<p>Significant statistical heterogeneity without investigation is concerning. Highest fluoride levels vs. lowest fluoride for each included study concerning as not comparing like with like.</p> <p><u>Quality of this systematic review:</u> Adequate search and selection criteria, with risk of bias assessment with validated tool. Very high statistical heterogeneity with very little explanation/investigation for the sources. Concerns about using highest vs. lowest fluoride level in each primary study which are not the same. Sensitivity analysis with removal of studies with a 'high' and/or "very high" risk of bias.</p> <p><u>Authors' conclusions:</u> "...we found a clear pattern of</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<p>(e.g., review articles, editorials, comments, or guidelines) or were written in languages other than English</p> <p><u>Studies included:</u></p> <ul style="list-style-type: none"> • Ahmed et al., 2022; • Andezhath et al., 2005; • Bachinsky et al., 1985; • Barberio et al., 2017; • Cui et al., 2020; • Day and Powell-Jackson, 1972; • Du et al., 2021; • Eltom et al., 1984; • Hall et al., 2023; • Hong et al., 2008; • Jooste et al., 1999; • Karademir et al., 2011; • Khandare et al., 2017, 2018; • Kheradpisheh et al., 2018; • Kumar et al., 2018; • Kutlucan et al., 2013; • Lathman and Grech, 1967; • Michael et al., 1996; • Peckham et al., 2015; • Siddiqui, 1960; 		<ul style="list-style-type: none"> • Water fluoride (N=13 studies) MD=1.17 µIU/ml I²=99.84% • Urinary fluoride (N=15 studies) MD=0.97 µIU/ml I²=99.57% • Serum fluoride (N=8 studies) MD=1.46 µIU/ml I²=98.83% • MD are 1.06, 0.52 and 1.09 µIU/ml, respectively when very high and high risk of bias studies are removed <p>T4 total (children)</p> <ul style="list-style-type: none"> • Water (N=6) MD=0.63 µg/dl • Urinary (N=7) MD=-0.05 µg/dl • Serum (N=2) MD=-0.01 µg/dl • all I²>96% 	<p>association between fluoride content in drinking water consumed by the study participants and their circulating TSH concentrations. However, this occurred only above 2 mg/L of water fluoride (2.5 mg/L when the studies with the best quality were considered), thus confirming the hypothesis of a non-linear, dose-dependent pattern of association,..."</p>

Author/year Study design/Country Funding Conflicts of interest	Search methods Inclusion/exclusion criteria Studies included Appraisal method	Exposure Comparator Outcome	Results	Comments Quality Authors' conclusions
	<ul style="list-style-type: none"> • Szczuko et al., 2019; • Wang et al., 2020, 2022; • Xu et al., 2022; • Yang et al., 2008; • Yasmin et al., 2013; • Zhang et al., 2015 • Hosur et al., 2012; • Shaik et al., 2019; • Singh et al., 2014; <p>Zulfiqar et al., 2019, 2020</p> <p>Appraisal: ROBINS-E tool</p>		<p>Other outcomes: T3-free, T3-total, T4-free, goitre, hypothyroidism – see full text.</p> <p>Dose-response meta-analysis:</p> 	

Appendix 7: Search Strategies

Appendix 7a: Search Strategy systematic reviews of benefit

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to April 19, 2024>, adapted for Embase, Cochrane, Scopus

Search Strategy:

- 1 Meta-Analysis as Topic/
- 2 meta analy*.ab,ti.
- 3 metaanaly*.ab,ti.
- 4 Meta-Analysis/
- 5 (systematic adj (review\$1 or overview\$1)).ab,ti.
- 6 1 or 2 or 3 or 4 or 5
- 7 Fluoridation/
- 8 exp Fluorides/
- 9 Fluorine/
- 10 (fluorid\$ or fluorin\$ or flurin\$ or flurid\$).mp.
- 11 7 or 8 or 9 or 10
- 12 Water supply/
- 13 water\$.mp.
- 14 12 or 13
- 15 11 and 14
- 16 6 and 15
- 17 exp TOOTH DEMINERALIZATION/
- 18 (caries or carious).mp.
- 19 (teeth adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 20 (tooth adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 21 (dental adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 22 (enamel adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 23 (dentin\$ adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 24 (root\$ adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 25 Dental plaque/
- 26 ((teeth or tooth or dental or enamel or dentin) and plaque).mp.
- 27 exp DENTAL HEALTH SURVEYS/
- 28 ("DMF Index" or "Dental Plaque Index").mp.

29 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30 16 and 29

31 limit 30 to (english language and yr="2018 -Current")

Medline = 34

Embase = 24

Scopus = 25

Cochrane = 2

Total = 85

Total After Duplication and False Drops Removed by Librarian = 26

Appendix 7b: Randomised trials and Observational Studies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to April 19, 2024>

Search Strategy:

- 1 Epidemiologic Studies/
- 2 exp case-control studies/
- 3 exp cohort studies/
- 4 cross-sectional studies/
- 5 (epidemiologic adj (study or studies)).ab,ti.
- 6 case control.ab,ti.
- 7 (cohort adj (study or studies)).ab,ti.
- 8 cross-sectional.ab,ti.
- 9 cohort analy*.ab,ti.
- 10 (follow up adj (study or studies)).ab,ti.
- 11 longitudinal.ab,ti.
- 12 retrospective.ab,ti.
- 13 prospective.ab,ti.
- 14 (observ\$ adj3 (study or studies)).ab,ti.
- 15 adverse effect*.ab,ti.
- 16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
- 17 Randomized Controlled Trials as Topic/
- 18 randomized controlled trial/
- 19 Random Allocation/
- 20 Double Blind Method/
- 21 Single Blind Method/
- 22 controlled clinical trial.pt.
- 23 randomized controlled trial.pt.
- 24 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).ab,ti.
- 25 randomly allocated.mp.
- 26 (allocat* adj2 random*).mp.
- 27 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
- 28 16 or 27
- 29 exp TOOTH DEMINERALIZATION/
- 30 (caries or carious).mp.
- 31 (teeth adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 32 (tooth adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 33 (dental adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 34 (enamel adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 35 (dentin\$ adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 36 (root\$ adj5 (cavit\$ or caries\$ or carious or decay\$ or lesion\$ or deminerali\$ or reminerali\$)).mp.
- 37 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
- 38 28 and 37

- 39** Fluoridation/
40 exp Fluorides/
41 Fluorine/
42 (fluorid\$ or fluorin\$ or flurin\$ or flurid\$).mp.
43 39 or 40 or 41 or 42
44 38 and 43
45 Water supply/ or water*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
46 44 and 45
47 limit 46 to (english language and yr="2018 -Current")
-

Medline = 182

Embase = 100

Scopus = 112

Cochrane = 39

Total= 433

Total after duplicates and obvious false drops removed by librarian=59

Appendix 7c: Search strategy for neurodevelopmental outcomes

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to March 15, 2024>

Search Strategy:

- 1 exp case-control studies/
 - 2 exp cohort studies/
 - 3 case control.ab,ti.
 - 4 (cohort adj (study or studies)).ab,ti.
 - 5 Longitudinal Studies/
 - 6 longitudinal.ab,ti.
 - 7 retrospective.ab,ti.
 - 8 prospective.ab,ti.
 - 9 Randomized Controlled Trials as Topic/
 - 10 randomized controlled trial/
 - 11 Random Allocation/
 - 12 Double Blind Method/
 - 13 Single Blind Method/
 - 14 controlled clinical trial.pt.
 - 15 randomized controlled trial.pt.
 - 16 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).ab,ti.
 - 17 randomly allocated.mp.
 - 18 (allocat* adj2 random*).mp.
 - 19 Meta-Analysis as Topic/
 - 20 meta analy*.ab,ti.
 - 21 metaanaly*.ab,ti.
 - 22 Meta-Analysis/
 - 23 (systematic adj (review\$1 or overview\$1)).ab,ti.
 - 24 Retrospective Studies/
 - 25 Prospective Studies/
 - 26 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
 - 27 fluoridation/
 - 28 exp Fluorides/ or fluorid*.mp.
 - 29 Fluoride Poisoning/ or Fluorosis, Dental/ or fluorosis.mp.
 - 30 27 or 28 or 29
 - 31 26 and 30
 - 32 neurobehavioral.mp. or Neurobehavioral Manifestations/
 - 33 Prenatal Exposure Delayed Effects/ or neurobehavioural.mp.
 - 34 Intelligence/ or intelligence or "executive function"
 - 35 iq.mp.
 - 36 exp Neurodevelopmental Disorders/ or neurodevelop*.mp. or exp Intellectual Disability/
 - 37 neurocognitive.mp. or exp Neurocognitive Disorders/
 - 38 exp Neurotoxicity Syndromes/ or neurotoxic*.mp.
 - 39 exp Cognition Disorders/ or Cognition/ or Cognitive Dysfunction/ or cognit*.mp.
 - 40 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
 - 41 31 and 40
 - 42 limit 41 to yr="2014 -Current"
-

Medline = 84
Embase = 119
Cochrane = 33
Scopus=91
Total after removal of duplicates and false drops = 43

Appendix 8: Referenced articles in NHNZ pleading

The following articles have been cited by NHNZ in their submission on community water fluoridation. The reviewers have identified and considered all references cited by NHNZ. Many of the references are out of scope, as they were published prior to the OPMCSA 2021 update.

McDonagh, M. S., et al. (2000). "Systematic review of water fluoridation." *BMJ* 321(7265): 855-859.

Iheozor-Ejiofor, Z., et al. (2015). "Water fluoridation for the prevention of dental caries." *Cochrane Database of Systematic Reviews*(6).

Age 5 and Year 8 oral health data from the Community Oral Health Service. Ministry of Health. <https://www.health.govt.nz/nz-health-statistics/health-statistics-and-data-sets/oral-health-data-and-stats/age-5-and-year-8-oral-health-data-community-oral-health-service>

Schluter P.J and 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 Feb 18;16:21.

"Draft NTP Monograph on the State of the Science Concerning Fluoride Exposure and neurodevelopmental and Cognitive health Effects: A systematic Review 2022."

Bashash et al. 2017; "Prenatal Fluoride exposure and cognitive outcomes in children at 4 and 6-12 years of age in Mexico." *Environ Health Perspect* 125(9): 1-12.

Green et al. 2019; Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada, *JAMA Pediatr.* E1-E9.

Till et al. 2020: Fluoride exposure from infant formula and child IQ in a Canadian birth cohort, *Environ Int* 134: 105315.

Broadbent JM, Thomson WM, Moffitt TE, Poulton R. 2015. Community water fluoridation and intelligence response. *Am J Public Health.* 105:3-4.

Guth S et al. Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses. *Archives of Toxicology* (2020) 94: 13 7 5-1415

Hirzy, J.H., et al., Developmental Neurotoxicity of Fluoride: A Quantitative Risk Analysis Toward Establishing a Safe Dose for Children. *Fluoride*, 2016. 49(4): p. 379-400 DOI:10.5772/intechopen.70852.

Grandjean, P., Developmental fluoride neurotoxicity: an updated review. *Environ Health*, 2019. 18(1): p. 110 DOI:10.1186/s12940-019-0551-x.

Childsmile: The Scottish Childsmile programme is a national toothbrushing programme in schools and preschools in Scotland.

<https://www.childsmile.nhs.scot/professionals/childsmile-toothbrushing/>

Appendix 9: Additional Study

An additional study assessing neurodevelopmental outcomes was published after the completion of the evidence brief. (Malin et al., 2024)

This was a study of 229 mother-child pairs drawn from 1065 predominantly Hispanic women and their children from the MADRES (Maternal and Developmental Risks from Environmental and Social Stressors) cohort. A single maternal urinary fluoride (MUF) level was measured in the third trimester and the Preschool Child Behavior Checklist (CBCL) was completed by the mothers when their child was about 36 months old. An association between MUF and a composite borderline clinical and clinical score (60-63 and >63, respectively) was found with a 0.68mg/l higher MUF associated with 1.8 times the odds of Total Problems T score being in borderline or clinical range (OR=1.83; 95%CI: 1.17 to 2.86; $p=0.008$).

There are several concerns regarding the validity of this finding including residual confounding, the uncertain clinical significance of a combining borderline and clinical range scores together, and the validity of a single MUF level (spot sample) as an approximation of chronic fluoride exposure. There are also concerns regarding the applicability of a specific population cohort to the population of Aotearoa New Zealand and community water fluoridation. Taking all these factors into account, the findings of this study do not alter the conclusions of this review or that undertaken in 2014 and 2021.