



HEALTH EFFECTS OF WATER FLUORIDATION

EVIDENCE EVALUATION REPORT

NHMRC CLINICAL TRIALS CENTRE

THE UNIVERSITY OF SYDNEY

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A team within the NHMRC which is separate from the grants management area of NHMRC is responsible for developing evidence-based clinical and public health guidelines and advice. It is this section of NHMRC that advertised for tenders from panellists of the NHMRC Health Evidence Panel to undertake this evaluation. The CTC participated in a transparent panel procurement process to win this contract to evaluate the evidence as documented in this report.

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ABBREVIATIONS

AIHW	Australian Institute of Health and Welfare
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ANOVA	analysis of variance
aOR	adjusted odds ratio
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
CPI	community periodontitis index
CWF	community water fluoridation
DAI	Dental Aesthetic Index
DDE	Developmental Defects of Enamel
dmfs	decayed, missing, and filled deciduous tooth surfaces
DMFS	decayed, missing, and filled permanent tooth surfaces
dmft	decayed, missing, and filled deciduous teeth
DMFT	decayed, missing, and filled permanent teeth
DBP	diastolic blood pressure
EPA	Environmental Protection Agency
FT3	free total triiodothyronine
FT4	free thyroxine
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GP	general practitioner
HR	hazard ratio
IQ	intelligence quotient
IQR	inter-quartile range
IRR	incidence rate ratio
IV	inverse variance
kg	kilogram
L	litre
LA	loss of attachment index
mg	milligram
mm	millimetre
mmHg	millimetres of mercury
mU	milliunit
ng	nanogram
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NOF	naturally occurring fluoride

NR	not reported
NRC	National Research Council
OR	odds ratio
PHE	Public Health England
PICOS	population, intervention, comparator, outcome, study type
ppm	parts per million
pyar	person-years at risk
RR	relative risk
SCHER	Scientific Committee on Health and Environmental Risks
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SES	socioeconomic status
SIGN	Scottish Intercollegiate Guidelines Network
T3	triiodothyronine
T4	thyroxine
TFI	Thylstrup-Fejerskov index
TSH	thyroid stimulating hormone
TSIF	Tooth Surface Index of Fluorosis
TT3	total triiodothyronine
TT4	total thyroxine
UK	United Kingdom
US	United States
WIS	water improvement scheme

EXECUTIVE SUMMARY

BACKGROUND

In 2007, the National Health and Medical Research Council (NHMRC) published *A Systematic Review of the Efficacy and Safety of Fluoridation* (NHMRC 2007a). Based on the findings presented in the review, NHMRC issued a public statement that recommended:

“that water be fluoridated in the target range of 0.6 to 1.1 mg/L, depending on climate, to balance reduction of dental caries and occurrence of dental fluorosis”.

The purpose of this review is to update the evidence on the health effects of water fluoridation from NHMRC’s 2007 review to assist NHMRC to provide evidence-based guidance on the potential benefits and harms of water fluoridation.

METHODS

The review process included the following activities:

1. a systematic review of the dental effects of water fluoridation, which consisted of:
 - a. an overview of reviews on the effects of water fluoridation on dental caries;
 - b. a systematic review of recent primary studies on the effects of water fluoridation on dental caries not identified in the reviews included in the overview;
 - c. a critical appraisal of the evidence on dental fluorosis included in the existing Cochrane review (Ihezor-Ejiofor et al 2015); and
2. a systematic review of the other health effects of water fluoridation.

Systematic review of the dental effects of water fluoridation

Two systematic literature searches were undertaken. The first was to identify and evaluate existing reviews that were published between 1 October 2006 and 12 November 2015 which evaluated evidence for the effect of water fluoridation on dental caries. The second was to identify primary studies published between 1 October 2006 and 17 November 2015 reporting on the effect of water fluoridation on dental caries not included in the identified reviews. Studies were included if they compared non-fluoridated drinking water (<0.4 ppm) with water fluoridated to within current Australian levels (0.4 ppm–1.5 ppm) and reported on dental caries.

Included reviews from the overview component were assessed for quality using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) tool. The primary studies included in these reviews were not individually assessed for risk of bias by the evidence reviewers. Included studies from the systematic review of recent primary studies component were assessed for their risk of bias and classified as being of high, acceptable or low quality. The strength of the evidence for each outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for rating the quality of evidence.

Systematic review of the health effects of water fluoridation

A comprehensive literature search was undertaken to identify primary studies reporting on health effects associated with water fluoride that were published between 1 October 2006 and 14 October 2014. Studies were included if they reported on a health effect (other than dental caries or dental fluorosis) in humans and assessed either:

- water with fluoride compared to unfluoridated water, or
- water with fluoride at one level compared to water with fluoride at a different level.

Included studies were assessed for their risk of bias and classified as being of high, acceptable or low quality. To aid in the interpretation of the results, the evidence for each outcome was presented

based on the applicability of the included studies. Study applicability was based on how similar the water fluoride levels reported within each study were to those experienced in Australia:

1. High applicability studies: unfluoridated water (<0.4 ppm¹ fluoride) vs. water with up to 1.5 ppm fluoride
2. Partial applicability studies: unfluoridated water (<0.4 ppm fluoride) vs. water with >1.5 ppm fluoride; and water with 0.4–1.5 ppm fluoride vs. water with >1.5 ppm fluoride
3. Limited applicability studies: studies in which all groups compared had water fluoride levels >1.5 ppm

The strength of the evidence for each outcome was assessed using the GRADE system for rating the quality of evidence.

RESULTS

Findings from the review on the dental effects of water fluoridation

The systematic review identified 3 relevant reviews and 25 primary studies that reported on dental caries. One of the identified reviews reported on dental fluorosis also. Seven other studies identified in the systematic review of other health effects reported on other dental outcomes and were included in this section. The results for dental caries and dental fluorosis are reported separately from other outcomes.

Dental caries in deciduous teeth

Studies reporting on dental caries in deciduous teeth measured caries by using the number of decayed, missing and filled deciduous teeth per individual (dmft) or the number of decayed, missing and filled tooth surfaces (dmfs). The results are reported as mean dmft/s, proportion of individuals caries-free (%dmft/s=0) or prevalence of caries experience (%dmft/s>0). The summary of findings for these outcomes is presented in Table 1.

The quality of the two included reviews that reported on caries in deciduous teeth was mixed with one review scoring high on the AMSTAR tool and the other scoring low. The primary studies included in one review were all of low quality—the other review did not undertake an assessment of methodological quality of the included primary studies.

Most of the primary studies identified in the systematic review of recent primary studies were assessed as being of acceptable quality with moderate risk of bias, representative included populations, and measurement of known confounding factors. Those studies assessed as low quality generally had high risk of bias due to poor or unclear selection methods.

The review identified consistent evidence that water fluoridation was associated with a reduced mean dmft/s and prevalence of caries in deciduous teeth and also an increase in the proportion of individuals with caries-free deciduous teeth.

¹ The units 'ppm' are equivalent to 'mg/L'

Table 1 Summary of findings for dental caries in deciduous teeth

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in deciduous teeth assessed using dmft	The pooled effect estimate was a reduction of 1.81 (95%CI: 1.31 to 2.31) in dmft for children aged 3–12 years. This indicates a reduction in dmft of 35% in the water fluoridation groups over and above that for the control groups.	44,268 (9 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
	Median caries reduction of 44% (range 29% to 68%) in children aged 3–12 years	NR (21 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
	Significant reduction in mean dmft in children (5–10 years) with exposure to community water fluoridation. Mean dmft decreased by 0.37 (95%CI: 0.48, 0.2) in one study.	>40,000 (3 observational studies)	⊕⊕○○	Includes one large study from England using national data and a single study set in Australia with good sample size. Both were of acceptable quality, with adjustment for confounders in a setting of CWF.
Caries in deciduous teeth assessed using dmfs	Median caries reduction of 33% (range: 14%–66%) in 5 to 11-year-olds	NR (21 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
	Significant reduction in mean dmfs in children (5–11 years) with exposure to community water fluoridation in two studies Significant inverse association between mean dmfs and increasing fluoride levels in two studies	5,546 (4 observational studies)	⊕⊕○○	Two acceptable quality studies set in Australia using national survey data with good sample size and adjustment for confounders in the setting of CWF. Two studies (one low quality and one acceptable quality) in the US and Vietnam of limited applicability to the Australian context.
Proportion of caries-free deciduous teeth assessed using %dmft/s=0	The pooled effect estimate was an increase of 15% (95%CI: 11% to 19%) in the proportion of caries-free infants and children (3–12 years) in areas with water fluoridation.	39,966 (9 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
-	The proportion of caries-free Indigenous children (5–10 years) was greater with exposure to community water fluoridation (OR=1.27; 95%CI: 0.98–1.63).	NR (1 observational study)	⊕⊕○○	A single acceptable quality study from Australia in the setting of CWF.
Caries prevalence in deciduous teeth assessed using %dmf/s>0	Significant reduction in the prevalence of caries in children (4–11 years) with exposure to community water fluoridation	>4,323 (6 observational studies)	⊕⊕○○	Includes one large study from England using national data and four studies set in Australia with good sample size. All were of acceptable quality, with adjustment for confounders in a setting of CWF.
Prevalence of early childhood caries	Water fluoridation was significantly associated with a reduction in the prevalence of early childhood caries in infants and children aged 36–71 months (OR=0.40; 95%CI: 0.25–0.63)	5,822 (1 observational study)	⊕○○○	A single study of acceptable quality set in South Africa using survey data. Downgraded for indirectness.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Note: We have attempted as far as possible to use the following definitions: infants (0–4 years); children (5–11 years); adolescents (12–17 years); adults (18–64 years) and later adulthood (65+ years)

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; NR = not reported

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Dental caries in permanent teeth

Studies reporting on dental caries in permanent teeth also measured caries by using the number of decayed, missing and filled permanent teeth per individual (DMFT) or the number of decayed, missing and filled tooth surfaces (DMFS). The results are reported as mean DMFT/S, proportion individuals caries-free (%DMFT/S=0) or prevalence of caries experience (%DMFT/S>0). The summary of findings for these outcomes is presented in Table 2.

The quality of the three included reviews for caries in permanent teeth was mixed with one review scoring high on the AMSTAR tool, one scoring in the middle range and the last scoring low. The primary studies included in one review were all of low quality—the other two reviews did not undertake an assessment of methodological quality.

Most of the primary studies identified in the systematic review of recent primary studies were assessed as being of acceptable quality with moderate risk of bias, representative included populations, and measurement of known confounding factors. Those studies assessed as low quality generally had high risk of bias due to poor or unclear selection methods.

The review identified consistent evidence that water fluoridation was associated with a reduced mean DMFT/S and prevalence of caries in permanent teeth and also an increase in the proportion of individuals with caries-free permanent teeth.

Table 2 Summary of findings for dental caries in permanent teeth

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in permanent teeth assessed using DMFT	The pooled effect estimate was a reduction of 1.16 (95%CI: 0.72 lower to 1.61 lower) in mean DMFT in the areas with water fluoridation for children aged 8–11 years. This indicates a reduction in DMFT of 26% in the water fluoridation groups over and above that for the control groups ⁶ .	78,764 (10 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
	The median percentage reduction of caries in permanent teeth was 37% (range: 5%–85%) in participants aged 8–51 years.	NR (37 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
	Significant reduction in mean DMFT in adults (18–65+years) with exposure to fluoridated water	3,080 (4 observational studies)	⊕○○○	A systematic review of reasonable methodological quality downgraded because of no clear reporting of assessment of risk of bias, and serious indirectness and imprecision
	Significant reduction in mean DMFT in adolescents and adults (≥11 years) with exposure to community water fluoridation (reduced by 0.19; 95%CI: 0.27 reduction, 0.11 reduction in one study)	>12,700 (7 observational studies)	⊕⊕○○	Five acceptable quality studies set in Australia in the context of CWF. Single large study of acceptable quality from England using a national database with adjustment for confounders in a setting of CWF.
Caries in permanent teeth assessed using DMFS	The median percentage reduction of caries in permanent teeth was 29% (range: 0%–50%) in participants aged 5–35 years.	NR (16 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
	Significant reduction in mean DMFS in children and adolescents (8–14 years) with exposure to community water fluoridation in two studies Significant inverse association between ≥75% lifetime exposure to water fluoridation and mean DFS (participants 15+ years) in one study. Non-significant inverse relationship between naturally occurring fluoride	12,344 (4 observational studies)	⊕⊕○○	Two studies of acceptable quality set in Australia in the context of CWF. One study set in Vietnam of limited applicability. One regression analysis from Australia.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
	levels and mean DMFS (participants 6–17 years) in one study.			
Caries prevalence (permanent teeth) assessed with %DMFT/S>0	Significant reduction in the prevalence of caries in children, adolescents and adults (6–21 years) with exposure to community water fluoridation	>39,750 (9 observational studies)	⊕⊕○○	Includes a single large study of acceptable quality from England using a national database with adjustment for confounders in a setting of CWF. Also six acceptable quality studies from Australia.
Proportion of caries-free children (permanent teeth) assessed with %DMFT/S =0	The pooled effect estimate was an increase of 14% (95%CI: 5% to 23%) in the proportion of caries-free children (8–12 years) in areas with water fluoridation.	53,538 (8 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
-	Significant increase in proportion of caries-free Indigenous children and adolescents (6–15 years) for permanent teeth with exposure to water fluoridation in one study (OR=1.30; 95%CI: 1.01–1.68). Non-significant positive association between water fluoridation and proportion of caries-free 12-year-olds in one study.	>97,809 (2 observational studies)	⊕○○○	One acceptable quality study from Australia of Indigenous children set in context of CWF. One acceptable study from Brazil using national data. Downgraded for imprecision.
Incidence of first molar occlusal caries in permanent teeth	Non-significant decrease in the incidence of first molar occlusal caries at age 13 with exposure to water fluoridation (OR=0.32; 95%CI: 0.10–1.02)	93,622 (1 observational study)	⊕○○○	A single study from US of acceptable quality. Downgraded for imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Note: We have attempted as far as possible to use the following definitions: infants (0–4 years); children (5–11 years); adolescents (12–17 years); adults (18–64 years) and later adulthood (65+ years)

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States; NR = not reported

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Dental caries in mixed dentition

There were no reviews that reported on dental caries of mixed dentition. The studies identified in the systematic review of recent primary studies used the number of decayed, missing and filled teeth of

both deciduous and permanent teeth as a measure of caries (dmft + DMFT). They were all assessed as being of acceptable quality. A combined measure of caries (dmft + DMFT) in mixed dentition is problematic due to the changing numbers of deciduous and permanent teeth over this stage of life (from 5 years to about 12 years) such that the combined measure does not necessarily reflect true caries experience during this period. The summary of findings for these outcomes is presented in Table 3.

The review identified insufficient evidence to reach a conclusion about any association between water fluoridation and caries in mixed dentition.

Table 3 Summary of findings for dental caries in mixed dentition

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in mixed dentition	Non-significant reduction in caries in one study in infants and children aged 3–12 years Non-significant inverse association between dmft/DMFT and water fluoridation in children aged 6–11 years	4,784 (2 observational studies)	⊕○○○	One study from Australia and another from Canada in the context of CWF. Downgraded for imprecision.
Caries incidence in mixed dentition	Non-significant inverse association between incidence of cavitated and non-cavitated caries in mixed dentition and water fluoridation (aged 3–13 years).	154 (1 observational study)	⊕○○○	A single study from the US using Iowa Fluoride Study data. Downgraded for indirectness and imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Note: We have attempted as far as possible to use the following definitions: infants (0–4 years); children (5–11 years); adolescents (12–17 years); adults (18–64 years) and later adulthood (65+ years)

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Disparities in dental outcomes

These studies used the difference in a caries measure between levels of socioeconomic status and deprivation or Indigenous status to estimate disparities in dental outcomes. The summary of findings for these outcomes is presented in Table 4.

One review was identified that investigated the effect of water fluoridation on disparities in caries levels. This review scored high on the AMSTAR tool. The studies identified in the systematic review of recent primary studies were of mixed quality: two of acceptable quality and two of low quality.

The review identified insufficient evidence to reach a conclusion about any association between water fluoridation and disparities in dental caries experience.

Table 4 Summary of findings for disparities in dental outcomes

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Disparities in caries by SES status	There is insufficient information to determine whether initiation of a water fluoridation programme results in a change in disparities in caries levels (deciduous teeth) across SES	>35,399 (3 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded once for high risk of bias. The authors reported the quality of evidence as being ⊕⊕○○ and provided no reason why they upgraded. GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
Disparities in caries by Indigenous status	Water fluoridation increased the gap in proportion caries-free children in deciduous and permanent teeth between Indigenous and non-Indigenous Australians aged 5–15 years	97,809 (1 observational study)	⊕○○○	A single Australian study of low quality in the context of CWF. Downgraded for risk of bias and imprecision.
Disparities in caries by deprivation	Water fluoridation had a greater effect in the most deprived subgroup of participants with respect to mean d ₃ mft and caries prevalence in 5-year-olds, mean D ₃ MFT and caries prevalence in 12-year-olds, and hospital admissions for caries of 1 to 4-year-olds compared to the four least deprived subgroups in one study. Difference in D ₄₋₆ MFT between most and least deprived groups was reduced in areas with fluoridated water for 11 to 13-year-olds in one study.	>1,783 (2 observational studies)	⊕○○○	A single large study of acceptable quality from England using a national database setting of CWF. Exploratory analysis of subgroups. No adjustment for confounding. Downgraded for risk of bias and imprecision. Another single large study from the UK downgraded for risk of bias.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: d₃mft/ D₃MFT = number of decayed (into dentine), missing and filled deciduous/permanent teeth; CWF = community water fluoridation; SES = socioeconomic status; UK = United Kingdom

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Other dental effects

Other dental effects included tooth loss, delayed eruption of permanent teeth, tooth wear and hospital admissions for caries in children aged 1–4 years. All included studies, except one, were of acceptable quality. The summary of findings for these outcomes is presented in Table 5.

The review identified insufficient evidence that water fluoridation reduces tooth loss or hospital admission for caries. In addition, the review identified limited evidence of no association between water fluoridation and reduced tooth wear and delayed eruption of permanent teeth.

Table 5 Summary of findings for other dental effects

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Number of missing permanent teeth	Four of five studies show lower prevalence of tooth loss with fluoridation of water	>120,625 (5 observational studies)	⊕○○○	Downgraded for inconsistency and indirectness.
Erupted permanent teeth assessed by clinical examination	No significant difference in mean number of permanent teeth erupted	13,348 (1 observational study)	⊕⊕○○	A single study of acceptable quality from the US with representative sample and adjustment for confounding factors.
Delayed eruption of permanent teeth (assessment method NR)	Prevalence of delayed eruption was 53% in 2.7 ppm fluoride area and 0% in 1.0 ppm area	70 (1 observational study)	⊕○○○	A single small, low quality study from India in school children aged 8–15 years with poor reporting of recruitment method and outcome ascertainment, no adjustment for confounding, and no statistical analysis. Set in the context of naturally occurring fluoride in water of up to 2.7 ppm
Tooth Wear assessed with modified version of the Smith and Knight index	No consistent association with water fluoridation	2,456 (1 observational study)	⊕○○○	A single study of acceptable quality from the Republic of Ireland. Downgraded in the GRADE assessment for imprecision and inconsistency.
Hospital admissions	The rate of hospital admissions for 1 to 4-year-olds was 55% lower in fluoridated areas (95%CI: 73% lower, 27% lower)	NR (1 observational study)	⊕○○○	A single population-based study using national admission data from England of acceptable quality in a setting of CWF. Downgraded for imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States; NR = not reported; ppm = parts per million

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Findings of the review of dental fluorosis

The evidence evaluation identified one review which provided consistent evidence that an increase in the fluoride concentration in water supplies is associated with an increase in the prevalence of dental fluorosis. However, the majority of the evidence is derived from countries where naturally occurring fluoride levels are up to five times greater than the levels of fluoride in artificially fluoridated water in Australia. This evidence has limited applicability in the Australian context and is of insufficient quality to predict the prevalence of any dental fluorosis or dental fluorosis of aesthetic concern associated with the current levels of water fluoridation in Australia. This is due to a lack of control for other fluoride sources and marked between-study variation across non-comparable populations. There is also some uncertainty as to what level of dental fluorosis is perceived to be of aesthetic concern. The summary of findings for these outcomes is presented in Table 6.

Table 6 Summary of findings for dental fluorosis

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Dental fluorosis of aesthetic concern (measured by Dean's Index, TFI, TSIF)	For a fluoride level of 0.7 ppm the percentage of participants with dental fluorosis of aesthetic concern was estimated to be 12% (95% CI 8% to 17%).	59,630 (40 observational studies)	⊕○○○ ²	A single well-conducted systematic review. The estimate for any level of dental fluorosis at 0.7 ppm was 40% (95% CI 35% to 44%; 90 studies). This includes dental fluorosis that can only be detected under clinical conditions and other enamel defects. The GRADE assessment has been revised and downgraded for high risk of bias, indirectness and inconsistency.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: CI = confidence interval; ppm = parts per million; TFI = Thylstrup-Fejerskov Index; TSIF = Tooth Surface Index of Fluorosis

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

² The quality assessment has been revised—the Iheozor-Ejiofor et al (2015) review reported the quality as ⊕⊕○○ but this should have been downgraded for high risk of bias and inconsistency

Findings of the systematic review of the other health effects of water fluoridation

The systematic review identified 41 relevant primary studies that reported on 23 separate health outcomes. As the studies reported on a wide range of different water fluoride levels, the results for each study were categorised based on the applicability of their comparison to the Australian setting.

Evidence from highly applicable comparisons

The highly applicable comparisons were those that compared unfluoridated water (<0.4 ppm) with water fluoride of between 0.4 ppm and 1.5 ppm. The individual studies that provided highly applicable comparisons were generally of low methodological quality, and many had a high risk of bias. The limitations of the evidence have affected the ability to draw conclusions from the available information. The summary of findings from these comparisons is presented in Table 7.

The review identified evidence that there is no association between water fluoridation at Australian levels and the IQ of both adults and children, compared to unfluoridated water. We have moderate confidence in this assessment because of the high methodological quality of the prospective cohort study and the high similarity between the Australian setting and New Zealand, where the study was conducted.

The review identified limited evidence of no association between water fluoridation at Australian levels and the outcomes of delayed tooth eruption, tooth wear, osteosarcoma, Ewing sarcoma, total cancer incidence, hip fracture and Down syndrome. However, our confidence in these assessments is limited due to the methodological shortcomings of the individual studies. The review also identified limited evidence suggesting that water fluoridation at Australian levels is associated with a small reduction in all-cause mortality; however, our confidence in this association is limited, and the size of the effect was small and may be due to chance.

The review included five outcomes where the available evidence was considered insufficient to draw any conclusions. Those outcomes were kidney stones, chronic kidney disease, gastric discomfort, headache, and insomnia.

Table 7 Summary of findings for other health outcomes with highly applicable fluoride level comparisons

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
All-cause mortality assessed using official mortality statistics	Adjusted incidence was 1.3% lower in areas with CWF (95%CI: 2.5% lower to 0.1% lower)	208,570,962 person-years at risk (1 observational study)	⊕⊕○○	A single large study of acceptable quality from England using a national database with adjustment for confounders in a setting of CWF.
Osteosarcoma assessed using official mortality statistics	No statistically significant difference in incidence of osteosarcoma between areas with water fluoridation and those without	519,128,941 person-years at risk (5 observational studies)	⊕⊕○○	Four of these studies were large population-based studies from countries with CWF all assessed as being of acceptable methodological quality. The fifth study was a population-based study of national statistics that reported only crude incidence rates.
Osteosarcoma (assessment method NR)	Participants with osteosarcoma lived in areas with higher fluoride water levels than people without osteosarcoma (1.30 ppm vs. 0.48 ppm)	20 (1 observational study)	⊕○○○	A single very small case-control study from India of low methodological quality (high risk of bias) with no information about participant demographics, recruitment, assessment of disease status, or the presence of potential confounding factors.
Ewing sarcoma assessed using national cancer registries	No significant increase in the risk of Ewing sarcoma with increasing fluoride level	992,213 person-years at risk (1 observational study)	⊕⊕○○	A single population-based study using national cancer registries from England of acceptable quality in a setting of CWF
All cancer incidence assessed using a national cancer register	Adjusted incidence of all cancer was 0.4% lower in areas with CWF (95%CI: 1.2% lower to 0.4% higher)	208,570,962 person-years at risk (1 observational study)	⊕⊕○○	A single population-based study using national cancer register from England of acceptable quality in a setting of CWF
Bladder Cancer assessed using a national cancer register	Adjusted bladder cancer incidence was 8.0% lower in areas with CWF (95%CI: 9.9% lower to 6.0% lower)	555,127,448 person-years at risk (1 observational study)	⊕⊕○○	Single population-based study using a national cancer register from England of acceptable quality in a setting of CWF.
Eye Cancer assessed using a national cancer register	Negative correlation between incidence of eye cancer and water fluoride level	NR (1 observational study)	⊕⊕○○	A single acceptable quality study of the correlation between the proportion of the population each US state exposed to CWF with eye cancer incidence
Hip Fracture assessed by national hospital statistics	Effect estimates from both studies found no statistically significant difference in the incidence of hip fracture.	313,045,314 person-years at risk (2 observational studies)	⊕⊕○○	Two population-based studies from Sweden and England of methodologically acceptable quality.
Down Syndrome assessed using a national register	Incidence of Down syndrome births were 0.9% higher (95%CI: 0.8% lower to 2.6% higher) in areas with CWF	2,727,330 person-years at risk (1 observational study)	⊕⊕○○	A single population-based study of methodologically acceptable quality from England in the setting of CWF

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
IQ assessed using Wechsler Intelligence Scales	No significant difference in IQ scores between people exposed to CWF compared to those not exposed	1,037 (1 observational study)	⊕⊕⊕○	A longitudinal population-based study of high methodological quality from New Zealand with all major fluoride intakes considered and confounders adjusted for in a setting of CWF.
Kidney Stones assessed with national hospital statistics	Incidence of emergency admissions for kidney stones was 7.9% lower (95%CI: 9.6% lower to 6.2% lower) in the areas with CWF	312,856,448 person-years at risk (1 observational study)	⊕⊕○○	A population-based study of methodologically acceptable quality from England in a setting of CWF.
Chronic kidney disease assessed using existing prevalence studies	Prevalence of chronic kidney disease of unknown aetiology in the three villages was 96%, 0%, and 84%	5,685 (1 observational study)	⊕○○○	A single study from Sri Lanka of low methodological quality (high risk of bias) in three villages with mean water fluoride levels of 0.74, 1.03, and 1.02 ppm, respectively. No trend was observed.
Gastric Discomfort assessed with self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	3,764 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.
Headache assessed by self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	3,283 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.
Insomnia assessed by self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	3,283 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: CI = confidence interval; CWF = community water fluoridation; IQ = intelligence quotient; ppm = parts per million; US = United States; NR = not reported

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Evidence from partially applicable comparisons

Studies categorised as partially applicable included those that compared unfluoridated water to water containing >1.5 ppm fluoride; and those that compared water with 0.4–1.5 ppm fluoride to water with >1.5 ppm fluoride. The summary of findings from these comparisons is presented in Table 8.

The review found limited evidence of no association between higher levels of fluoride (>1.5 ppm) and the risk of hip fracture. Our confidence in this assessment is moderate, due to the acceptable methodological quality of the study and the low risk of bias in the study estimates. For all other outcomes, the quantity and quality of the evidence were insufficient to allow any conclusions to be drawn.

Table 8 Summary of findings for other health outcomes with partially applicable fluoride level comparisons

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Atherosclerosis assessed by carotid ultrasound	Higher prevalence in areas with fluoride levels >1.20 ppm	585 (1 observational study)	⊕○○○	A single study in adults >40 years from China of acceptable quality in the context of high naturally occurring water fluoride levels. Important known confounders not included in analysis e.g. smoking, exercise, diabetes
Hypertension assessed by sphygmomanometer	Conflicting results from the two continuous analyses Significantly higher odds of hypertension for ≥3.01 ppm fluoride compared to ≤1.20 ppm fluoride exposure only (all other comparisons between intermediate levels and lowest level not significant)	NR (2 observational studies) 487 (1 observational study)	⊕○○○	Two studies of low methodological quality from Iran using regression analysis to investigate a correlation between prevalence of hypertension and water fluoride levels (range 0.02–2.2 ppm). Single small study of adults 40–75 years from China of acceptable methodological quality found only significant raised odds with ≥3.01 ppm fluoride compared to lowest comparator (≤1.20 ppm)
Hip Fracture assessed by national hospital statistics	Hazard ratio = 0.98 (95%CI: 0.93–1.04)	13,736 person-years at risk (1 observational study)	⊕⊕⊕○	One population-based study from Sweden of methodologically acceptable quality.
Osteoporosis assessed by x-ray	Prevalence of osteoporosis: 6.2% with 1.5–7.0 ppm exposure 6.8% with 0.5–1.0 ppm exposure	675 (1 observational study)	⊕○○○	A single study in adults from China of low methodological quality with poor reporting of selection method, no consideration of known confounding factors, the uncertain accuracy of diagnosis, and no statistical analysis.
Birth weight assessed with baby scale	Increased odds of low birth weight associated with exposure to high fluoride levels (4.7 ppm)	324 (1 observational study)	⊕○○○	A single study from Africa of low methodological quality in a setting of high naturally occurring fluoride levels (4.7 ppm).
IQ and cognitive function assessed with various instruments	11 of 13 analyses reported a significantly lower IQ score with high fluoride levels (range 2.3–9.2 ppm) No association between fluoride water levels and cognitive performance in one analysis	1,565 (11 observational studies)	⊕○○○	Nine studies from China, Iran, and India were of low methodological quality (high risk of bias) due to poor recruitment reporting, no consideration of confounding factors, and no blinding of outcome assessors. One study from Mexico and another from China were of acceptable quality.
Thyroid function assessed with thyroid function tests	All thyroid function tests within reference range	240 (2 observational studies)	⊕○○○	Two studies of low methodological quality from India and China of school children in areas with high naturally-occurring levels of fluoride in water.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Thyroid volume assessed with ultrasound	Thyroid volumes were inconsistent using two measures of thyroid volume	559 (1 observational study)	⊕○○○	A single study from Iran in schoolchildren of low quality found no difference in thyroid volume but a significant difference in Echobody index. The clinical validity of this measure and its implications are unclear.
Musculoskeletal pain assessed with self-report health survey	Odds of lower back pain significantly greater in the high fluoride area. Prevalence of joint pain higher in the high fluoride area.	3,266 (2 observational studies)	⊕○○○	One small study of low quality (high risk of bias) from India and a single study from Thailand of low methodological quality in adults 50–90 years.
Gastric discomfort assessed with self-report health survey	Higher prevalence of complaints of gastric discomfort in >1.5 ppm fluoride exposed group	2,814 (2 observational studies)	⊕○○○	Two studies of adults and children in India of low methodological quality. No statistical analysis was done.
Headache assessed by self-report health survey	Higher prevalence in >1.5 ppm fluoride group	2,937 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.
Insomnia assessed by self-report health survey	Higher prevalence in >1.5 ppm fluoride group	2,937 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: CI = confidence interval; IQ = intelligence quotient; NR = not reported; ppm = parts per million

¹ For details of the assessment please see the individual outcome in the Results section of this report.

Evidence from low applicability comparisons

Low applicability comparisons compared groups that all had water fluoride levels >1.5 ppm. The summary of findings from these comparisons is presented in Table 9. The evidence for all outcomes was insufficient to draw any conclusions about the differential effect of multiple high water fluoride levels.

Table 9 Summary of findings for other health outcomes with limited applicability in fluoride level comparisons

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Atherosclerosis assessed by carotid ultrasound	No significant difference in prevalence	399 (1 observational study)	⊕○○○	A single acceptable quality study from China in adults >40 years in the context of high naturally occurring fluoride levels. All comparisons were >1.21 ppm.
Skeletal fluorosis (assessment NR)	Skeletal fluorosis prevalence (range): grade II: 4.7% to 20.1%; grade III: 0% to 3.9%	2,816 (2 observational studies)	⊕○○○	Two low quality prevalence studies from India in the setting of naturally occurring fluoride levels from 1.5 ppm to >6.0 ppm. The diagnostic method was not reported and no statistical analysis was done.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
IQ assessed with various IQ instruments	One of two studies reported statistically significant lower IQ score in high fluoride group	392 (2 observational studies)	⊕○○○	Two low quality studies from India and Iran of schoolchildren 6–13 years old from villages with drinking water fluoride levels of 2–3 ppm and >5 ppm, respectively.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: CI = confidence interval; IQ = intelligence quotient; NR = not reported; ppm = parts per million

¹ For details of the assessment please see the individual outcome in the Results section of this report.

QUALITY OF THE EVIDENCE

Overall, the quality of the evidence for dental outcomes was low or very low. This was largely due to the limitations of observational studies, however restricting the inclusion to studies which adjusted for known confounding factors resulted in most of the included studies for caries being assessed as of acceptable quality. Any individual studies assessed as being of low quality were generally considered to be at risk of selection bias.

Overall, the quality of evidence across all of the other health outcomes was low or very low. This is primarily due to the poor methodological quality of the included studies, which results in a high risk of bias. In many studies, the quality of the reporting of both study methods and results was very poor. Many studies also have small numbers of participants, which undermines the ability of the study to detect meaningful differences in health outcomes. The majority of the included studies made only a rudimentary assessment of the fluoride exposures and did not include any adjustment in their analyses for the effects of potential confounding variables. The lack of adjustment for confounding variables has seriously limited the ability of this review to draw conclusions from the majority of the results identified.

CONCLUSIONS

The evidence collected in this review supports the findings of the previous NHMRC review (2007), that water fluoridation at levels comparable to those used in Australia reduces the incidence of dental caries in the deciduous and permanent teeth of children by approximately 35%², compared to unfluoridated water. Water fluoridation also increases the proportion of children who have no dental caries by approximately 15%³. Fluoridation of water at levels comparable to that used in Australia increases the prevalence of dental fluorosis. The prevalence of dental fluorosis of aesthetic concern was estimated to be 12%⁴ for 0.7 ppm fluoride. These estimates are largely consistent with the evidence collected from the other included reviews and the systematic review of recent primary studies.

There is limited evidence that there is no association between water fluoridation at Australian levels and the IQ of children and adults. There is also limited evidence that there is no association between water fluoridation at Australian levels and the outcomes of delayed tooth eruption, tooth wear, osteosarcoma, Ewing sarcoma, total cancer incidence, hip fracture and Down syndrome. The review also identified evidence suggesting that water fluoridation at Australian levels are associated with a small reduction in all-cause mortality; however, our confidence in this association is limited, and this small reduction may be due to chance. For all other outcomes canvassed in this review, the evidence was of insufficient quality to draw any conclusions.

² Illustrative proportion from Iheozor-Ejiofor et al (2015)

³ Illustrative proportion from Iheozor-Ejiofor et al (2015)

⁴ Illustrative proportion from Iheozor-Ejiofor et al (2015)

Taken together, the evidence in this review indicates that water fluoridation, as implemented in Australia, improves the dental health of children and adults. There is evidence that water fluoridation increases the number of people who experience dental fluorosis but does not appear to be associated with any other significant harm. This evidence has limited applicability in the Australian context and is of insufficient quality to predict the prevalence of any dental fluorosis or dental fluorosis of aesthetic concern associated with the current levels of water fluoridation in Australia. There is also some uncertainty as to what level of dental fluorosis is perceived to be of aesthetic concern.

The evidence available to assess the effects of water fluoridation will likely always come from observational studies, some of which will be of low methodological quality. Decision-makers must recognise these limitations and be prepared to make pragmatic decisions based on the best available evidence about the implementation and maintenance of water fluoridation programs in Australia.

INTRODUCTION

BACKGROUND INFORMATION

Fluoride and dental caries

Dental caries is a chronic and progressive disease of the mineralised and soft tissues of the teeth. It has a multifactorial aetiology related to interactions between tooth substance, certain acid-producing bacteria and dietary carbohydrates. Acids produced during the metabolism of carbohydrates by oral bacteria cause the demineralisation of the tooth enamel and without treatment this can extend into the dentine and the dental pulp (Cate & Featherstone 1991). Dental caries is a major public health problem in most industrialised countries, affecting 60% to 90% of school children (Petersen 2003).

Fluoride has three predominant mechanisms of action to prevent dental caries: inhibiting demineralisation of tooth enamel during attack by acid-producing plaque bacteria, enhancing the early remineralisation of enamel lesions, and inhibiting bacterial metabolism (Featherstone 2000; Robinson 2009). Even though the predominant effect is topical, fluoride incorporated into tooth enamel pre-eruption also has a role (Singh et al 2003; Singh et al 2007). The concentration of fluoride in saliva and plaque liquid is raised by drinking water containing fluoride or brushing teeth with fluoridated toothpaste. When water containing fluoride is ingested, fluoride is absorbed and secreted back into saliva, where it can act to inhibit enamel demineralisation. In addition, ingested fluoride is incorporated into the developing enamel in pre-erupted teeth, making those teeth more resistant to decay (RSNZ 2014).

Intentional water fluoridation

Water fluoridation is the intentional addition of a fluoride compound to a public water supply so that the level of fluoride in the water reaches an optimal level that balances the prevention of dental caries with the avoidance of dental fluorosis. The concentration of fluoride in water is most commonly measured in parts per million (ppm), which is equivalent to mg/L. Fluoridation of public water supplies began in the 1940s in the United States after epidemiological studies were published that showed that populations with high levels of naturally occurring fluoride in their water supply had a reduced prevalence of dental caries (RSNZ 2014).

In Australia, naturally-occurring fluoride levels in water are generally very low at <0.1 ppm and fluoride has been added to water artificially for more than 55 years (AIHW 2012). Water fluoridation of a public water supply in Australia first occurred in Beaconsfield, near Launceston, Tasmania in 1953 (NHMRC 2007a). Subsequently all state and territory capitals have implemented water fluoridation, including Brisbane in 2009. The number of people with access to fluoridated water increased from around 11.7 million in 2002 to 17.6 million in 2009 (British Fluoridation Society 2004). Percentages of the resident population that have access to fluoridated public water supplies, by state or territory as at August 2013⁵ is as follows:

- Australian Capital Territory (100%)
- New South Wales (96%)
- Queensland (80%)
- Western Australia (92%)
- South Australia (90%)
- Victoria (90%)
- Tasmania (83%)
- Northern Territory (70%)

The World Health Organization has concluded that water fluoridation is a safe and cost-effective way to prevent dental decay (Petersen 2008; WHO 2006). This conclusion is supported by the

⁵ Sourced from data from jurisdictional health authorities in August 2013 and published by NSW Health

findings of a number of studies of cost-effectiveness from different jurisdictions. A study assessing the cost savings resulting from water fluoridation in the US found that the reduction in costs of restorative treatment due to averted dental decay exceeded the cost of water fluoridation (Griffin et al 2001). A study from New Zealand concluded that fluoridation was cost-effective, especially for communities with high proportions of children, indigenous people or people of low socioeconomic status (Wright et al 2001). Two recent Australian studies have shown that for every dollar spent on fluoridation, between \$7 and \$18 is saved due to avoided treatment costs (Ciketic et al 2010; Cobiac & Vos 2012). Finally, another Australian economic study found that over 25 years, water fluoridation had saved the state of Victoria about \$1 billion through avoided dental costs, days away from work or school and other costs (Department of Health Victoria 2009)

Trends in caries in Australia

In Australia, there has been a drop in the number of decayed, missing, or filled deciduous teeth in 6-year-old children from an average of 3.13 in 1977 to 1.45 in 1996. There has, however, been a gradual rise since 1996 to around an average of 2.5 teeth affected. The trend has been similar for permanent teeth at age 12 which decreased from an average of 4.79 permanent teeth affected by dental caries in 1977 to less than 1 tooth affected in 1998, with an increase to more than 1 in 2010 (AHIW 2014). In adults there has been also a trend of decreasing caries experience, with national surveys reporting a fall in the average number of teeth affected by decay from nearly 15 teeth in 1987–88 to around 13 teeth in 2004–6. This decrease was a result of a decrease in both the average number of teeth with untreated decay and the average number of teeth missing as a result of decay (AHIW 2014).

Potential adverse effects of water fluoridation

One known adverse effect associated with the use of fluoride is dental fluorosis. Dental fluorosis is due to excess fluoride ingestion by young children during tooth formation. This causes hypomineralisation of tooth enamel and shows up as differences in enamel opacity (DenBesen and Li 2011). The appearance of the teeth depends on the severity of the fluorosis. In its mild form there are faint white spots or lines; moderate fluorosis appears as mottling of the teeth with opaque white patches; in severe fluorosis there is brown staining or pitting of the enamel (Rozier 1994). Dental fluorosis associated with water fluoridation is usually graded as mild or less, which affects the appearance of teeth but is not of clinical or aesthetic concern (NFIS 2011).

Another known adverse effect is skeletal fluorosis which is a condition where there is an excessive amount of fluoride incorporated into bone. Symptoms include bone pain, joint stiffness, and other arthritic symptoms. It occurs in individuals exposed to excessively high levels of fluoride, and is endemic in several parts of the world including India, China, parts of the Middle East and Africa, where water supplies have fluoride levels much greater than that used for community water fluoridation (CWF) in Australia. It is extremely rare in the developed world (British Fluoridation Society 2004).

Fluoride levels used in Australia

In 2007, the National Health and Medical Research Council (NHMRC) published *A Systematic Review of the Efficacy and Safety of Fluoridation* (NHMRC 2007a). Based on the findings presented in the review, NHMRC issued a public statement that recommended “*that water be fluoridated in the target range of 0.6 to 1.1 mg/L, depending on climate, to balance reduction of dental caries and occurrence of dental fluorosis*” (NHMRC 2007b). The 2011 *Australian Drinking Water Guidelines* developed by NHMRC in collaboration with the Natural Resource Management Ministerial Council recommended that, based on health considerations (namely to protect children from the risk of dental fluorosis), the concentration of fluoride in drinking water should not exceed 1.5 mg/L (NHMRC 2011). The Australian Fluoride Guidelines which were updated at a workshop of the Australian Research Centre for Population Oral Health (ARCPOH) in 2012 recommended the continuation of water fluoridation in Australia, in addition to the extension to as many people as possible living in non-fluoridated areas, within the range of 0.6 ppm to 1.1 ppm with a variation within that range according to the mean maximum daily temperature (ARCPOH 2012).

PURPOSE OF THIS REVIEW

Controversy around water fluoridation in Australia sometimes arises due to concerns focussed on ethical issues or possible harmful effects of fluoride. The purpose of this evidence evaluation is to update the evidence on the health effects of water fluoridation from NHMRC's 2007 review to assist NHMRC to provide evidence based guidance on the benefits and harms of water fluoridation.

The evidence evaluation focuses on the effects of fluoride in drinking water and will not consider other sources of fluoride, including topical fluoride, fluoridated milk or salt and fluoride in infant formula. Outside of the scope of the review is consideration of the specific chemicals used to fluoridate water and the impact of consuming bottled water or juice in place of fluoridated water. The review will not include a formal cost-benefit analysis for water fluoridation and will not recommend any particular range of concentrations for fluoridation.

CONTEXT FOR THIS REVIEW: EXISTING REVIEWS OF THE HEALTH EFFECTS OF WATER FLUORIDATION

A number of reviews examining the health effects of water fluoridation had been undertaken both in Australia and internationally prior to the commencement of this review. A summary of the findings of key reviews is presented below to provide context for the new body of work.

NHMRC (2007) and McDonagh (2000)

The NHMRC published a systematic review in 2007 that evaluated evidence relating to the efficacy and safety of topically applied fluoride or fluoride added to water, milk or salt (NHMRC 2007a). The research questions related to the caries-reducing benefits and associated potential health risks. A total of six systematic reviews were identified in the literature search and one (McDonagh et al 2000) was used as the basis of the NHMRC review, as it was considered to be the most comprehensive and was also of good methodological quality. The literature search used by the McDonagh review was updated by the NHMRC review and any relevant primary studies published since 2000 were included. The NHMRC review extended the McDonagh review's inclusion criteria to include cross-sectional studies.

The NHMRC review concluded that the existing body of evidence suggested strongly that water fluoridation was beneficial at reducing dental caries. This was based on the McDonagh systematic review that found, after adjustment for potential confounders, a significant increase of about 14% in the proportion of caries-free children and a mean decrease of 2.6 decayed, filled, or missing primary or permanent teeth in areas where water fluoridation was introduced compared to areas which were non-fluoridated. The number of people needed to be exposed to fluoridated water to prevent one person from developing dental caries was around 6. The review also suggested that stopping water fluoridation resulted in a reduction in the difference in caries prevalence between the fluoridated and non-fluoridated populations. Only one additional primary study was identified in the NHMRC review and it did not change the conclusion.

With respect to dental fluorosis, there was consistent evidence that water fluoridation resulted in dental fluorosis, but that most was mild and not considered to be of 'aesthetic concern'. This conclusion was based on two systematic reviews (McDonagh et al 2000; Khan et al 2005) that found a clear increase in the prevalence of dental fluorosis with increasing levels of fluoride. Six extra people would have to be exposed to water fluoride levels of 1.0 or 1.2 ppm for one additional person to develop fluorosis of any degree. Twenty-two extra people would have to be exposed for an extra person to develop fluorosis of 'aesthetic concern'. Meta-analysis of the 10 additional primary studies published since 2000 provided results consistent with these two reviews: the risk of developing fluorosis of 'aesthetic concern' was four times greater in areas with optimal water fluoridation compared with areas with sub-optimal fluoridation. The absolute increase in prevalence of fluorosis of 'aesthetic concern' was between 4 and 5%.

Three systematic reviews (Demos et al 2001; Jones et al 1999; McDonagh et al 2000) were identified that considered whether water fluoridation had any effect on fracture risk and they all agreed that it had little effect at levels used to prevent caries. Three additional original studies were included that encompassed much higher fluoridation levels than those used in Australia and they did not change the conclusion.

When any effect on cancer incidence or mortality was considered, only one systematic review (McDonagh et al 2000) was included which found no clear association between water fluoridation and cancer incidence or mortality (for 'all cause' cancer and, more specifically, for bone cancer and osteosarcoma). The four additional studies that were included had mixed results. For other adverse effects (including Alzheimer's disease, Down syndrome, mortality and goitre), the NHMRC review found that there was insufficient evidence to make any conclusions.

The Royal Society of New Zealand (2014)

The Royal Society of New Zealand published a report in 2014 of the health effects of water fluoridation (RSNZ 2014). It aimed to evaluate the current state of scientific knowledge on the health effects of fluoridation in order to inform decision-making about continuing or implementing CWF. Several existing systematic reviews of good quality were used as a basis for this report and subsequent studies both in animals and humans were identified from several scientific literature databases.

The report concluded that there is substantial evidence of the beneficial effect of CWF on reducing dental caries in both children and adults. This included studies conducted recently that considered the reduced prevalence of dental caries from the widespread use of topical fluoride products. The authors also found contemporary evidence in New Zealand that significant differences in decay rates between fluoridated and non-fluoridated communities still exist, even with widespread use of fluoridated toothpaste. They also concluded that CWF had a beneficial effect over and above that of other fluoride sources, and that CWF most substantially benefitted those in deprived socioeconomic groups with the highest rates of tooth decay.

With respect to dental fluorosis, the authors concluded that its prevalence was not increasing in New Zealand and that levels of fluorosis were similar between fluoridated and non-fluoridated areas and mainly related to inappropriate consumption of fluoride products like toothpaste and other fluoride supplements.

Other potential adverse events were investigated and the authors noted that many had only been reported in areas where the natural level of fluoride in water was much higher than that used for CWF. They concluded that based on the available evidence there was no appreciable risk of cancer (particularly osteosarcoma) or risk of bone fractures, and no effect on cognition arising from CWF. They also reported that there was no evidence of appreciable risks on reproduction, endocrine or kidney function, or the cardiovascular and immune systems.

US National Research Council (2006)

The National Research Council (NRC) report was intended to evaluate the safety of levels of naturally occurring fluoride in drinking water of between 2 and 4 mg/L in the US (National Research Council 2006). The report reviewed both animal and human studies related to the possible effects of fluoride at these levels of exposure. It was noted that these exposure values were not recommendations for the artificial fluoridation of drinking water for caries prevention, but were guidelines for areas that were contaminated or had high concentrations of naturally occurring fluoride in their drinking water. Moreover, the report stated that any conclusions regarding the potential for adverse effects of fluoride at 2 to 4 mg/L in drinking water were not applicable to the lower exposures commonly experienced by most US citizens of 0.7 to 1.2 mg/L for caries prevention.

The NRC found that strong evidence existed that the prevalence of severe dental fluorosis would be reduced to almost zero if water fluoride levels were below 2 mg/L. The evidence indicated that fewer than 15% of children would experience dental fluorosis of aesthetic concern (discolouration of front teeth) at that concentration. What was not known was the extent to which fluorosis of aesthetic concern may adversely affect psychological or social function.

There was evidence that life-long exposure to fluoride at 4 mg/L may cause skeletal fluorosis and increase the risk of fractures, compared to exposure at 1 mg/L, particularly in some subgroups of people such as those with kidney disease. The available evidence for exposure around 2 mg/L, however, was inadequate to draw any firm conclusions about the risk or safety at that concentration. Overall the studies on fluoride in drinking water at approximately 1.0 mg/L indicated no effect on fractures. Moreover, the NRC concluded that there was likely no effect on arthritis at environmental doses.

The evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, was mixed, however, the committee did recommend that additional research was needed to more fully explore the potential effects of fluoride on intelligence. Other studies have suggested that higher levels of fluoride may be associated with changes in thyroid function (particularly when iodine levels are low) and may impact on calcium and/or parathyroid function. The NRC noted that even though many of these effects could be considered subclinical, further research was needed to explore these possibilities. No human studies were found on drinking water with fluoride at 4 mg/L in which gastrointestinal, renal, liver, or immune effects were clearly documented. However, the committee could not rule out such effects occurring at higher concentrations, or in people with kidney disease.

After consideration of the body of evidence on health effects and total exposure data to fluoride, the NRC concluded that the U.S. Environmental Protection Agency's maximum contaminant level goal of 4 mg/L should be lowered, and that this would prevent children from developing severe dental fluorosis and also reduce the lifelong accumulation of fluoride in bone in susceptible people.

EU Scientific Committee on Health and Environmental Risks (2011)

The European Commission requested advice from its Scientific Committee on Health and Environmental Risks (SCHER) to obtain updated advice on intentional CWF, specifically to critically review any information in the public domain on the hazard profile and epidemiological evidence of beneficial and/or adverse health effects of fluoride, and to conduct an integrated exposure assessment for fluoride covering all possible known sources (SCHER 2011).

They concluded that water fluoridation appeared to prevent caries, primarily in permanent dentition and that there was a risk for early stages of dental fluorosis in children in European Union (EU) countries but that a threshold level could not be determined. The occurrence of endemic skeletal fluorosis had not been reported in the EU and there was insufficient data to evaluate the risk of bone fracture at the fluoride levels seen in areas with fluoridated water. There was no clear link with osteosarcoma or cancer in general, nor was there enough evidence to conclude that fluoride in drinking water at concentrations permitted in the EU impaired the IQ of children or influenced reproductive capacity.

Parnell (2009)

This was a summary of the evidence from systematic reviews and evidence-based guidelines of the effectiveness and safety of water fluoridation. Both the McDonagh et al (2000) and NHMRC (2007a) reviews summarised above were included, as well as one by Griffin et al (2007) that looked at the effectiveness of fluoride for caries prevention in adults. The results all confirmed the conclusions already reported: that water fluoridation was effective at reducing caries in children and adults; the only adverse event associated with water fluoridation was dental fluorosis; water fluoridation reduced caries for all social classes; and, there was some evidence that it may reduce the oral health gap between social classes.

Three evidence-based guidelines were also included: two (Centers for Disease Control and Prevention 2001; Spencer 2006) recommended the continuation and extension of water fluoridation and the other (SIGN 2005), largely based on McDonagh et al (2000), made the recommendation to prioritise the robust evaluation of the benefits as well as the potential risk of fluorosis in the current environment in Scotland.

Canadian Agency for Drugs and Technologies in Health (2009)

This Health Technology Assessment reviewed the clinical- and cost-effectiveness of fluoridation for caries prevention (CADTH 2009). The authors identified the two systematic reviews by Griffin et al (2007) and NHMRC (2007a), as well as two economic evaluations and one guideline by SIGN (2005). Their conclusions are consistent with the source reviews.

INTERPRETATIVE ISSUES AND LIMITATIONS OF THE EVIDENCE

Limitations of GRADE in a public health setting

There is debate about the appropriateness of GRADE for public health interventions. One reason is that evidence from randomised controlled trials (RCTs) may never be available for certain public health interventions due to the unfeasibility of conducting such trials, with CWF being one such area.

GRADE automatically scores RCTs 'high' to begin with, and scores non-randomised studies as 'low' to begin with. This has been a key criticism of using GRADE for non-randomised studies (Rehfuess & Akl 2013).

Another concern about using GRADE for assessing public health studies is that GRADE provides limited opportunities to 'upgrade' the rating of the quality of evidence from observational studies based upon the assessment of whether the study designs were strong, moderate, or weak quality (Bruce et al 2014). Upgrading the rating is possible, but it seems to be rare for observational studies done in the public health area.

Many public health interventions, including water fluoridation, are complex undertakings with many technical, social, financial, and political constraints on the implementation of the intervention that may never allow an RCT to be conducted (Ihezor-Ejiofor et al 2015). In fact ecological and cross-sectional studies may be the best available evidence to assess the effects of water fluoridation. In these cases, the GRADE framework will almost always give a low quality rating to the evidence (to start with), and all stakeholders need to acknowledge this limitation (Burford et al 2012). Indeed stakeholders must rely on the best available evidence to make decisions about public health interventions which in many cases will be rated as low using the GRADE system.

It should be noted that the application of GRADE to research evidence in public health, and in environmental and occupational health settings, is being improved constantly (Morgan et al 2016).

Assessment of observational studies

Challenges arise at all stages of conducting a review of non-randomised studies, which include deciding which study designs to include, searching for studies, assessing studies for potential bias, and deciding whether to pool results (Reeves et al 2011). Observational studies include controlled before-and-after studies, concurrent cohort studies, historical cohort studies, case-control studies, before-and-after studies, cross-sectional studies, and case series (Deeks et al 2003).

Study limitations and biases that affect RCTs also affect non-randomised studies, but typically to a greater extent. Sources of bias in research studies include selection bias, performance bias, attrition bias, detection bias, and reporting bias. For cohort studies, as an example of an observational study, each respective bias should be addressed properly by controlling for confounders, measuring exposures, doing a complete follow-up, and blinding the outcome assessment (Deeks et al 2003). Study limitations in observational studies may fall under four domains: (1) a failure to develop and apply appropriate selection criteria, (2) flawed measurement of both exposure and outcome, (3) failure to adequately control confounding, and (4) incomplete follow-up of patients (Guyatt GH et al 2011). A failure to develop and apply appropriate eligibility criteria (inclusion of control population) could manifest as either under- or over-matching in case-control studies, or selection of exposed and unexposed in cohort studies from different populations. Flawed measurement of both exposure and outcome is another study limitation. This may manifest as either differences in measurement of exposure, or differential surveillance of the outcome in exposed and unexposed in cohort studies. The third limitation of failure to adequately control confounding may manifest as either the failure of accurate measurement of all known prognostic factors, or failure to match for prognostic factors and/or lack of adjustment in statistical analysis (Guyatt et al 2011).

As mentioned previously, GRADE rates non-randomised studies, such as observational studies, as generally low quality studies to start with. Due to the variety of study designs classified as non-randomised studies, with their varying susceptibility to different biases, it is difficult to use a single recommended instrument for appraising the risk of bias in non-randomised studies (Reeves et al 2011; Viswanathan et al 2012). In such circumstances researchers usually add specific risk of bias instruments or items to help with their assessment (Reeves et al 2011).

Because of the diversity of non-randomised studies, assessment of observational studies requires attention to the design features rather than the design labels (e.g. 'cohort' study, 'cross-sectional' study). Assessing what the studies did to control for confounding may be difficult though. Observational studies require particular noting of any confounding factors, and how they were measured or fitted as covariates in regression models, if done at all. For studies that follow populations over time, the list of potential confounders may increase over time (Reeves et al 2011). The reason why observations studies need to consider and report any/all confounders is because: (1) the direction of bias introduced by confounders is unpredictable; (2) methods to control for confounding are likely to vary between studies; (3) the extent of residual confounding in any particular study is unknown; and (4) residual confounding and other biases mean that the confidence intervals underestimate the true uncertainty around an effect estimate. Even if a study reports what confounders were considered, one needs to note which ones were adjusted for in the analysis and which ones were not (Reeves et al 2011; Viswanathan et al 2012).

In general, non-randomised studies have methodological limitations due to their study design and are often also poorly reported. This makes assessing methodological quality and risk of bias consistently across primary studies difficult or impossible (Kwan & Sandercock 2004; Viswanathan et al 2012). A consensus statement, "STrengthening the Reporting of OBservational studies in Epidemiology" ("STROBE"), guides the best-practice reporting of observational epidemiological studies, however not all published observational studies may comply with such reporting standards (STROBE 2016). This particularly applies to older studies that were not subject to these reporting standards.

Interpreting a body of evidence consisting of few studies and/or poor quality studies

When a body of evidence consists of few studies and/or poor quality studies, caution should be used when interpreting it and making any recommendations.

Interpreting a body of evidence with few studies:

Caution needs to be exercised when interpreting a systematic review with few studies, even when the quality of the few studies is good. The danger of interpreting evidence with few studies is the uncertainty that the results from (any) study are replicable. Relying on one or two studies, especially small and poorly quality studies, done in a particular population/setting with a particular intervention regime for a particular outcome, limits the how we can interpret the transferability of those results to other populations/settings, intervention regimes, or outcome measures. Extrapolation beyond what is presented in the few included studies may not be possible or valid.

In addition to this, there is also the factor of publication bias. Typically researchers may not publish their findings because they found no effect. Systematic reviews can usually estimate the likelihood of publication bias (STROBE 2016; Guyatt et al 2002). As such, we cannot be confident that what has been found is truly the whole body of research evidence. Again, caution is needed when interpreting outcomes or recommendations with few studies.

Interpreting a body of evidence containing poor quality studies:

One key issue with public health interventions is the use of non-randomised studies. Non-randomised studies may contain heterogeneity that can arise through differences in participants, interventions and outcome assessments across studies. The possibility that bias is the cause of heterogeneity must be considered. However, as a general principle in evidence synthesis, a lack of

heterogeneity does not necessarily indicate a lack of bias, since it is possible that a consistent bias applies in all studies (Reeves et al 2011).

It is usually recommended to consider confounders in any non-randomised study, if reported, when interpreting the findings. These reported confounders should also be considered when interpreting the body of evidence across many studies to help highlight any heterogeneity between studies. Each study may have different confounders, and this may make interpretation across the body of evidence difficult.

Researchers may opt to not collect a great detail about the risk of confounding and other biases. However, if this approach is taken, systematic review groups such as the Cochrane Collaboration recommend that researchers acknowledge the potential extent of the heterogeneity between studies with respect to potential residual confounding and other biases (Reeves et al 2011).

Implications of established risk factors on health outcomes

When synthesising the body of evidence for any health intervention, one needs to consider any established risk factors on the health outcomes of interest. Health outcomes are influenced by a number of intrinsically related biological, lifestyle/behavioural, societal and environmental factors (AIHW 2012a). These influences may be commonly accepted factors such as age or disease severity.

When looking at water fluoridation, the primary health outcomes relate to dental health. There are some known risk factors, which are mainly lifestyle or behavioural risk factors that may affect dental health. These factors may include: the consumption of sugar and processed foods, food preparation behaviours at home using locally sourced water, consumption of fluoride-containing beverages (e.g. drinking tea); and oral health behaviours (e.g. use of toothpaste).

Since this review is also looking at other health outcomes (e.g. cancers), a brief discussion about risk factors on these health outcomes is also warranted. Biological factors, such as genetic make-up, could be a factor in certain adverse health outcomes. Lifestyle/behavioural factors such as poor diet, low activity levels, and substance abuse (e.g. smoking, alcohol), may contribute to other adverse health outcomes. Biological risk factors such as high blood pressure or high cholesterol may contribute to adverse health outcomes. Negative societal and environmental factors could include exposure to hazardous chemicals (e.g. lead, environmental pollution) in the environment due to living in poorer geographical regions (AIHW 2014). In considering societal and environmental factors we also need to consider the dose, exposure time, mode of exposure, and any agonistic/synergistic factors that could influence a factor's action on the body and therefore the health outcome of interest.

A source of heterogeneity and complexity for synthesizing and interpreting the body of evidence is when there are differing exposures to underlying risk factors between studies. Another problem with considering established risk factors when interpreting the body of evidence present in studies is from differing length of follow-up between studies (Deeks et al 2011). Furthermore, some established risk factors in studies may be measured and accounted for, but many may go unnoticed and are not assessed (Deeks et al 2003).

Limitations of ecological studies

Ecological studies can be useful:

Ecological studies are descriptive studies where the unit of study are populations or groups of people. They describe the characteristics of a group, usually by describing exposure data often only available at an (geographical) area level. Ecological studies can be used to demonstrate patterns of disease and associated factors in populations, and can be used to generate hypotheses about possible causes of disease by using geographical/spatial information. They are used for health service planning, and may be used to investigate possible correlations, provide surveillance of

health states, study disease clustering, and monitor the effectiveness of health interventions (Jekel et al 2007).

The ecological fallacy limits how much potential associations can be explored:

However, ecological studies cannot be used to provide or explore associations in any depth. One reason is the “ecological fallacy”. This is an error due to inappropriate interpretation of data and conclusions made about individuals from the aggregated/population data. The ecological fallacy assumes, by proxy, that individuals all have the average characteristics of the group/population as a whole (Jekel et al 2007). In reality, any association observed between variables/factors at the group/population level does not necessarily mean that the same association exists for any randomly selected individual chosen from the group/population. Reasons for the ecological fallacy include: (1) it is not possible to link exposure with disease in individuals; (2) data used in ecological studies are usually collected for other purposes and may not be in an ideal format or be complete; (3) average exposure levels of a substance of interest (e.g. water fluoridation) may mask more complicated relationships with the disease/s of interest; (4) usually there is an inability to control for confounding in these studies; (5) there may be potential systematic differences between geographical areas in recording disease frequency (e.g. disease coding and classification, diagnosis, completeness of reporting); and (6) there may be potential systematic differences between geographic areas in the measurement of exposures (e.g. water fluoridation) (Blumenthal et al 2001; dos Santos Silva 1999).

For ecological studies on the health effects of water fluoridation, it may be difficult to measure the actual fluoride intake of individuals or populations, as well how it contributes to the outcomes of interest. Examples of other sources of fluoride could include food preparation behaviours at home using locally sourced water; fluoride-containing beverage consumption behaviours (e.g. drinking tea); and oral health behaviours (e.g. use of toothpaste). It may also be difficult to measure “competing” factors that may influence the same health outcomes of interest. For example, confounders for tooth decay may include such things like a very high intake of sugar and processed foods.

METHODOLOGY

The research questions were:

- What is the effect of water fluoridation (CWF between 0.4–1.5 ppm) compared to a non-fluoridated water supply (defined as <0.4 ppm) on dental caries and dental fluorosis?
- What are the health effects (excluding dental caries and dental fluorosis) of water fluoridation (CWF or naturally occurring) compared to a non-fluoridated water supply (defined as <0.4 ppm) or fluoridation at a different level?

An additional comparator for the other health effects (i.e. fluoridation at a different level) was included in the interest of being comprehensive due to concerns about some health effects expressed by some members of the Australian community.

The review process included four components:

1. a systematic review of the dental effects of water fluoridation, which consisted of:
 - a. an overview of reviews on the effects of water fluoridation on dental caries,
 - b. a systematic review of recent primary studies on the effects of water fluoridation on dental caries not identified in the reviews included in the overview,
 - c. a critical appraisal of the evidence on dental fluorosis included in the existing Cochrane review (Iheozor-Ejiofor et al 2015); and
2. a systematic review of the other health effects of water fluoridation.

HISTORY OF THE REVIEWS

This review was initially commissioned as a systematic review of the health effects of water fluoridation, excluding dental effects, paired with a critical appraisal of the Cochrane Review (Iheozor-Ejiofor et al 2015) on the dental effects of water fluoridation. It was anticipated that the Cochrane Review (Iheozor-Ejiofor et al 2015) would provide the necessary data for the assessment of the dental effects of water fluoridation.

The Cochrane Review (Iheozor-Ejiofor et al 2015) adopted similar criteria to McDonagh et al (2000) for the inclusion of studies. In both reviews for the caries outcomes considered in these reviews, only prospective studies with a concurrent negative control, with at least two points in time evaluated and a change in fluoridation in the experimental arm were included. Few contemporary studies met these inclusion criteria, and therefore the review was unable to assess the role of CWF in a contemporary setting. Furthermore, the study designs included are unable to assess the effects of water fluoridation on adults due to the long follow up time which would be required in order to approach lifetime exposure. A more detailed assessment of the strengths and limitations of the Cochrane review (Iheozor-Ejiofor et al 2015) can be found on page 49.

Therefore supplementary data was requested by the Fluoride Reference Group and a second review was commissioned to examine the effects of water fluoridation on dental caries. This review was undertaken in two parts; an overview of existing systematic reviews (including the Cochrane review) and a systematic review of recent primary studies. However, the existing Cochrane review (Iheozor-Ejiofor et al 2015) was considered sufficient for the assessment of the effects of water fluoridation on dental fluorosis as it had broader inclusion criteria and no further searches or data extraction were undertaken for this outcome.

COMMON METHODOLOGY

For all systematic reviews, following a unique electronic database search the following standard methodology was undertaken. As described in the research protocol, searches of additional relevant resources were conducted. General internet searches were conducted to identify relevant reports, guidelines and health technology assessments concerning water fluoride levels. All citation review

activities were carried out independently by two reviewers. Disagreements between the reviewers were resolved by discussion, or a third reviewer.

Review of citations

All citations retrieved from the searches of electronic databases and other resources were downloaded into Reference Manager software and duplicate citations were removed.

Review of titles and abstracts

All citations were initially reviewed by consideration of their title and abstract. In this stage studies were excluded based on the PICOS (population, intervention, comparator, outcome, study type) criteria for the individual research question

Review of full text

All studies remaining after the review of titles and abstracts were assessed using the full text of the publication. Studies were excluded if they did not meet the specified PICOS criteria.

Classification of evidence

The NHMRC Evidence Hierarchy was used to assess the level of evidence for each included study (NHMRC 2009). The outcome being assessed affects the type of study design sought. As water fluoridation is an intervention that is implemented with the aim of reducing dental caries, the level of evidence of included studies for the dental caries component of the review was based on the intervention hierarchy. Additional study designs not included in the intervention hierarchy were classified as Level IV evidence.

For other health effects (potential harms) of fluoridated water, where the outcomes are likely to be rare and due to prolonged exposure, the aetiology hierarchy was the most appropriate.

Table 10 NHMRC evidence hierarchy: designations of 'levels of evidence' for intervention and aetiology research questions

Level	Intervention ^a	Aetiology ^b
I ^c	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A prospective cohort study
III-1	A pseudorandomised controlled trial	All or none ^d
III-2	A comparative study with concurrent controls: Non-randomised experimental trial ^e Cohort study Case-control study Interrupted time series with a control group	A retrospective cohort study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study ^f Interrupted time series without a parallel control group	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	A cross-sectional study or case series

a. Definitions of these study designs are provided on pages 7–8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

b. If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

c. A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review

should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

- d. All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.
- e. This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).
- f. Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

Ecological studies are not normally included in the levels of evidence for aetiology research questions. For the purposes of this review ecological studies were classed as Level IV evidence.

Quality assessment of included studies

The quality and risk of bias for each individual study was assessed by two independent reviewers. Any disagreements were resolved through discussion. The method used to assess quality and risk of bias was based on study type. The assessment methods for each study type are presented below. For samples of each instrument please see the Technical Report.

Existing reviews

The quality of identified reviews was assessed using the AMSTAR quality assessment tool. The assessment involves considering the risk of bias caused by study design, restrictive search strategies, publication sources (i.e. grey literature), reporting inaccuracies, assessment of the scientific quality of included studies, the use of appropriate statistical techniques, the likelihood of publication bias and the possibilities of conflicts of interest. Scoring using the AMSTAR tool is calculated by the accumulation of positive (“yes”) answers, and a higher score indicates a lesser risk of bias within the individual review.

Cohort studies and case-control studies

The quality of identified cohort or case-control studies was assessed using the cohort and case-control checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN). The checklists include an overall assessment of the study, which is classified as:

- High quality: Majority of the criteria were met with little or no risk of bias. The results are unlikely to be changed by further research.
- Acceptable: Most of the criteria were met. There were some flaws in the study with an associated risk of bias. The conclusions may change in light of further studies.
- Low quality: Either most of the criteria were not met, or there were significant flaws relating to key aspects of the study design. The conclusions are likely to change in light of further studies.

Cross sectional studies and ecological studies

The quality of identified cross-sectional and ecological studies was assessed using the National Institute for Health and Care Excellence (NICE) quality appraisal checklist for quantitative studies reporting correlations and associations. This checklist produces an overall study quality grading for internal validity (IV) and a separate one for external validity (EV); it is described in more detail in the Technical Report. Studies were also classified as high quality, acceptable quality or low quality, to be consistent with the assessments generated with the SIGN checklists.

Data extraction

Data were extracted from individual studies using a standardised data extraction form designed specifically for each review. Where necessary, the form was adapted to best present the results of individual studies. Data extraction was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion or consultation with a third reviewer.

Missing data from individual studies was not sought. Samples of the data extraction forms are presented in the Technical Report.

Presentation of the results

The results from the included studies about dental caries were discussed by outcome. The results from the included studies about other health effects were discussed by the applicability of the fluoride level comparisons to the Australian context (see page 44 for details). This was not applied to the dental caries outcomes as the fluoride level comparisons were all directly applicable to the Australian context.

Results were presented in tables with the exception of studies where only β coefficients were reported. Where available, the results presented were stratified by participant age (infants, children, adolescents, adults and later adulthood age), high needs groups, high risk groups or special needs groups (see the Technical Report for definitions).

Based on initial scoping undertaken during development of the research protocol, it was not anticipated that sufficient evidence would be identified for any individual outcome that would warrant a pooled analysis. The systematic review did not identify any outcomes with sufficient quantity and quality of evidence to justify a pooled analysis and so no such analyses were performed. Consequently, no formal assessment of publication bias was undertaken. However the review authors did note if any publication bias was suspected.

Outcome definition and prioritisation

GRADE guidelines (Guyatt et al 2011) specify that outcomes should be pre-specified and undergo an initial classification into three categories according to their importance for decision making (critical, important but not critical, or low importance) prior to undertaking the review. The relative importance of the outcomes is to be reassessed after reviewing the evidence.

Classification of the importance of the outcomes was performed by the Fluoride Reference Group prior to the start of review activities and confirmed as part of the GRADE process of interpreting the body of evidence identified in the review.

The pre-specified outcomes to be included for the review of the dental effects of water fluoridation are presented in Table 11, with their importance as confirmed by the Fluoride Reference Group.

Table 11 Outcomes from the systematic review to be included in the evidence evaluation

Outcome	Definition of outcome (examples)	Importance of the outcome
Dental caries	Chronic and progressive disease of the mineralised and soft tissues of the teeth.	Critical for decision making
Dental fluorosis	Hypomineralisation of the dental enamel. It can appear on the teeth as white flecks, brown staining or pitting of the enamel and in severe cases could cause aesthetic concern.	Critical for decision making
Neuro-cognitive disorders	Disturbances in the mental process related to thinking, reasoning, and judgment (delirium, Alzheimer disease)	Important, but not critical
Dementia	The impairment of brain function, involving memory, thinking and concentration (dementia)	Important, but not critical
Neuro-developmental disorders	Disorders of brain function that affect emotion, learning, and memory (intellectual disability, communication disorders, autism spectrum disorder, attention deficit/hyperactivity disorder, specific learning disorders, motor disorders)	Important, but not critical

Outcome	Definition of outcome (examples)	Importance of the outcome
All cancers (malignant neoplasms) other than bone cancer	A range of diseases in which some of the body's cells become defective, begin to multiply out of control, can invade and damage the area around them, and can also spread to other parts of the body to cause further damage (site specific cancers e.g. lung, bladder)	Important, but not critical
Cancers of the bone, and specifically osteosarcoma	Cancer that forms in cells of the bone (osteosarcoma, chondrosarcoma, Ewing sarcoma)	Important, but not critical
Congenital abnormalities	Structural or functional abnormalities present at birth that can cause physical disability, intellectual and developmental disability, and other health problems (Congenital malformation (e.g. cleft lip or palate, heart defects, limb defects), functional, or developmental abnormalities (e.g. behavioural disorders, speech or language difficulties, congenital hypothyroidism, congenital hyperthyroidism), chromosomal disorders (e.g. Trisomy 21, Prader-Willi syndrome, Fragile X syndrome))	Important, but not critical
Skeletal effects (other than bone cancers)	Diseases of or relating to a skeleton (bone fracture, skeletal fluorosis, osteosclerosis)	Important, but not critical
All-cause mortality	All deaths reported in a given population (all-cause mortality)	Important, but not critical
Renal effects	Pathological processes of the kidney or its component tissues (kidney stones, chronic kidney disease)	Important, but not critical
Thyroid dysfunction	Pathological processes involving the thyroid gland (acquired hypothyroidism, acquired hyperthyroidism, goitre, thyroiditis, Graves' disease, thyrotoxicosis)	Important, but not critical
Any other adverse event	An adverse outcome that occurs during or after the use of the intervention but is not necessarily caused by it.	Important, but not critical

The Fluoride Reference Group decided that for the outcome of skeletal fluorosis the outcome measures would be restricted to stage II and stage III of the disease. For all other outcomes, any method of measuring the outcome was to be included, as reported in each included study.

GRADE assessment

The evidence for each outcome was assessed using the GRADE system for rating the quality of evidence (Guyatt et al 2011) with some modification for the assessment of a public health intervention (Harder et al 2015). The GRADE assessment was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion or consultation with a third reviewer.

Under the GRADE system, the overall quality of the evidence for an outcome is categorised as high, moderate, low or very low depending on the study design. On the advice of the NHMRC, and with the approval of the Fluoride Reference Group, this review adopted the GRADE categorisation suggested by Harder et al (2015), in which non-randomized designs which are less prone to bias are categorised in the GRADE system as being of moderate quality. It should be noted that this modification has not been tested in public health settings. For this review, all Level II, Level III-1 and Level III-2 studies were initially categorised as moderate quality and all Level III-3 and Level IV studies were initially graded as low quality.

The quality of the evidence was decreased if any of the following conditions were met:

- Serious or very serious limitation to study quality
- Important inconsistency
- Some or major uncertainty about directness

- Imprecise or sparse data
- High probability of reporting bias

The quality of the evidence was increased if the evidence had not been downgraded and if any of the following conditions are met:

- Strong or very strong evidence of association based on consistent evidence from two or more observational studies, with no plausible confounders
- Very strong evidence of association based on direct evidence with no major threats to validity
- Evidence of a dose-response gradient
- All plausible confounders would have reduced the effect

The review also allowed the possibility for upgrading the evidence if the effects observed were consistent across study designs, as suggested by Harder et al (2015). For this review, this was applied if consistent results were observed across different levels of evidence.

The reasoning behind any increase or decrease in the rating of evidence was recorded in the footnotes to the GRADE assessment tables. Full GRADE evidence profiles are presented separately for each outcome and the Summary of Findings tables that collect the evidence for all outcomes are presented in the discussion section.

The GRADE system for assessing evidence was not originally designed to consider evidence for public health interventions. Consequently, for public health interventions like water fluoridation, where evidence of efficacy comes from observational studies, much of the evidence will ultimately be rated as 'low' or 'very low' quality. Due to concerns that the potential pejorative connotations of these descriptors may result in the evidence being disregarded and/or misinterpreted, the Fluoride Reference Group decided to omit the descriptors and describe the evidence in terms of the confidence in the reported results.

Development of evidence statements

Evidence statements on the health effects of water fluoridation for each outcome were developed by the Fluoride Reference Group. The NHMRC conducted a quality assurance process to ensure that evidence was summarised consistently across all of the identified outcomes.

In developing the evidence statements, the Fluoride Reference Group took into account the limitations of the evidence, including the often small numbers of studies, the poor methodological quality of many studies and, in some cases, the rarity of health outcomes. The Fluoride Reference Group drew conclusions based upon the balance of probabilities and, in some cases, was unable to definitively rule out the possibility of health effects.

Each evidence statement includes a summary of the evidence identified in the current review. The outcomes for caries (e.g. dmft/DMFT, dmfs/DMFS, prevalence, proportion caries-free and incidence, where applicable) have been combined into a single evidence statement for deciduous and permanent teeth each. The evidence statements for each outcome are presented following the GRADE assessment and take into account the extent and strength of the evidence from the studies identified through the systematic review.

The Fluoride Reference Group adopted consistent language in the Evidence Statements to reflect these factors. The Evidence Statements generally fit within one of the following categories:

- *Consistent evidence of a health outcome*: this wording was used when the Fluoride Reference Group was confident that the body of evidence was valid, applicable to the Australian context and consistently did show an association between water fluoridation and the health outcome.

- *The evidence shows no association of a health outcome:* this wording was used when the Fluoride Reference Group was confident that the body of evidence was valid, applicable to the Australian context and demonstrated that there was no association between water fluoridation and the health outcome.
- *Limited evidence of a health outcome:* this wording was used when there was some evidence of either no association or of an association between water fluoridation and the health outcome, but the Fluoride Reference Group was uncertain about this finding due to limitations in the body of the evidence.
- *Insufficient evidence to draw any conclusion:* this wording was used when the Fluoride Reference Group was not convinced that there was enough valid evidence to draw any conclusion about the relationship between water fluoridation and the health outcome. While it may be highly unlikely, the Fluoride Reference Group was unable to definitively rule out the possibility of these health outcomes.

METHODOLOGY: REVIEW OF THE DENTAL EFFECTS OF WATER FLUORIDATION

This review consisted of three components:

1. An overview of existing reviews about the effect of water fluoridation on dental caries
2. A systematic review of primary studies about the effect of water on dental caries not identified in the overview, and
3. A critical appraisal of the evidence on dental fluorosis included in the existing Cochrane review (Iheozor-Ejiofor et al 2015)

For dental fluorosis, the Cochrane review (Iheozor-Ejiofor et al 2015) was considered sufficient as it had broader inclusion criteria and no further searches or data extraction were undertaken for this outcome.

Overview of reviews

Research question

What is the effect of water fluoridation (CWF between 0.4–1.5 ppm) compared to a non-fluoridated water supply (defined as <0.4 ppm) on dental caries?

The PICOS criteria for the research question are outlined in Table 12.

Table 12 PICOS criteria for the evaluation of the dental effects of water fluoridation, overview of reviews

Criterion	Description
Population	Populations of all ages Subgroup analysis: Life stage: infants (ages 0–4), children (ages 5–11), adolescents (ages 12–17), adults (ages 18–64) and later adulthood age (ages 65+) People with special needs: including low income and social disadvantage Rural and remote communities
Intervention/Exposure	Drinking water with a fluoride level within current Australian levels (0.4 ppm–1.5 ppm)
Comparator	Non-fluoridated drinking water (<0.4 ppm)
Outcome	Dental caries
Study type	Reviews of primary studies. To be included in this overview a review must include a systematic search that attempts to identify all relevant primary studies.

Abbreviations: ppm = parts per million

Literature search

The following electronic databases were searched on the 12th November, 2015:

- EMBASE.com (includes EMBASE and MEDLINE)
- PreMedline (via Ovid)
- PsycInfo (via Ovid)
- Global Health (via Ovid)
- EBM (Cochrane Database of Systematic Reviews, Health Technology Assessment, NHS Economic Evaluation Database, ACP Journal Club, Database of Abstracts of Reviews of Effects)

The EBM databases for the Cochrane Methodology Register and the Cochrane Central Register of Controlled Trials were not included for this search, as only reviews were to be identified, and these databases do not report reviews.

To identify reviews of primary studies on the effects of water fluoridation on dental caries, databases were searched from 1st October 2006 onwards, updating the search from the NHMRC (2007a) review with a two-month overlap. An additional study design (systematic review) filter was applied, adapted from the filter published by the NHMRC (1999). The search strategies used and the results of the database searches are presented in the accompanying Technical Report.

The reference lists of all included studies were searched for additional relevant publications. General internet searches were also conducted to identify relevant reports, including guidelines and health technology assessments. A list of the international health technology agencies websites that were searched is provided in the accompanying Technical Report.

Studies were included based on the PICOS criteria shown in Table 13.

Table 13 Inclusion criteria used in the review of citations

Criterion	Explanation
Population	A study of human participants
Intervention	Fluoride in drinking water within current Australian levels (0.4 ppm 1.5 ppm)
Comparator	Non-fluoridated drinking water (<0.4 ppm)
Outcome	Dental caries
Study type	A review of primary studies. To be included in this overview a review must include a systematic search that attempts to identify all relevant primary studies.
Publication date	Published after 1st October 2006

Abbreviations: ppm = parts per million

In addition to the PICOS criteria, the following exclusion criteria were applied:

- Narrative reviews, letters, editorials, animal studies, in-vitro studies, laboratory studies, conference abstracts and technical reports were excluded.
- Non-English language studies were excluded. This was the final exclusion criterion applied.

Systematic review of primary studies

Research question

What is the effect of water fluoridation (CWF between 0.4–1.5 ppm) compared to a non-fluoridated water supply (defined as <0.4 ppm) on dental caries?

The PICOS criteria for the research question are outlined in Table 14.

Table 14 PICOS criteria for the evaluation of the dental effects of water fluoridation, systematic review of primary studies

Criterion	Description
Population	Populations of all ages Subgroup analysis: Life stage: infants (ages 0–4), children (ages 5–11), adolescents (ages 12–17), adults (ages 18–64) and later adulthood age (ages 65+) People with special needs: including low income and social disadvantage Rural and remote communities
Intervention/Exposure	Drinking water with a fluoride level within current Australian levels (0.4 ppm–1.5 ppm)
Comparator	Non-fluoridated drinking water (<0.4 ppm)
Outcome	Dental caries
Study type	Any comparative study that was not included in the reviews identified in the Overview of Reviews

Abbreviations: ppm = parts per million

Literature search

The following electronic databases were searched on the 17th November, 2015:

- EMBASE.com (includes EMBASE and MEDLINE)
- PreMedline (via Ovid)
- PsycInfo (via Ovid)
- Global Health (via Ovid)
- All EBM (Includes the Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, Health Technology Assessment and Cochrane Methodology Register)

For each database, a comprehensive literature search strategy was developed to update the literature from the NHMRC's 2007 Review. This search strategy was restricted to studies that were not included in the reviews identified in the overview of reviews. The search strategies used and the results of the database searches are presented in the accompanying Technical Report.

Studies were included based on the PICOS criteria shown in Table 15.

Table 15 Inclusion criteria used in the review of citations

Criterion	Explanation
Population	A study of human participants
Intervention	Fluoride in drinking water
Comparator	Compares: Fluoride within current Australian levels (0.4 ppm–1.5 ppm) vs. unfluoridated water (<0.4 ppm)
Outcome	Dental caries
Study type	A comparative study design
Publication type	Published after 1st October 2006 Not included in the reviews identified in the overview of reviews

Abbreviations: ppm = parts per million

In addition to the PICOS inclusion criteria, the following exclusion criteria were applied:

- Narrative reviews, letters, editorials, animal studies, in-vitro studies, laboratory studies, conference abstracts and technical reports were excluded.
- Non-English language studies were excluded.
- The study did not report any outcome data that could be used in the review, this included studies which did not undertake a multivariate analysis of dental caries
- Where articles report on a regular dental survey, only the results from the most recent survey will be included

METHODOLOGY: SYSTEMATIC REVIEW OF OTHER HEALTH EFFECTS OF WATER FLUORIDATION

Research question

What are the health effects (excluding dental caries and dental fluorosis) of water fluoridation (CWF or naturally occurring) compared to a non-fluoridated water supply (defined as <0.4 ppm) or fluoridation at a different level?

The PICOS criteria for the research question are outlined in Table 16.

Table 16 PICOS criteria for the evaluation of the health effects of water fluoridation

Criterion	Description
Population	Populations of all ages Subgroup analysis: <ul style="list-style-type: none"> • Life stage: infants (ages 0–4), children (ages 5–11), adolescents (ages 12–17), adults (ages 18–64) and later adulthood age (ages 65+) • People with special needs: including low income and social disadvantage • Rural and remote communities
Intervention/Exposure	Fluoride at any concentration present in drinking water
Comparator	1. Non fluoridated drinking water (<0.4 ppm); or 2. Drinking water with a different concentration of fluoride.
Outcome	Any reported health effects (excluding dental caries and dental fluorosis) including: <ul style="list-style-type: none"> • Neuro-cognitive disorders • Dementia • Neuro-developmental disorders • All cancers (malignant neoplasms) other than bone cancer • Cancers of the bone, and specifically osteosarcoma • Congenital abnormalities • Skeletal effects • Mortality • Renal effects • Thyroid dysfunction • Any other adverse effects
Study type	Any comparative study design

Abbreviations: ppm = parts per million

Literature search

The following electronic databases were searched on the 14th of October, 2014:

- EMBASE.com (includes EMBASE and MEDLINE)
- PreMedline (via Ovid)
- PsycInfo (via Ovid)
- Global Health (via Ovid)
- All EBM (Includes the Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, Health Technology Assessment and Cochrane Methodology Register)

For each database, a systematic search strategy was developed to identify all relevant published evidence on the health effects of water fluoridation by using index terms and text words based on key elements of the research question and PICOS criteria. All databases were searched from 1st October 2006 onwards, updating the search from the NHMRC (2007a) review with a two month overlap. The search strategies used and the results of the database searches are presented in the accompanying Technical Report.

Searches of additional Australian resources included the Trove database of the National Library of Australia, the NHMRC website, State and Federal health department websites, and State and Federal environment and water authority websites. Searches of international resources included searches of the websites of health and water authorities in the United Kingdom, United States of America, Ireland, New Zealand and the European Union. General internet searches were conducted to identify guidelines and health technology assessments concerning water fluoride levels. The

website of the Fluoride Action Network was also searched for relevant published studies. The reference lists of all studies included in the report and all relevant systematic reviews identified in the literature search were checked for additional studies.

Studies were included based on the PICOS criteria shown in Table 17.

Table 17 Inclusion criteria used in the review of citations

Criterion	Explanation
Population	A study of human participants
Intervention	Fluoride in drinking water
Comparator	Compares either: Fluoride at a given concentration vs. unfluoridated water Fluoride at a given concentration vs. fluoride at different concentration
Outcome	Report on health effects other than dental caries and dental fluorosis
Study type	A comparative study design
Publication type	Published after 1st October 2006

In addition to the PICOS inclusion criteria, the following exclusion criteria were applied:

- Narrative reviews, letters, editorials, animal studies, in-vitro studies, laboratory studies, conference abstracts and technical reports were excluded.
- The full text publication could not be retrieved
- The study was not published in the English language
- The study did not report any outcome data in a form that could be used in the review

As specified in the research protocol, systematic reviews were not eligible for inclusion, but relevant reviews were collected and their contents noted in the review.

To aid in the interpretation of the results, the evidence for each outcome was presented based on the applicability of the included studies. Study applicability was based on how similar the water fluoride levels reported within each study were to those experienced in Australia:

1. High applicability studies: unfluoridated water (<0.4 ppm⁶ fluoride) vs. water with up to 1.5 ppm fluoride
2. Partial applicability studies: unfluoridated water (<0.4 ppm fluoride) vs. water with >1.5 ppm fluoride; and water with 0.4–1.5 ppm fluoride vs. water with >1.5 ppm fluoride
3. Limited applicability studies: studies in which all groups compared had water fluoride levels >1.5 ppm

Public Call for Evidence

The Australian community was invited by NHMRC to submit published studies to be evaluated as part of the systematic review. To be accepted by NHMRC, published studies were required to be all of the following:

- Published after 1 October 2006;
- An examination of fluoridated drinking water, not other fluoride interventions (e.g. fluoridated milk, salt, bottled water or topical fluoride applications such as toothpaste, varnish, gel or mouth rinse);
- Publicly available in English;

⁶ The units 'ppm' are equivalent to 'mg/L'

- Available in full text;
- A study or systematic review that includes a group exposed to drinking water that contains fluoride and a comparison group exposed to drinking water with a lower concentration of fluoride or non-fluoridated water (defined as having a concentration of fluoride less than 0.4 mg/L); and
- A study which reports outcomes relevant for human health.

The following topics were considered by NHMRC to be outside the scope of the systematic review:

- Dental caries and dental fluorosis
- Chemicals used to fluoridate drinking water
- Ethics of water fluoridation
- Studies published before 1 October 2006
- Studies based on a type of evidence that is not appropriate to the systematic review, e.g. personal story, medical record, raw data, narrative review, case series or case report.

Literature that met the scope of the systematic review was provided to the evidence review team at the University of Sydney. The University of Sydney assessed these studies against the results of the systematic literature search. Studies that had already been identified in the literature search were excluded from further consideration and the remaining studies were assessed using the same methods described above for the review of full text publications.

RESULTS OF THE REVIEW OF DENTAL CARIES

RESULTS OF THE LITERATURE SEARCH

Systematic reviews

All citations retrieved from the systematic review were downloaded into Reference Manager software. The 102 records were checked for duplicate citations. A total of 13 duplicate citations were removed, leaving 89 citations eligible for review. A summary of the citation review process is presented in Figure 1.

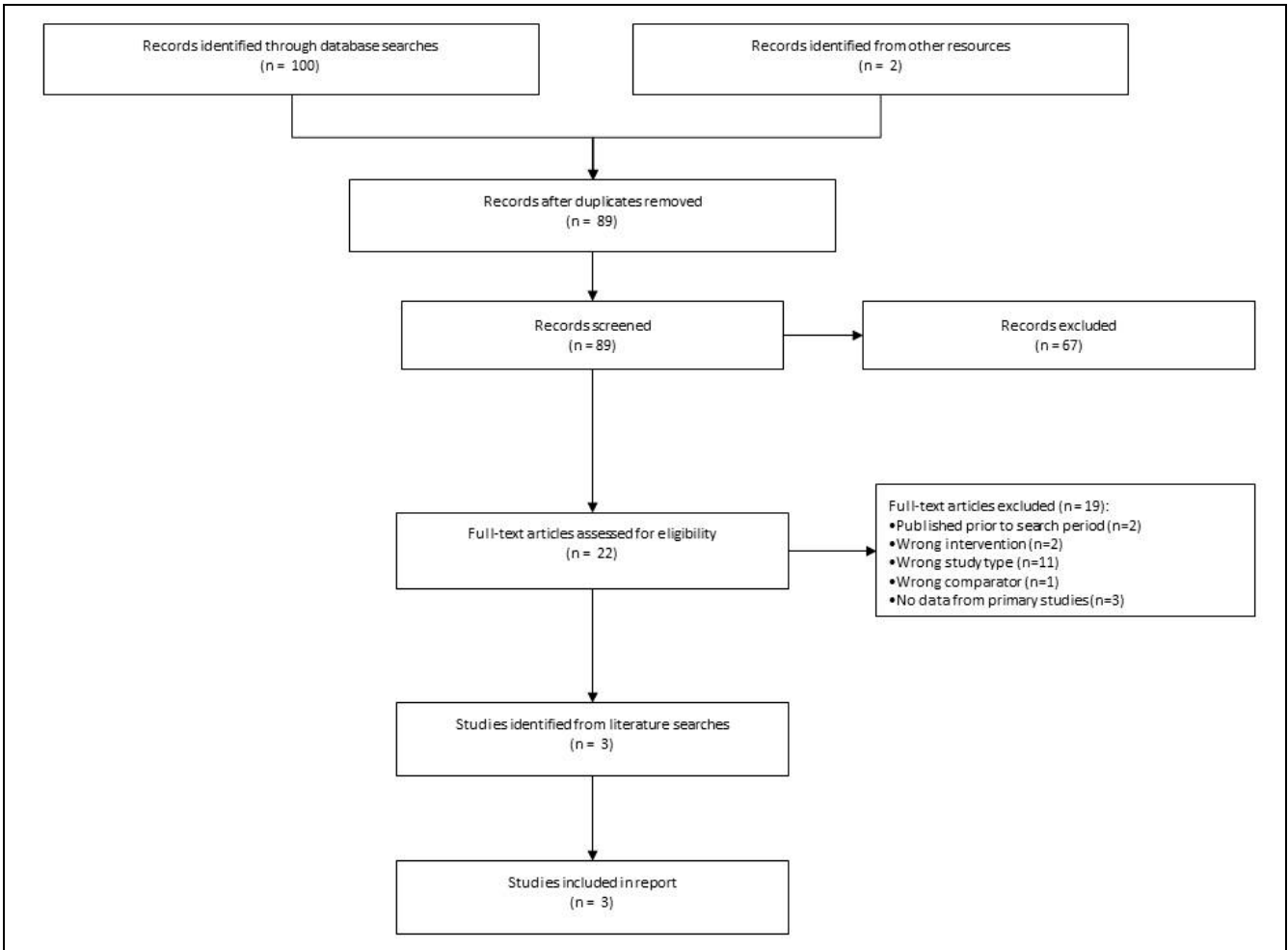


Figure 1 Summary of review of systematic review citations

Recent primary studies

All citations retrieved from the systematic review were downloaded into Reference Manager software. The 1,568 records were checked for duplicate citations. A total of 1,314 duplicate citations were removed, leaving 854 citations eligible for review. A summary of the citation review process is presented in Figure 2.

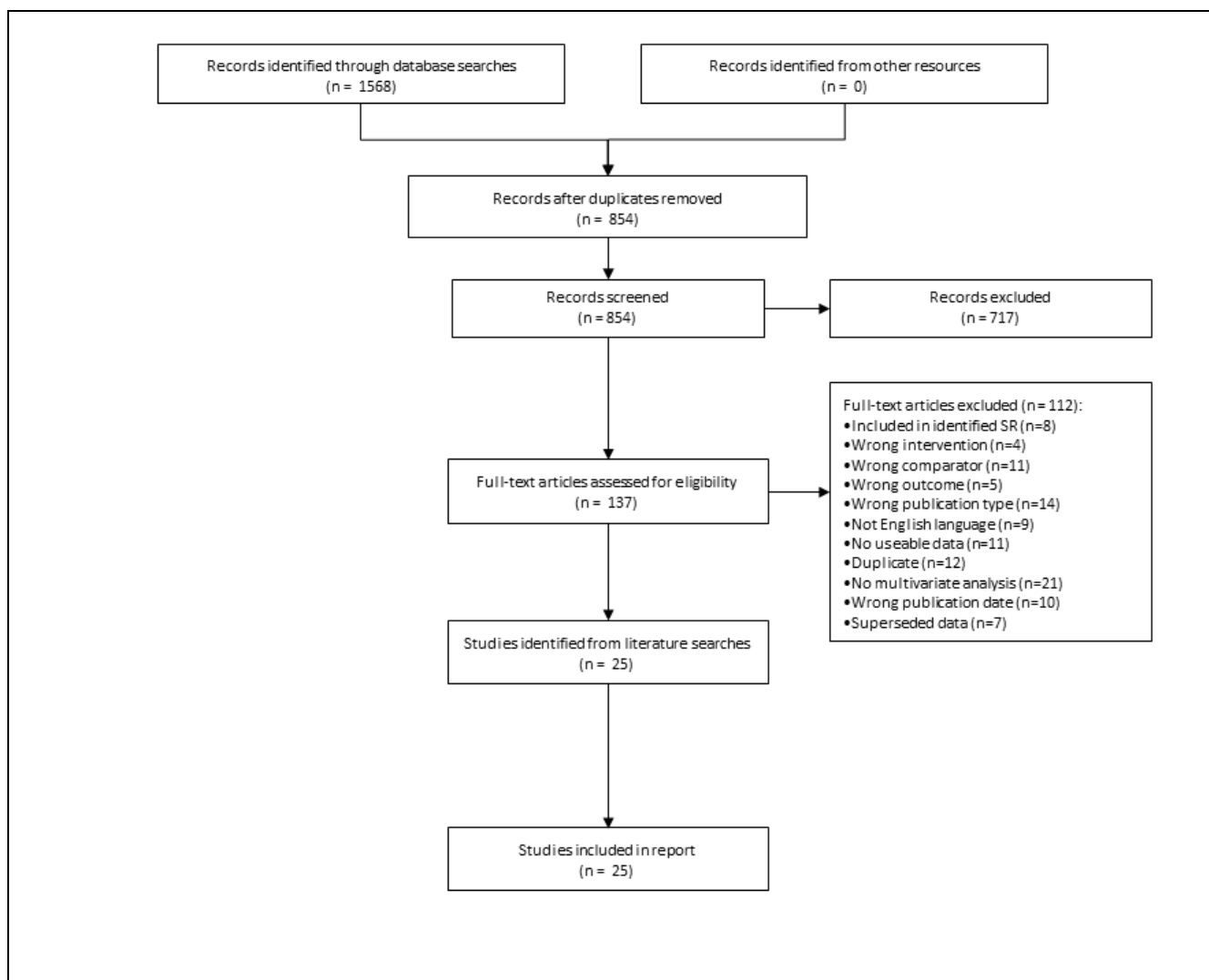


Figure 2 Summary of review of primary study citations

Review of titles and abstracts

Systematic reviews

Application of the inclusion criteria based on the PICOS resulted in the exclusion of 67 citations. A list of the studies excluded at this stage is included in the Technical Report. For the remaining 22 citations, the full text of the publication was retrieved for further review.

Primary studies

Application of the inclusion criteria based on the PICOS resulted in the exclusion of 717 citations. A list of the studies excluded at this stage is included in the Technical Report. For the remaining 137 citations, the full text of the publication was retrieved for further review.

Review of full text

Systematic reviews

The 22 studies were assessed using the full text of the publication. Two studies had been published prior to the specified start date of 1st October, 2006 and were excluded.

The remaining studies were assessed against the exclusion criteria used in the review of titles and abstracts, leading to the exclusion of 18 studies as described below:

- Intervention: 2 studies were excluded because they did not assess fluoride in drinking water within current Australian levels (0.4–1.5 ppm).
- Study type: 12 studies were excluded due to being the wrong study type. Of these, 6 were economic evaluations, 5 did not use systematic methods to identify primary studies and one included non-comparative studies only.

A further three studies were excluded because they did not report any data for their included primary studies. A list of the studies excluded at this stage is included in the Technical Report.

Primary studies

The 137 studies were assessed using the full text of the publication. Eight studies had been published prior to the specified start date of 1st October, 2006 and two were republications of studies originally published prior to this start date and were excluded.

The remaining studies were assessed against the exclusion criteria used in the review of titles and abstracts, leading to the exclusion of 102 studies as described below:

- Intervention: 3 studies were excluded because they did not assess fluoride in drinking water within current Australian levels (0.4–1.5 ppm) and 1 other study the intervention was not water fluoridation.
- Comparator: 11 studies were excluded because the comparator was not <0.4 ppm fluoride
- Publication type: 14 studies were excluded due to being the wrong study type. Of these, 5 were narrative reviews, 3 were commentaries, 4 were conference abstracts or proceedings, and 1 was an interview and 1 was a letter.
- Included in identified systematic review: 8 studies were excluded as they had been included in a systematic review already identified
- Wrong outcome: 2 studies were excluded due to not measuring dental caries and 3 studies due to not measuring dental caries with a valid measure.
- Duplicate: 12 studies were identified as duplicates
- Not in English: 9 studies were excluded as they were not published in English
- No multivariate analysis: 21 studies were excluded because they did not conduct a multivariate analysis including known confounders
- No useable data: 11 studies were excluded for not having any useable data
- Superseded data: 7 studies were excluded because a more recent study had been identified using the same survey data

A list of the studies excluded at this stage is included in the Technical Report.

STUDIES INCLUDED IN THE REVIEW

Systematic reviews

Three systematic reviews were included in this review.

Iheozor-Ejiofor et al (2015) sought to update McDonagh et al (2000) systematic review of public water fluoridation. Of the 155 studies (162 publications) that met the inclusion criteria for this systematic review, 107 had sufficient data to be included in the quantitative synthesis. Fourteen studies provided sufficient data for analysis of caries levels following a change in water fluoridation levels. Three studies met the inclusion criteria for disparities in caries but did not provide sufficient data for quantitative synthesis.

Griffin et al (2007) aimed to examine the effectiveness of self- and professionally-applied fluoride and water fluoridation on adults aged 20 years and over. Of the nine studies that met the inclusion criteria for water fluoridation, seven were included in a meta-analysis.

Rugg-Gunn and Do (2012) aimed to review the effectiveness of water fluoridation in the prevention of dental caries with a focus on results of studies published since 1990 and to discuss aspects of the design and reporting of these studies compared with those published before 1990. A total of 58 studies were included in this review. No meta-analysis was undertaken and the results were reported narratively.

Quality

The review by Ihezor-Ejiofor et al (2015) scored 11 out of 11 on the AMSTAR tool. The authors published the research questions and inclusion criteria before conducting the review. The search strategies and database coverage were comprehensive. There was a robust process for study selection and data extraction. Lists of included and excluded studies, including the reason for exclusion, and the characteristics of all included studies were provided. The methodological quality of all included studies was assessed and used appropriately to formulate conclusions. The methods to pool the study results were adequate, but it should be noted that 30% of the studies were not used in the quantitative synthesis and that the reasons for the substantial statistical heterogeneity were not discussed in detail. Exploration of potential publication bias was not conducted, with the justification that the protocol stipulated that this would only occur if there were more than 10 studies in the meta-analysis. Finally, internal and external sources of funding were reported. An important limitation that was not highlighted by the AMSTAR tool was the restrictive inclusion criteria of only study designs of comparative before-and-after studies. This resulted in most contemporary evidence being excluded as these studies were cross-sectional or ecological studies.

Griffin et al (2007) scored 6 of a possible 10 on the AMSTAR tool. The review did not assess the quality of the included primary studies and therefore did not use this information in formulating conclusions. The research questions and inclusion criteria were not published before conducting the review. Three electronic databases were searched and the search strings were reported. Unpublished clinical studies were sought from the FDA, American Dental association and manufactures of fluoride products. Lists of included and excluded studies, including the reason for exclusion, and the characteristics of all included studies were provided. The methods to pool the studies were adequate. Heterogeneity was not discussed in any detail. Potential publication bias was not discussed and the funding for the review was mentioned.

The methods used for the review by Rugg-Gunn and Do (2012) were very poorly reported and it scored only 2 out of 10 on the AMSTAR tool. The research questions and inclusion criteria were not published prior to the review being conducted. No details besides a “professional internet search conducted” were supplied regarding the literature search and search strategy. Government reports were included if relevant. A list of included studies was published and included limited details. No methodological appraisal of the primary studies was conducted. Conclusions focussed on differences between the results and characteristics of studies published pre- and post-1990. The results from the primary studies were reported in a table. There was no discussion or exploration of publication bias and the source of funding of the review was not mentioned.

Inclusion and exclusion criteria

Ihezor-Ejiofor et al (2015) only included prospective studies with a concurrent control that compared at least two populations—one exposed to naturally or artificially fluoridated water and the other to non-fluoridated water—and measured outcomes at a minimum of two time-points were included for the prevention of caries. Studies could assess the effect of initiation or cessation of water fluoridation but the comparison groups had to be comparable in terms of water fluoride levels at baseline. The change in fluoride level also had to have occurred within three years of baseline. The comparison groups could be exposed to other sources of fluoride as long as these were similar across groups, but if this information was not provided, it was assumed that in industrialised

countries after 1975 the groups had been exposed to fluoridated toothpaste. Outcome measures could be any measure of dental caries including change in the number of decayed, missing, and filled deciduous and permanent teeth/surfaces (dmft/s and DMFT/S, respectively), incidence of caries and percentage of caries-free children. Data on disparities of dental caries was also collected if it had been reported in the primary study. The inclusion criteria for study design severely limited the number of studies that were finally included and resulted in exclusion of most of the contemporary evidence on water fluoridation which employ other observational study designs. This has implications for the conclusions reached by this review which does not reflect the contemporary evidence concerning water fluoridation.

Griffin et al (2007) included studies published in English, lasting for a year or more, and examining the association between fluoride and caries in adults with intact teeth were included. Cross-sectional studies were included if participants lived most of their lives in fluoridated or non-fluoridated communities or the authors estimated the effect of exposure to water fluoridation controlling for potential confounding factors.

Rugg-Gunn and Do (2012) included studies published between 1990 and 2010 examining intentional water fluoridation that reported numbers of decayed, missing and filled deciduous or permanent teeth for fluoridated and non-fluoridated communities.

Risk of bias in the included studies

In the Iheozor-Ejiofor et al (2015) review all included studies were assessed for risk of bias using a modified Cochrane 'Risk of Bias' assessment tool adapted for non-randomised studies. The domains included: sampling, confounding, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential bias sources. The following factors were identified by the review authors to be important confounders: sugar consumption/dietary habits, socioeconomic status, ethnicity and use of other fluoride sources. For each study an assessment of the overall risk of bias was undertaken: a low risk of bias was given when the risk of bias was low across all domains, an unclear risk when there was an unclear risk of bias for one or more domains and high risk of bias when there was a high risk of bias for one or more domains. In addition, a summary assessment of the risk of bias for each outcome across all studies was conducted.

It is unclear in Griffin et al (2007) what, if any, assessment of risk of bias was conducted. A section about validity assessment is included and it emphasises the study design of included papers. The review states that other measures of validity were examined (e.g. drop-out rate and examiner/participant blinding) and reported for included studies but were not used to exclude studies. Only blinding was reported for the water fluoridation studies and drop-out rate was recorded as 'not applicable'.

Rugg-Gunn and Do (2012) did not report on an assessment of the risk of bias of the included studies.

Analyses performed

In Iheozor-Ejiofor et al (2015) the difference in mean change in dmft/s and DMFT/S scores and the difference in the proportion caries-free between fluoridated and control groups were calculated. These estimates were then used to calculate an overall pooled estimate of the mean difference in dmft/DMFT scores and proportion of caries-free children across all of the included studies. For both outcomes the average number of participants in the before-and-after groups were displayed on the forest plots to give an indication of the size of the studies. Only unadjusted results were reported as the data did not allow adjusted results to be calculated.

If data was missing and could not be calculated from the available data, the authors were contacted. If the number of participants was not reported, then the data was not included in the analyses. If standard deviations were missing then they were estimated using a standard equation for both before-and-after mean caries values. A sensitivity analysis was conducted to determine the effect of

the imputed standard deviations. Due to the lack of clarity of reporting and the limited data, heterogeneity in fluoridation technique, fluoride level, outcome measure and technique was not assessed for caries data. Fluoride level was explored as part of the fluorosis analysis. Publication bias was not investigated because there were not enough studies for a robust analysis.

A post hoc subgroup analysis of studies conducted prior to 1975 was done to investigate any potential effect of the widespread use of fluoride toothpaste on outcomes. The planned sensitivity analyses based on risk of bias and timing of baseline measurement were not undertaken because of insufficient numbers of trials. Due to the small number of studies and lack of clear reporting, sources of heterogeneity were not explored using meta-regression or subgroup analysis by study design.

The GRADE approach was used to assess the quality of the evidence within the review. Due to concerns about its use in the context of a public health intervention, the review authors decided to omit the GRADE terminology of 'very low, low, moderate, and high quality' and discuss the findings in terms of their confidence in the results.

Griffin et al (2007) used Fisher's inverse chi-squared method to calculate whether the combined p-values were statistically significant. To measure the size of the effect of water fluoridation, the relative risk ratio was calculated for each of the cross-sectional studies that excluded participants without continuous residency. Summary measures were estimated if there were five or more studies and a random effects model was used. Heterogeneity was tested for using a chi-square test. If heterogeneity was present then the I^2 was estimated.

Rugg-Gunn & Do (2012) reported limited information from the primary studies. A table of findings reported the country the study was conducted in, the year that water fluoridation began, the age of subjects, the caries index used (dmft/s or DMFT/S), the mean score in the non-fluoridated group, the percentage caries reduction and the study type. The caries measure for the fluoridated groups were not reported. Tables were included comparing the percentage caries reduction for studies using historical controls versus concurrent controls, percentage caries reductions of pre- and post-1990 studies, percentage caries reduction of Australian studies compared to other studies, and caries reduction of post-1990 studies that adjusted for confounders compared to those with no adjustment.

Quality of the evidence

In Iheozor-Ejiofor et al (2015) all included studies were observational and the authors' confidence in the effect estimate was limited. The quality of the evidence was downgraded due to an overall high risk of bias in the included studies, mainly due to confounding and lack of blind outcome assessment. The evidence was also downgraded for indirectness because the majority of the studies were conducted before 1975. There was significant heterogeneity in all four caries analyses however, given the direction of effect was in the same direction in all but one of the studies, they did not downgrade for inconsistency. In addition, the evidence was upgraded for consistent very large effect which according to the GRADE system is not recommended once the evidence has been downgraded. The quality assessments have been revised in this report accordingly.

Griffin et al (2007) included eight cross-sectional studies (Level IV evidence) and one prospective cohort (Level III-2). The cohort study was not included in the meta-analysis. As all the studies in the meta-analysis were the lowest level of evidence and there was no adequate assessment of the risk of bias of individual studies, the quality of the evidence should be considered low.

Rugg-Gunn & Do (2012) All included studies were level IV (ecological, cross-sectional and before-and-after studies). This is the lowest level of evidence and therefore, without an adequate assessment of the risk of bias of individual studies, the quality of the evidence should be considered low.

Primary studies

In total, 25 primary studies were included in the current review. A full listing of the citations for the included studies is provided in the references section of this report and in the Technical Report. Note that there are seven other studies identified from the systematic review of other health effects that report on dental outcomes other than dental caries that are included under 'other dental effects'.

The literature search identified three Level III-2 studies (Broffitt 2013; Wang 2012; Chankanka et al 2011), which were analyses of data from the Iowa Fluoride Study. All of the remaining 22 included studies were ecological studies and so were Level IV evidence.

Quality of the included studies

All studies except six were assessed as being of acceptable quality.

Overall, the quality of the evidence identified through the literature search was considered to be acceptable. This was largely due to good reporting and low risk of residual confounding. Information about participant selection methods and participant characteristics was usually adequate. The quality of the individual studies is discussed further under each of the presented outcomes.

DENTAL CARIES

Dental caries is defined as a chronic and progressive disease of the mineralised and soft tissues of the teeth. Fluoride impedes the demineralisation of tooth enamel and enhances its remineralisation, hence shifting the balance of these two processes away from cavitation.

The following outcomes are extracted for the assessment of dental caries:

- Decayed, missing and filled deciduous and permanent teeth (dmft and DMFT respectively)
- Decayed, missing and filled deciduous and permanent tooth surfaces (dmfs and DMFS respectively)
- Caries prevalence
- Percentage of caries-free children
- Incidence of dental caries.

Caries prevalence and percentage caries-free have been presented together as they are closely related—one represents the inverse of each other. The results for each outcome have been presented separately for deciduous and permanent teeth. Then a single evidence statement was developed for each dentition incorporating the body of evidence from all the dental outcomes for each dentition.

Studies that reported results for combined deciduous and permanent teeth outcomes have been reported separately as it is not possible to separate the contribution of each dentition to the results.

In addition we extracted data on disparities in dental caries across different groups of people where this was reported in the included studies. These outcomes are consistent with the Cochrane review (Iheozor-Ejiofor et al 2015).

Moreover, we have presented a separate section of dental outcomes other than those listed above. These include tooth loss, delayed tooth eruption, tooth wear and hospital admissions for the treatment of dental caries. These outcomes have been extracted from studies located in both the systematic review of dental caries and the systematic review of other health effects.

NUMBER OF DECAYED, MISSING AND FILLED DECIDUOUS TEETH

This is a measure of the number of decayed, missing and filled deciduous teeth (dmft).

Evidence from prior reviews

The McDonagh et al (2000) systematic review combined dmft and DMFT measures. Like the Cochrane review (Iheozor-Ejiofor et al 2015), it only included comparative longitudinal studies, in which fluoride was either introduced or withdrawn at the beginning of the study.

Twenty-six studies of the effect of water fluoridation on dental caries were included in the review of which nine reported on change in dmft/DMFT. The measure of effect is the difference of the change in caries from the baseline to the final examination in the fluoridated compared with the control area. The range of mean change in dmft/DMFT was 0.5 to 4.4 teeth with a median of 2.25 teeth. Of the sixteen analyses (9 studies), fifteen showed a statistically significant decrease in the number of decayed, missing, and filled primary/permanent teeth. These results are summarised in Figure 3.

The 2007 NHMRC review did not identify any additional studies which reported on dmft.

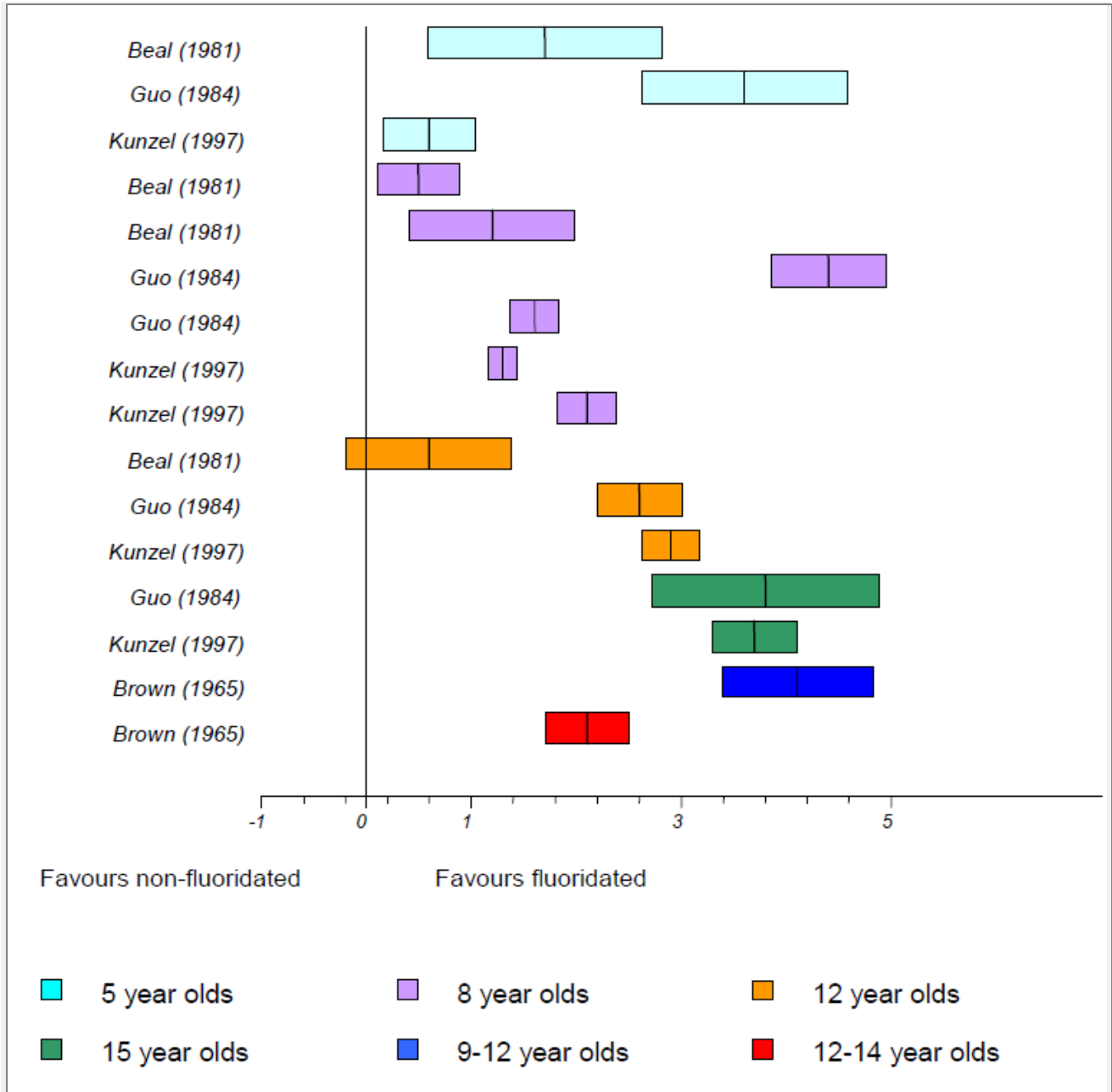


Figure 3 Change in dmft/DMFT score (mean difference and 95% CI) from McDonagh et al (2000)

Literature search results for systematic reviews

The literature search identified two systematic reviews (Level IV evidence) that included studies which reported on the relationship between the number of decayed, missing and filled deciduous teeth (dmft) and water fluoridation (Iheozor-Ejiofor et al 2015; Rugg-Gunn & Do 2012). The methodological quality of the systematic reviews varied greatly with one review scoring 11 out of 11 on the AMSTAR tool (Iheozor-Ejiofor et al 2015) and the other 2 out of 10 (Rugg-Gunn & Do 2012).

Results

Iheozor-Ejiofor et al (2015) included nineteen studies in their systematic review with 15 studies providing sufficient data for analysis of caries levels following a change in fluoridation status. Nine of these studies, with 44,268 participants, were included in the meta-analysis. Overall, the studies were assessed as being at high risk of bias.

The pooled effect estimate was a reduction of 1.81 (95%CI: 1.31 to 2.31) in dmft. The mean dmft at follow-up for the low/non-fluoridated areas ranged from 1.21 to 7.8 (median 5.1). This translates into a 35% reduction in dmft in the fluoridation groups over and above that for the control groups. Although statistical heterogeneity was high ($I^2 = 91\%$), the authors pooled the data as the direction of all the mean difference estimates was in the same direction and they considered that some of the heterogeneity was due to the large sample sizes in the studies i.e. narrow confidence intervals. Excluding studies with imputed data resulted in a similar effect estimate (1.83, 95%CI: 0.68 to 2.98; 5 studies). The meta-analysis for dmft is presented below in Figure 4. Please note that the unpublished study by Blinkhorn is reducing the pooled result and appears to be rather inconsistent with the other studies findings. The GRADE assessment is presented in Table 21.

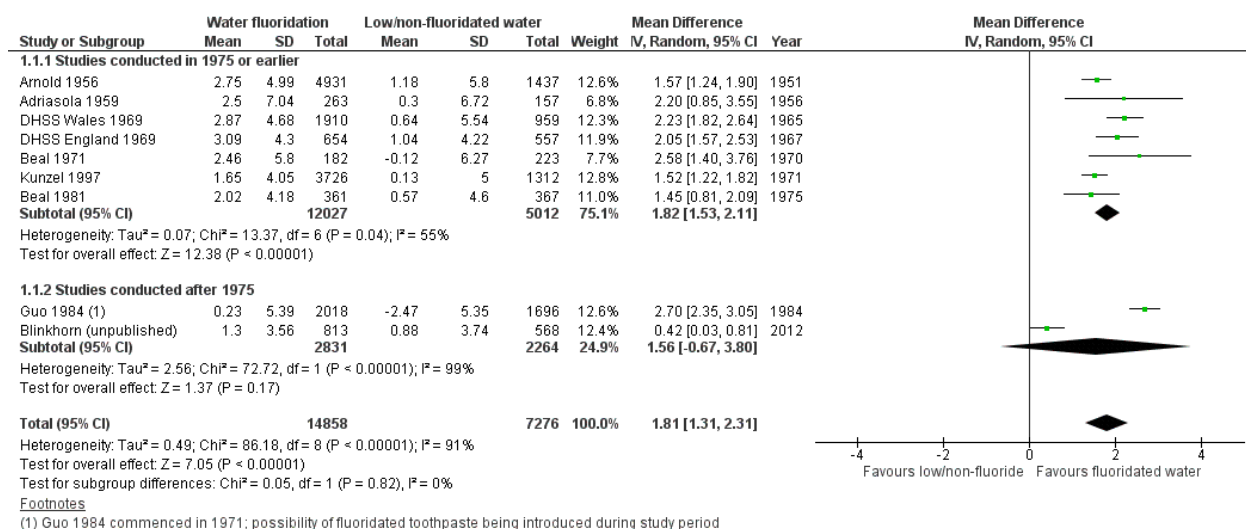


Figure 4 Initiation of water fluoridation compared with low/non-fluoridated water: change in dmft

Rugg-Gunn and Do (2012) included twenty-one studies that compared mean dmft in populations exposed to fluoridated water with groups not exposed. No assessment of the methodological quality of the included studies was carried out by the authors and the method of identifying relevant studies was very poorly reported. The percentage reduction in caries was calculated for each study. For the 21 studies reporting dmft the median percentage reduction in caries was 44% (range: 29%–68%). The results from this study are presented in Table 18. The GRADE assessment is presented in Table 22.

Table 18 Summary of results from primary studies in Rugg-Gunn (2012)

Author year	Age of subjects	Index	Mean dmft in non-fluoride group	% Caries reduction	Study type
Armfield 2010	5–10	dmft	2.33	29	X adj
Booth et al 1992 ¹	3	dmft	0.74	59	X
Brown et al 1990	8	dmft	3.5	31	X
Chin et al 2007	5	dft	4.12	34	X
Cortes et al 1996	6–12	dmft	2.1	29	X adj
Cypriano et al 2003 ¹	5	dmft	5.5	49	X
Dini et al 1998	5–6	dmft	5.3	51	X
Evans et al 2009	5	dmft	0.88	30	H
Foster et al 2009	5	dmft	1.58	46	X adj
Evans et al 2009	6	dmft	1.96	68	H
Jones et al 1997	5	dmft	1.9	44	X adj
Kanagaratnam et al 2009 ¹	9	dmft	2.42	31	X adj
Kang et al 2005	6	dft	4.13	59	H
O'Mullane et al 1996 ²	5	dmft	2.1	52	X
O'Mullane et al 1996 ²	5	dmft	1.8	33	X
Riley et al 1999	5	dmft	1.8	52	X adj
Saliba et al 2008	5	dmft	3.36	31	X
Whelton et al 2004 ¹	5	dmft	1.7	41	X adj
Whelton et al 2006 ¹	5	dmft	1.8	44	X adj
Zadik et al 1992 / Kelman 1996	5	dmft	3.89	55	X
Tickle et al 2003	5	dmft	1.43	29	X adj

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth; dft = number of decayed & filled deciduous teeth; X = cross-sectional study; H = historical (before-&-after) study; adj = results adjusted for confounders in multivariate analysis

¹ Included in Iheozor-Ejiofor et al (2015) Cochrane review but not included in meta-analysis

² Different Health Board regions

Literature search results for recent primary studies

The literature search identified three ecological studies (Level IV evidence) of acceptable quality (Armfield 2013; Blinkhorn et al 2015; Public Health England 2014) that reported the relationship between dmft and water fluoridation.

Results

Armfield (2013) randomly selected 10,369 children aged 5 to 10 years enrolled in the Australian School Dental Service between 2002 and 2005 from four Australian states. The participants' percentage lifetime exposure to fluoridated water was calculated from their residential history, drinking water source at each residence, and the fluoride level in the public water supply for each postal code of the residence. Using a general linear model adjusted for confounders (age, gender, household income, parental education, remoteness, tooth brushing frequency, & sugar-sweetened beverage consumption) the investigators found a statistically significant inverse association between mean dmft and percentage lifetime exposure to fluoridated water (β coefficient -0.66 ; 95%CI: $-0.77, -0.54$).

Blinkhorn et al (2015) investigated any changes in dmft of 5 to 7-year-old schoolchildren resident in four Australian areas—one which had fluoridated its water for about 40 years; one which had started fluoridating its water in 2008; and two that had unfluoridated water. The number of dmft was measured in 2008, 2010 and 2012. The data for the area that began water fluoridation in 2008 has been captured in the Iheozor-Ejiofor et al (2015) review discussed above. Here we report only the findings for the comparison of mean dmft in the area with 40 years of fluoridated water with the areas with unfluoridated water. Approximately 1,000 participants in each area (fluoridated and unfluoridated) were selected for inclusion at each time point. The multivariate analysis adjusted for confounders (see table below for details) found that there was a statistically significant higher mean dmft score in the unfluoridated area compared to the fluoridated area for each year. The results from this study can be seen in Table 19 below.

Public Health England (2014) compared the weighted mean number of d_3mft^7 of 5-year-olds in small local residence areas supplied with fluoridated drinking water with areas not supplied with fluoridated drinking water. These areas are standardised English small areas of 1000–3000 persons used for decennial census data. Small local residence areas located in drinking water supply zones classified as naturally fluoridated were excluded from the analysis. d_3mft data from 2012 was retrieved from the National Dental Epidemiology Programme surveys of 5-year-olds (2012) & 12-year-olds (2009) involving visual examination of school children for missing teeth, filled teeth, & teeth with obvious decay into dentine. When adjusted for deprivation and ethnicity, the mean d_3mft in the fluoridated areas was statistically significantly less than in the unfluoridated areas. These results from this study can be seen in Table 20.

The GRADE assessment for mean dmft from these three studies is presented in Table 23.

Discussion

The systematic review by Iheozor-Ejiofor et al (2015) was assessed as scoring 11 out of 11 on the AMSTAR tool indicating that the review was methodologically sound. However, due to the highly restrictive nature of the inclusion criteria which excluded most of the contemporary evidence concerning water fluoridation, the conclusions of the review are limited to studies largely published pre-1990. Another limitation of the methodology is that the evidence reviewers have relied on the analyses conducted by the authors of Iheozor-Ejiofor et al (2015). Generally, for all the dental outcomes from Iheozor-Ejiofor et al (2015), the GRADE assessment of quality is lower than the dental outcomes from the systematic review of recent primary studies. This is largely due to the differing risk of bias tools used for each review and the Iheozor-Ejiofor et al (2015) review downgrading the GRADE assessment for a lack of contemporary evidence. However, even when

⁷ The '3' in d_3mft denotes obvious decay into dentine

taking these issues into account, Iheozor-Ejiofor et al (2015) found a statistically significant decrease in the mean dmft score with exposure to water fluoridation.

The review by Rugg-Gunn and Do (2012) in contrast scored only 2 out of 10 on the AMSTAR tool mostly due to poor reporting. The inclusion criteria used were very broad and included any study published between 1990 and 2010 examining intentional water fluoridation that reported numbers of decayed, missing and filled deciduous or permanent teeth for fluoridated and non-fluoridated communities. There was no reported restriction by study design. This review simply reported the dmft score of the group not exposed to fluoridated water and the percentage reduction in caries in the group exposed to fluoridated water. No pooling of results was conducted. The review found that all twenty-one studies reported a reduction in caries ranging from 29% to 68% with a median reduction of 44%.

The three ecological studies (Armfield 2013; Blinkhorn et al 2015; Public Health England 2014) which included mean dmft as an outcome were of acceptable quality. They all included good sample sizes, reliable outcome measurement, and incorporated known confounding factors in their final analysis. Armfield (2013) had a relatively high non-response rate (32.6%) however this was compensated for in the analysis and not considered to be a major threat to study validity. Blinkhorn et al (2015) had non-response rates of 34–45% in the non-fluoridated group but this was again not considered to be a major threat to validity as the mean dmft in 2008 was very similar to the other area which had begun fluoridation in 2008.

It should also be noted that the Blinkhorn et al (2015) study is the final published version of the unpublished Blinkhorn study in the Iheozor-Ejiofor et al (2015) systematic review. The Iheozor-Ejiofor et al (2015) review report the difference in the change of dmft over four years in the area which started fluoridating its water in 2008 and the areas with unfluoridated water. The findings reported here are the dmft ratios of the area with 40 years of water fluoridation compared to the areas with unfluoridated water for each time point. The only data duplicated up is that from the unfluoridated areas. Due to the published paper reporting different comparisons and relative effects at one time point rather than changes in absolute values, it was decided to retain this study and to acknowledge the rationale.

These studies, overall, provide consistent evidence that water fluoridation is associated with a reduction in the number of decayed, missing and filled deciduous teeth in children.

These findings contribute to the overall evidence statement on dental caries in deciduous teeth on page 82.

Table 19 Results for mean dmft from Blinkhorn et al (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results (95%CI)			Effect Estimate (95%CI)		
					2008	2010	2012	2008	2010	2012
Blinkhorn 2015 Ecological Acceptable	Children (5–7 years) attending schools in three areas in Australia	Water fluoridation for over 40 years	Mean dmft	Multivariate analysis ¹	1.40 (1.22–1.58)	0.96 (0.83–1.09)	0.69 (0.57–0.81)	Reference	Reference	Reference
		No water fluoridation	-	-	2.09 (1.84–2.35)	2.06 (1.79–2.33)	1.21 (1.03–1.39)	Mean dmft ratio ² 2.06 (1.48–2.85)	Mean dmft ratio ² 2.81 (2.16–3.64)	Mean dmft ratio ² 2.23 (1.66–2.98)

Abbreviations: dmft = number of decayed, filled & missing deciduous teeth; IRR = incidence rate ratio

¹ Adjusted for age, gender, Indigenous status, cardholder status, maternal country of birth, education achievement of parents, tooth brushing behaviour, & sugary drink consumption

² Reported as incidence rate ratio (IRR)

Table 20 Results for mean d3mft from Public Health England (2014)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results (95%CI)		Effect Estimate (95%CI)	Sig	
Public Health England 2014 Ecological Acceptable	Residents (aged 5 years) in areas with and without CWF in England	CWF (0.8–1.0 ppm)	No CWF ¹	Weighted mean d3mft ²	Unadjusted univariate model	0.81 (0.71–0.90)	1.01 (0.95–1.07)	Difference in mean d3mft: –0.20 (–0.36, –0.04)	p<0.001
		-	-	-	Adjusted multivariate model ³	NR	NR	Difference in mean d3mft: –0.37 (–0.48, –0.27)	p<0.001

Abbreviations: d3mft = number of decayed, missing & filled deciduous teeth; CWF = community water fluoridation; NR = not reported; ppm = parts per million

¹ Areas classified as naturally fluoridated to 1 ppm were excluded

² Data from the National Dental Epidemiology Programme surveys of 5-year-olds (2012) & 12-year-olds (2009) involving visual examination of school children for missing teeth, filled teeth, & teeth with obvious decay into dentine (denoted by the '3' in d3mft/D3MFT)

³ Adjusted for deprivation & ethnicity

Table 21 Caries in deciduous teeth from Ihezor-Ejiofor et al (2015) – GRADE Report (measured by mean dmft)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
9	Observational studies	Serious ¹	Not serious ²	Serious ³	Not serious	Very strong association ⁴	44,268 ⁵	The pooled effect estimate was a reduction of 1.81 (95%CI: 1.31 to 2.31) in dmft for children aged 3–12 years. This indicates a reduction in dmft of 35% in the water fluoridation groups over and above that for the control groups ⁶	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth

¹ Studies at high risk of bias; quality of the evidence downgraded

² Substantial heterogeneity present, however, given that the direction of effect was the same in all but one of the studies/outcomes we did not downgrade due to heterogeneity

³ Indirectness of evidence due to lack of contemporary evidence; quality of the evidence downgraded. 71% of the studies conducted prior 1975; the use of fluoridated toothpaste, the availability of other caries prevention strategies, diet and tap water consumption are all likely to have changed in the populations in which the studies were conducted. No studies on the effect of water fluoridation in adults met the inclusion criteria

⁴ The authors of this systematic review judged that there was a very large effect size and upgraded the quality twice, however as this has been downgraded for risk of bias, there is no ability to upgrade in the GRADE approach

⁵ Total number of participants measured. Analysis undertaken on average number of participants measured at baseline and follow-up for each study

⁶ Mean dmft in low/non-fluoridated areas ranged from 1.21 to 7.8 (median 5.1)

Table 22 Caries in deciduous teeth from Rugg-Gunn and Do (2012) – GRADE Report (measured by mean dmft)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
21	Observational studies	Serious ¹	Not serious ²	Serious ³	Serious ⁴	None	NR	Median caries reduction of 44% (range 29% to 68%) in children aged 3–12 years	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth; NR = not reported

¹ Unclear risk of bias

² All report a reduction in caries

³ Unclear due to poor reporting of primary study details

⁴ Wide range of effects (29–68%)

Table 23 Difference in mean dmft score – GRADE Report

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
3	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	>40,000 ⁶	Significant reduction in mean dmft in children (5–10 years) with exposure to community water fluoridation.	⊕⊕○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth

¹ Ecological studies

² All of acceptable quality with large representative sample size, good outcome measurement and adjustment for confounders

³ Results from all studies consistently favour water fluoridation

⁴ Two studies set in Australia and one in the UK in the context of community water fluoridation

⁵ Good sample size and narrow confidence intervals

⁶ Number of subjects not available for the Public Health England (2014) study

NUMBER OF DECAYED, MISSING AND FILLED DECIDUOUS TOOTH SURFACES

This is a measure of the number of decayed, missing and filled deciduous tooth surfaces (dmfs).

Evidence from prior reviews

No studies reporting dmfs were identified in McDonagh (2000) or NHMRC (2007).

Literature search results for systematic reviews

The literature search identified one systematic review (Level IV evidence) that scored low on the AMSTAR tool which included studies that investigated the association between the mean number of decayed, missing and filled deciduous surfaces (dmfs) and exposure to differing levels of fluoride in drinking water (Rugg-Gunn & Do 2012).

Results

Rugg-Gunn and Do (2012) included eight studies that measured dmfs and one dfs in populations exposed to water fluoridation and compared the results with groups not exposed to water fluoridation. The limitations of this review have been described previously. The authors reported that the median percentage reduction in caries was 33% (range: 14%–66%). The results from this study are presented in Table 24 and the GRADE assessment is presented in Table 26.

Table 24 Summary of results from primary studies in Rugg-Gunn (2012)

Author year	Age of subjects	Index	Mean dmfs in non-fluoride group	% Caries reduction	Study type
Evans et al 1995	5	dmfs	5.77	52	X
Gillcrust et al 2001	5–11	dmfs	8.8	21	X adj
Kumar et al 2001	8	dmfs	4.18	14	X adj
Lee and Dennison 2004	5	dmfs	3.80	31	X adj
Mackay and Thomson 2005 ²	9	dmfs	5.11	33	X
Slade et al 1995	5	dmfs	3.18	43	X adj
Slade et al 1996	5	dmfs	2.98	55	X adj
Stockwell et al 1990	5	dfs	2.18	17	X adj
Treasure and Dever 1992	5	dmfs	4.41	66	X

Abbreviations: dmfs = number of decayed, missing & filled deciduous surfaces; dfs = number of decayed & filled deciduous surfaces; X = cross-sectional study; H = historical (before-&-after) study; adj = results adjusted for confounders in multivariate analysis

Literature search results for recent primary studies

The literature search identified one prospective cohort study (Level III-2) of acceptable quality (Wang 2012), two ecological studies (Level IV evidence) of acceptable quality (Do & Spencer 2015; Do 2014) and one ecological study (Level IV evidence) of low quality (Do et al 2011) that investigated the association between the mean number of decayed, missing and filled deciduous surfaces (dmfs) and exposure to differing levels of fluoride in drinking water.

Results

Wang (2012) included 575 children aged 5 years from an ongoing longitudinal study: the Iowa Fluoride Study (participant recruitment 1992–1995). Fluoride intake from water (considering intake amounts and the composite fluoride concentration from all major water sources used by children) were reported by parents. The investigators measured the number of tooth surfaces with frank cavitated or filled caries experience (denoted as d2ft). Separate logistic and linear regression analyses were conducted adjusted for age, gender & tooth-brushing frequency. The authors did not report the β coefficient values—only p-values were reported and they were all <0.05. The authors concluded that higher fluoride intake from water was found to act as a protective factor against caries.

Do (2014) took a stratified random sample of 1,406 children aged 8–10 years from each randomly selected school in New South Wales based on age and gender distribution. Each participant's percentage exposure to water fluoridation from birth to three years of age was calculated from data collected via a parental questionnaire on time at residence during age period, public water fluoride level and public water use. Having higher percentage of 3-year lifetime exposure to fluoride in water was significantly associated with lower mean dmfs counts. This was adjusted for the following confounding factors: household income, parental education, dietary fluoride supplement use, age and gender. The results from this study can be seen in Table 25.

The study by Do & Spencer (2015) used a stratified two-stage sample design to randomly select 2,214 children aged 5–8 years from participating schools in Queensland. The state was divided into 16 areas; one had CWF (Townsville). The dmfs score was significantly lower in the participants exposed to CWF (mean dmft ratio = 0.61; 95%CI: 0.44–0.82) after adjustment for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age first used fluoride toothpaste, age of first dental visit, sugary drink consumption, and school type. The results from this study can be seen in Table 25.

Do et al (2011) randomly recruited 1,351 children aged 6–11 years from selected schools in Vietnam based on their date of birth and age group. A parental questionnaire detailed the children's socioeconomic status, oral hygiene habits, and dental care utilisation. The study reports that drinking water was analysed for naturally-occurring fluoride levels but gives no more details. The participants were divided into three groups based on water fluoride level: <0.3 ppm; 0.3–0.5 ppm; >0.5 ppm. The study found a significant inverse association between dmfs score and fluoride level (β coefficient: -2.99 ; SE: 1.12; $p=0.008$) after adjustment for age, gender, age tooth-brushing started, age toothpaste use started, brushing frequency, household income, dental visit, residential status, parental education, and area.

The GRADE assessment for these studies is presented in Table 27.

Discussion

The single review by Rugg-Gunn (2012) found a median caries reduction of 33% from nine studies. Due to poor reporting, it is difficult to assess the validity and applicability of this result.

Three studies that reported mean dmfs as an outcome were of acceptable quality (Do & Spencer 2015; Do 2014; Wang 2012). They had good numbers of participants (range: 575–2,214), good outcome measurement and adjusted for known confounding factors in their final analysis. The study assessed as being low quality (Do et al 2011) mainly due to poor reporting about the fluoride level measurement and uncertainty about the representativeness of the participants. In addition, it was assessed as being having an uncertain applicability to the Australian context.

Do and Spencer (2015) and Do (2014) reported a statistically significant reduction in mean dmfs score associated with CWF. Do et al (2011) and Wang (2012) found a significant inverse association between mean dmfs score and increasing fluoride levels in drinking water.

Overall, these studies used a variety of methods to assess the association between water fluoride level and dental caries in deciduous teeth (measured by dmfs) and all found a significant reduction of deciduous caries associated with water fluoride levels applicable to the Australian context.

These findings contribute to the overall evidence statement on dental caries in deciduous teeth on page 82.

Table 25 Results for mean dmfs from Do (2014) and Do & Spencer (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate (95%CI)
Do 2014 Ecological Acceptable -	Children (8–10 years) who were participants in the NSW Child Dental Health Survey 2007 -	100% lifetime exposure to water fluoridation ¹	Mean dmfs	Multivariate regression analysis ²	2.38 (SE:0.18)	mean dmfs ratio ³ 0.65 (0.54–0.78)
		0% lifetime exposure to water fluoridation ¹	-	-	3.82 (SE: 0.43)	Reference
Do & Spencer 2015 Ecological Acceptable -	Children (5–8 years) participating in the Queensland Child Oral Health Survey 2010–2011 -	Community water fluoridation	Mean dmfs	Multilevel multivariable analysis ⁴	2.75 (95%CI: 2.16–3.34)	mean dmfs ratio ³ 0.61 (0.44–0.82)
		No community water fluoridation	-	-	4.31 (95%CI: 3.79–4.84)	Reference

Abbreviations: dmfs = number of decayed, missing & filled deciduous teeth surfaces; SE = standard error

¹From birth to 3 years

²Adjusted for household income, parental education, dietary fluoride supplement use, age & gender

³Reported as rate ratios in respective publications

⁴Adjusted for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age first used fluoride toothpaste, age of first dental visit, sugary drink consumption, & school type

Table 26 Caries in deciduous teeth from Rugg-Gunn and Do (2012) – GRADE Report (measured by mean dmfs)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
21	Observational studies	Serious ¹	Not serious ²	Serious ³	Serious ⁴	None	NR	Median caries reduction of 33% (range: 14%–66%) in 5 to 11-year-olds.	⊕○○○ ○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth; NR = not reported

¹ Unclear risk of bias — no assessment of risk of bias conducted

² All report a reduction in dmfs with exposure to water fluoridation

³ Unclear due to poor reporting of primary study details

⁴ Wide range of effects (14–66%)

Table 27 Difference in mean dmfs score from recent primary studies – GRADE Report

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
4	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	5,546	Significant reduction in mean dmfs in children (5–11 years) with exposure to community water fluoridation in two studies Significant inverse association between mean dmfs and increasing fluoride levels in two studies	⊕⊕○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth

¹ Four ecological studies

² Three were of acceptable quality with good sample size and outcome measurement and adjustment for confounders

³ Results from all studies consistently favour water fluoridation

⁴ Two studies set in Australia and one in the US in the context of community water fluoridation; one study set in Vietnam in the context of naturally-occurring fluoride in drinking water

⁵ Good sample size in all studies and narrow confidence intervals in two

CARIES PREVALENCE AND PROPORTION CARIES-FREE: DECIDUOUS TEETH

As caries prevalence is closely related to caries prevalence (i.e. caries prevalence = 1–proportion caries-free) these two outcomes have been reported in one section.

Caries prevalence is the proportion of participants with a dmft/s score of above zero (%dmft/s>0) and proportion caries-free is the proportion of participants with a dmft/s score of zero (%dmft/s=0).

Evidence from prior reviews

The McDonagh et al (2000) systematic review reported a range of mean difference in the proportion (%) of caries-free children of –5.0% to 64% with a median of 14.6%. There was a statistically significant change, favouring fluoridation, in 19/30 analyses. One analyses found a statistically significant change favouring non-fluoridated water. The remaining analyses were non-significant. The authors calculate that a median of six people need to receive fluoridated water for one extra person to be caries-free (IQR 4–9). The McDonagh review combined measures for deciduous and permanent teeth. The results are summarised in Figure 5.

NHMRC (2007) identified one additional study (Seppa et al, 2000) which reported on the percentage of caries free children. This study was a controlled before-and-after study examining the effect of the discontinuation of water fluoridation. It was rated as poor quality and earlier timepoints were included in McDonagh (2000). The results of the study were mixed and likely to be affected by concurrent policy change in preventative dental measures.

The McDonagh et al (2000) and NHMRC (2007a) reviews did not include caries prevalence as an outcome.

Literature search results for systematic reviews

The literature search identified one systematic review (Level IV evidence) that reported on the change in proportion of caries-free children with exposure to water fluoridation (Iheozor-Ejiofor et al 2015). No systematic reviews were identified from the literature search that reported caries prevalence as an outcome.

Results

Iheozor-Ejiofor et al (2015) included ten studies with 39,966 participants in their systematic review that measured the proportion of caries-free children for deciduous dentition. All studies were judged to be at high risk of bias. The pooled data estimated that there was an increase of 15% in caries-free children in areas where water fluoridation was initiated (95%CI: 5% to 23%). The proportion of caries-free children at follow-up in the low/non-fluoridated areas ranged from 0.06 to 0.67 (median 0.22). The I^2 value for the meta-analysis was 84%. The authors of the review decided to undertake meta-analyses because the value for Tau² was low i.e. the between-study variance was low. Please note again that the unpublished study by Blinkhorn is reducing the pooled result and appears to be rather inconsistent with the other studies findings. The results of the meta-analysis for the change in proportion of caries-free children in deciduous teeth are presented below in Figure 6. The GRADE assessment is presented in Table 34.

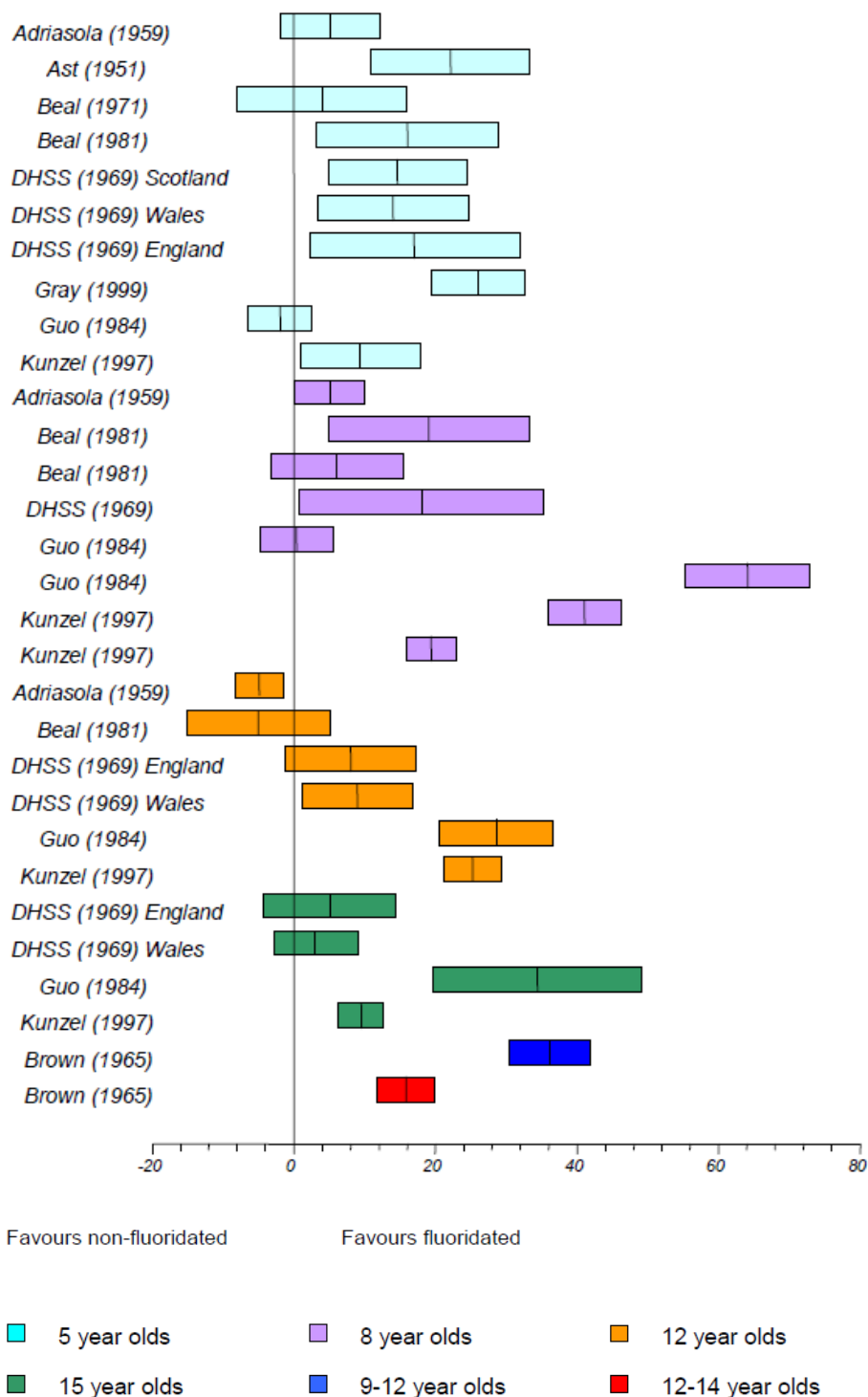


Figure 5 Increase in the proportion (%) of caries-free children in fluoridated compared to non-fluoridated areas (mean difference and 95% CI) from McDonagh (2000)

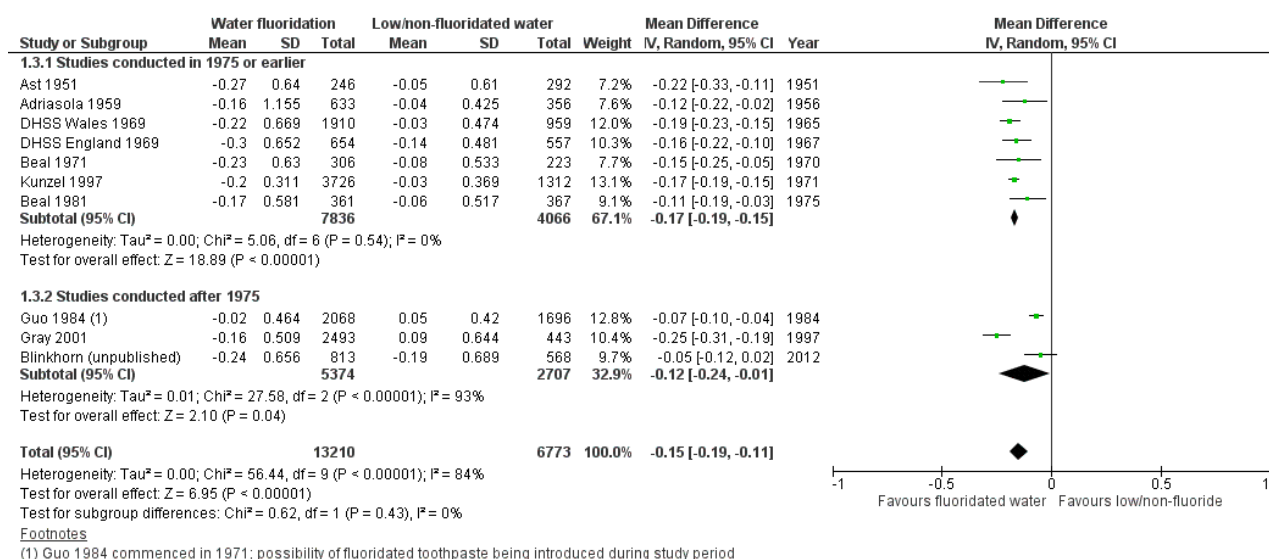


Figure 6 Initiation of water fluoridation compared with low/non-fluoridated water: change in proportion of caries-free children (deciduous teeth)

Literature search results for recent primary studies

The literature search identified one ecological study (Level IV evidence) of low quality that reported on the change in proportion of caries-free children with exposure to water fluoridation (Laloo et al 2015) and seven ecological studies (Level IV evidence) that investigated the effect of water fluoridation on caries prevalence in deciduous teeth (Blinkhorn et al 2015; Centers for Disease Control and Prevention 2011; Do et al 2015; Do 2014; Do & Spencer 2007; Postma et al 2008; Public Health England 2014). Six were assessed as being of acceptable quality (Blinkhorn et al 2015; Do et al 2015; Do 2014; Do 2007; Postma et al 2008; Public Health England 2014) and one was assessed as being low quality (Centers for Disease Control and Prevention 2011).

In three studies the prevalence was estimated from the proportion of participants with a dmft score greater than zero (Blinkhorn et al 2015; Do & Spencer 2007; Public Health England 2014). Two studies estimated the prevalence of any dental caries from the proportion of participants with a dmfs score of greater than zero (Do et al 2015; Do 2014). One study measured the prevalence of decayed and filled deciduous teeth only (%dft>0) and did not count teeth missing due to caries (Centers for Disease Control and Prevention 2011) and one study measured the prevalence of any early childhood caries (Postma et al et al 2008).

Results

Laloo et al (2015), in their low quality study, investigated the proportion of children aged 5–10 years with caries-free deciduous teeth and the effect that water fluoridation may have on this outcome. The mean dmft was 3.29 (95%CI: 3.05–3.54) in the group exposed to ≥0.5 ppm water fluoride levels compared to 4.16 (95%CI: 3.91–4.41) in the group exposed to <0.3ppm water fluoride levels. This is a 23.4% decrease in mean dmft with exposure to ≥0.5 ppm. The authors also found, after adjustment for age and gender, that the proportion of caries-free Indigenous children was greater in those participants exposed to ≥0.5 ppm compared to those exposed to <0.3 ppm fluoride in the water supply (OR=1.27; 95%CI: 0.98–1.63). It should be noted that despite the difference being statistically non-significant there was an increase in the proportion of caries-free children with exposure to higher water fluoride levels. The results from this study can be seen in Table 28 and the GRADE assessment is presented in Table 35.

The Blinkhorn et al (2015) study previously described in the section on mean dmft also reported on caries prevalence. Consistent with the findings for mean dmft, the study found a statistically

significantly lower prevalence of caries in the fluoridated area in New South Wales compared to the unfluoridated areas in 2008, 2010 and 2012 after adjusting for confounding factors (age, gender, Indigenous status, cardholder status, maternal country of birth, education achievement of parents, tooth brushing behaviour, and sugary drink consumption). Note that the results have been transformed to present the no water fluoridation comparator as the reference group. The results from this study can be seen in Table 29.

The Public Health England (2014) also reported on caries prevalence (defined as any dmft score greater than 0). The study found that the weighted prevalence of dental caries was 28% less (95%CI: 35% less, 21% less; $p < 0.001$) in the areas with CWF compared to areas without water fluoridation after adjusting for deprivation and ethnicity. The results from this study can be seen in Table 30.

Do & Spencer (2007) investigated the relationship between the proportion of lifetime exposure to fluoridated water from birth to 3 years old and the prevalence of caries in 6-year-olds' canines and molars. The 667 participants were from a large-scale population-based study, the Child Oral Health Study, conducted in 2002–04 among South Australian children attending the School Dental Service. The study found that, after controlling for confounding factors (see table for full details), the prevalence of caries was significantly less in both the group of participants exposed to fluoridated water for >50% of their life from birth to age 3 years and those exposed for between >0% to 50% of their life from birth to 3 years compared to those never exposed to fluoridated water between birth and 3 years. In addition the study reported that exposure to fluoridated water between birth and 3 years of age prevented 34% of the cases of caries at age 6. Given a prevalence of 32.3%, 111 cases per 1000 children with deciduous caries at age 6 years would be prevented by exposure to fluoridated water. The results can be seen in Table 31.

The Centers for Disease Control and Prevention (2011) conducted a study investigating the association between caries prevalence (defined as the % of any decayed and filled deciduous teeth) and water fluoridation in a convenience sample of 270 children aged 4–11 years in five villages in Alaska. The study was assessed as being of low quality mainly due to a high risk of selection bias and poor reporting. The study found that the prevalence of caries was significantly lower in the group exposed to water fluoridation compared to those not exposed. (after adjustment for soda pop consumption & frequency of tooth brushing). Note again the reciprocal of the reported odds ratio has been reported in the results table to make no exposure to water fluoridation the referent comparator. The results can be seen in Table 31.

Both Do et al (2015) and Do (2014) calculated the proportion of participants with a dmfs score greater than zero and found that the prevalence of caries was lower with exposure to water fluoridation. Each study measured fluoride exposure differently (see Table 32 for details). Do et al (2015) also estimated that the lack of water fluoridation attributed to 21% of deciduous dental caries and that 99 cases for every 1,000 population could be prevented should CWF be introduced (given a prevalence of deciduous caries of 47.1%). Results for both these studies can be found in Table 32.

The GRADE assessment for these five studies can be found in Table 36.

Postma et al (2008) investigated the association between early childhood caries (ECC) and water fluoridation in 5,822 infants aged 36–71 months participating in the 1999/2002 South African National Children's Oral Health Survey. Fluoride exposure was assessed using previously reported data regarding the fluoride content in public drinking water supplies and the dental outcomes were assessed using dmft. Severity of ECC was assessed using a standard classification system. The study found that the prevalence of ECC was significantly lower with exposure to fluoride levels of 0.10–0.29 ppm, 0.30–0.6 ppm, and >0.6 ppm compared to <0.1 ppm. The results from this study can be seen in Table 33 and the GRADE assessment is presented in Table 37.

Table 28 Results for proportion caries-free children (deciduous dentition) from Lalloo et al (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate (95%CI)
Lalloo 2015 Ecological Low	Indigenous children (5–10 years) participating in the Child Dental Health Survey 2010 in Australia	Fluoride level in water supply ≥ 0.5 ppm	% caries-free deciduous teeth ¹	Logistic regression ²	27.3% (23.7–31.2)	OR=1.27 (0.98–1.63)
-		Fluoride level in water supply <0.3 ppm	-	-	22.9% (20.2–25.9)	Reference

Abbreviations: OR = odds ratio; ppm = parts per million

¹ measured using number of decayed, missing & filled deciduous teeth (dmft) = 0

² adjusted for age & gender

Table 29 Caries prevalence results from Blinkhorn et al (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results			Effect Estimate (95%CI)		
					2008	2010	2012	2008	2010	2012
Blinkhorn 2015 Ecological Acceptable	Children (5–7 years) attending schools in three areas in Australia	Water fluoridation for over 40 years	Caries prevalence (%dmft>0)	Multivariate analysis ¹	37.4%	31.8%	24.2%	OR=0.34 (0.23–0.49)	OR=0.41 (0.32–0.54)	OR=0.51 (0.39–0.67)
-		No water fluoridation	-	-	51.4%	44.6%	32.7%	Reference	Reference	Reference

Abbreviations: dmft = number of decayed, filled & missing deciduous teeth; OR = odds ratio

¹ Adjusted for age, gender, Indigenous status, cardholder status, maternal country of birth, education achievement of parents, tooth brushing behaviour, & sugary drink consumption

Table 30 Caries prevalence results from Public Health England (2014)

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results - (95%CI)		Effect Estimate (95%CI)	Sig
Public Health England 2014 Ecological Acceptable -	Residents (aged 5 years) in areas with and without CWF in England -	CWF (0.8–1.0 ppm) -	No CWF ¹ -	Weighted caries prevalence (%d3mft>0) ² -	Unadjusted univariate model	26% (24,28)	29% (28,30)	% difference in odds: -15 (-29, 2.5)	NR
					Adjusted multivariate model ³	NR	NR	% difference in odds: -28 (-35, -21)	<i>p</i> <0.001

Abbreviations: CWF = community water fluoridation; d3mft = number of decayed (into dentine), filled & missing deciduous teeth; NR = not reported; ppm = parts per million

¹ Areas classified as naturally fluoridated to 1 ppm were excluded

² Data from the National Dental Epidemiology Programme surveys of 5-year-olds (2012) & 12-year-olds (2009) involving visual examination of school children for missing teeth, filled teeth, & teeth with obvious decay into dentine (denoted by the '3' in d3mft/D3MFT)

³ Adjusted for deprivation & ethnicity

Table 31 Caries prevalence results from Do & Spencer (2007) and Centers for Disease Control and Prevention (2011)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate (95%CI)	Sig
Do & Spencer 2007 Ecological Acceptable	Children (5–8 years) in the Child Oral Health Study 2002–4 in South Australia	>50% lifetime exposure to fluoridated water from birth to 3 years of age ¹	Prevalence of caries on molars & canines at age 6 years (%dmft>0) ²	Logistic regression ³	25.5%	OR=0.4 (0.2–0.7)	p<0.05
		>0% to 50% lifetime exposure to fluoridated water from birth to 3 years of age ¹	-	-	30.1%	OR=0.5 (0.3–0.9)	p<0.05
		0% lifetime exposure to fluoridated water from birth to 3 years of age ¹	-	-	45.8%	Reference	-
		Exposed to fluoride in water from birth to age 3 years	-	-	-	PPF=34.3% (5.7–50.9) N=111	-
Centers for Disease Control and Prevention 2011 Ecological Low	Children (4–11 years) from 5 villages in Alaska, USA	Water fluoridation (level NR)	Caries prevalence (%dft>0)	Multivariate analysis ⁴	4–5 years: 67% 6–8 years: 73% 9–11 years: 68%	OR=0.29 (0.23–0.36)	p<0.001
		No water fluoridation	-	-	4–5 years: 100% 6–8 years: 97% 9–11 years: 71%	Reference	-

Abbreviations: CDC= Centers for Disease Control and Prevention; dmft = decayed, filled & missing deciduous teeth; 95%CI = 95% confidence interval; OR = odds ratio; PPF = population prevented fraction (proportion of cases prevented by exposure); N = number of cases per 1000 children with deciduous caries at age 6 years prevented by the exposure, given the population prevalence of 32.3%; NR = not reported

¹ Fluoride exposure history of each child was collected through a 12-page self-administered parental questionnaire

² Caries experience data recorded at the first available dental visit after a child turned six years old were extracted from School Dental Service-archived clinical records

³ Adjusted for age in months at 6-year examination, gender, birth cohort, fluoride supplements, infant formula, household income, age toothpaste use started, brushing frequency, amount toothpaste used, after brushing routine, eating/licking toothpaste habit, & parental education

⁴ Adjusted for soda pop consumption & frequency of tooth brushing

Table 32 Caries prevalence results from Do (2014) and Do and Spencer (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results (SE)	Effect Estimate (95%CI)
Do 2014 Ecological Acceptable	Children (8–10 years) who were participants in the NSW Child Dental Health Survey 2007	100% lifetime exposure to water fluoridation ¹	Caries prevalence (%dmfs>0)	Multivariate regression analysis ²	32.6% (1.4)	PR=0.83 (0.70–0.99)
		0–99% lifetime exposure to water fluoridation ¹	-	-	31.5% (2.3)	PR=0.81 (0.65–1.01)
		0% lifetime exposure to water fluoridation ¹	-	-	39.0% (2.6)	Reference
Do 2015 Ecological Acceptable	Children (5–8 years) participating in the Queensland Child Oral Health Survey 2010–2011	Community water fluoridation	Caries prevalence (%dmfs>0)	Complementary log-log regression ³	36.9% (95%CI: 58.7–67.4)	Reference
		No community water fluoridation	-	-	47.7% (95%CI: 44.3–51.1)	PR=1.29 (1.11–1.50) PAF=21% N=99

Abbreviations: PR = prevalence ratio; dmfs = number of decayed, missing & filled deciduous teeth surfaces; SE = standard error; PAF = population attributable fraction; N=number of cases for every 1,000 population to be prevented should community water fluoridation be introduced given a prevalence of caries of 47.1%; RR = rate ratio

¹ From birth to 3 years

² Adjusted for household income, parental education, dietary fluoride supplement use, age & gender

³ Adjusted for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age first used fluoride toothpaste, age of first dental visit, sugary drink consumption, & school type

Table 33 Results for prevalence of early childhood caries from Postma et al (2008)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate	Sig		
Postma 2008 Ecological Acceptable	Participants (36–71 months) in South African National Children's Oral Health Survey 1999/2002	Public drinking water supply: fluoride >0.6 ppm	Prevalence of early childhood caries ¹	Logistic regression analysis ²	59.42% (≥0.3 ppm)	OR=0.40 (95%CI: 0.25–0.63)	NR		
-		Public drinking water supply: fluoride 0.30–0.6 ppm				-	-	OR=0.62 (95%CI: 0.44–0.87)	NR
-		Public drinking water supply: fluoride 0.10–0.29 ppm			-	-	65.62%	OR=0.80 (95%CI: 0.64–0.99)	NR
-		Public drinking water supply: fluoride <0.10 ppm			-	-	74.15%	Reference	-

Abbreviations: dft = number of decayed & filled deciduous teeth; OR = odds ratio; NR = not reported; ppm = parts per million

¹ Measured using dmft score — severity was described using Wyne's classification (adapted to a per tooth basis) and the Significant Caries Index (SiC)

² Adjusted for age, gender, locality, ethnicity & income

Discussion

There is evidence from one systematic review that water fluoridation significantly increases the proportion of caries-free children aged 3–12 years by an estimated 15%. This estimate came from pooling the results of ten studies with almost 40,000 participants.

There is also evidence from a single large ecological study of low quality that the proportion of caries-free Indigenous children aged 5–10 years was greater with exposure to ≥ 0.5 ppm fluoride in the water supply even though it did not quite reach statistical significance (the lower 95%CI was 0.98). This lack of statistical significance is likely due to residual confounding as the study only included Indigenous status, age and gender and did not measure other known strong confounders such as use of fluoridated toothpaste, consumption of sugar and access to dental socioeconomic status.

Five studies (Blinkhorn et al 2015; Do et al 2015; Do 2014; Do & Spencer 2007; Public Health England 2014) that included caries prevalence as an outcome were of acceptable quality and the other (Centers for Disease Control and Prevention 2011) was of low quality (largely due to the participants being a convenience sample). Four studies found that the odds of having dental caries was reduced in areas with water fluoridation or with higher lifetime exposure to water fluoridation. Moreover two studies found that the prevalence of caries was reduced in areas with water fluoridation or with higher lifetime exposure to water fluoridation.

The other study included (Postma et al 2008) used dmft scores to estimate the prevalence of early childhood caries in 36–71 month old infants. It was assessed as being of acceptable quality and reported finding a reduction in the prevalence of early childhood caries being associated with exposure to water fluoridation.

Overall, these studies provide consistent evidence that water fluoridation is associated with a reduction in caries prevalence and an increase in the proportion of caries-free deciduous teeth in children.

These findings contribute to the overall evidence statement on dental caries in deciduous teeth on page 82.

Table 34 Change in proportion of caries-free children (deciduous teeth) from Ihezor-Ejiofor et al (2015) – GRADE Report (measured by %dmft=0)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
9	Observational studies	Serious ¹	Not serious ²	Serious ³	Not serious	Very strong association ⁴	39,966 ⁵	The pooled effect estimate was an increase of 15% (95%CI: 11% to 19%) in the proportion of caries-free children (3–12 years) in areas with water fluoridation. ⁶	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth

¹ Studies at high risk of bias; quality of the evidence downgraded

² Substantial heterogeneity present, however, given that the direction of effect was the same in all but one of the studies/outcomes we did not downgrade due to heterogeneity

³ Indirectness of evidence due to lack of contemporary evidence; quality of the evidence downgraded. 71% of the studies conducted prior 1975; the use of fluoridated toothpaste, the availability of other caries prevention strategies, diet and tap water consumption are all likely to have changed in the populations in which the studies were conducted. No studies on the effect of water fluoridation in adults met the inclusion criteria

⁴ The authors of this systematic review judged that there was a very large effect size and upgraded the quality twice, however as this has been downgraded for risk of bias, there is no ability to upgrade in the GRADE approach—the quality has been revised accordingly

⁵ Total number of participants measured. Analysis undertaken on average number of participants measured at baseline and follow-up for each study

⁶ The proportion of caries-free children at follow-up in the low/non-fluoridated areas ranged from 6% to 67% (median 22%)

Table 35 Difference in proportion of caries-free children (deciduous teeth) – GRADE Report (measured by %dmft=0)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	NR ⁶	The proportion of caries-free Indigenous children (5–10 years) was greater with exposure to community water fluoridation (OR=1.27; 95%CI: 0.98–1.63).	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth; NR = not reported

¹ Ecological study

² One study of low quality which did not include known confounders other than age and gender e.g. socioeconomic status

³ Only one study

⁴ Set in Australia in the context of community water fluoridation

⁵ Confidence intervals narrow and good sample size

⁶ Actual numbers in the deciduous teeth analysis were not reported—total number of participants (deciduous and permanent teeth) was 97,809 children and young people aged 5–15 years

Table 36 Difference in caries prevalence (deciduous teeth) – GRADE Report (prevalence assessed with: %dmft/s>0 or %dft>0)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
6	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	>6,537 ⁶	Significant reduction in the prevalence of caries in children (4–11 years) with exposure to community water fluoridation	⊕⊕○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth

¹ Six ecological studies

² Six studies of acceptable quality with good sample size, outcome measurement and adjustment for confounders

³ Results from all studies consistently favour water fluoridation

⁴ Four studies set in Australia, one in the UK and the other in the USA in the context of community water fluoridation

⁵ Adequate confidence intervals in four studies

⁶ The number of participants were not available for the Public Health England (2014) study

Table 37 Difference in prevalence of early childhood caries – GRADE Report (assessed with: dmft score)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Not serious ²	Not serious ³	Serious ⁴	Not serious ⁵	None	5,822	Water fluoridation was significantly associated with a reduction in the prevalence of early childhood caries in children aged 36–71 months (OR=0.40; 95%CI: 0.25–0.63)	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dt = number of decayed deciduous teeth

¹ Ecological study

² One study of acceptable quality

³ Only one study

⁴ Set in South Africa in the setting of naturally occurring fluoride in drinking water; health system and socioeconomic factors likely to be different to the Australian setting

⁵ Good sample size

GRADE ASSESSMENTS (DECIDUOUS TEETH)

The summary of findings tables for the GRADE assessments of caries in deciduous teeth are presented Table 38 below. The review authors decided to omit the GRADE terminology of ‘very low, low, moderate, and high quality’ and discuss the findings in terms of their confidence in the results. Instead they have included a comment on the extent of their confidence in the effect observed for each outcome.

Table 38 Summary of findings for dental caries in deciduous teeth

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in deciduous teeth assessed using dmft	The pooled effect estimate was a reduction of 1.81 (95%CI: 1.31 to 2.31) in dmft for children aged 3–12 years. This indicates a reduction in dmft of 35% in the water fluoridation groups over and above that for the control groups.	44,268 (9 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
	Median caries reduction of 44% (range 29% to 68%) in children aged 3–12 years	NR (21 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
	Significant reduction in mean dmft in children (5–10 years) with exposure to community water fluoridation. Mean dmft decreased by 0.37 (95%CI: 0.48, 0.2) in one study.	>40,000 (3 observational studies)	⊕⊕○○	Includes one large study from England using national data and a single study set in Australia with good sample size. Both were of acceptable quality, with adjustment for confounders in a setting of CWF.
Caries in deciduous teeth assessed using dmfs	Median caries reduction of 33% (range: 14%–66%) in 5 to 11-year-olds	NR (21 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
	Significant reduction in mean dmfs in children (5–11 years) with exposure to community water fluoridation in two studies Significant inverse association between mean dmfs and increasing fluoride levels in two studies	5,546 (4 observational studies)	⊕⊕○○	Two acceptable quality studies set in Australia using national survey data with good sample size and adjustment for confounders in the setting of CWF. Two studies (one low quality and one acceptable quality) in the US and Vietnam of limited applicability to the Australian context.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Proportion of caries-free deciduous teeth assessed using %dmft/s=0	The pooled effect estimate was an increase of 15% (95%CI: 11% to 19%) in the proportion of caries-free infants and children (3–12 years) in areas with water fluoridation. ⁶	39,966 (9 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
-	The proportion of caries-free Indigenous children (5–10 years) was greater with exposure to community water fluoridation (OR=1.27; 95%CI: 0.98–1.63).	NR (1 observational study)	⊕⊕○○	A single acceptable quality study from Australia in the setting of CWF.
Caries prevalence in deciduous teeth assessed using %dmft/s>0	Significant reduction in the prevalence of caries in children (4–11 years) with exposure to community water fluoridation	>4,323 (6 observational studies)	⊕⊕○○	Includes one large study from England using national data and four studies set in Australia with good sample size. All were of acceptable quality, with adjustment for confounders in a setting of CWF.
Prevalence of early childhood caries	Water fluoridation was significantly associated with a reduction in the prevalence of early childhood caries in infants and children aged 36–71 months (OR=0.40; 95%CI: 0.25–0.63)	5,822 (1 observational study)	⊕○○○	A single study of acceptable quality set in South Africa using survey data. Downgraded for indirectness.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Note: We have attempted as far as possible to use the following definitions: infants (0–4 years); children (5–11 years); adolescents (12–17 years); adults (18–64 years) and later adulthood (65+ years)

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; NR = not reported

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Evidence Statement

The evidence evaluation identified two reviews and 11 ecological studies which found consistent evidence that water fluoridation at current Australian level is associated with a decreased prevalence of dental caries in deciduous teeth of children (assessed using dmft, dmfs, proportion of caries free deciduous teeth and caries prevalence in deciduous teeth).

NUMBER OF DECAYED, MISSING AND FILLED PERMANENT TEETH

This is a measure of the number of decayed, missing and filled permanent teeth (DMFT).

Evidence from prior reviews

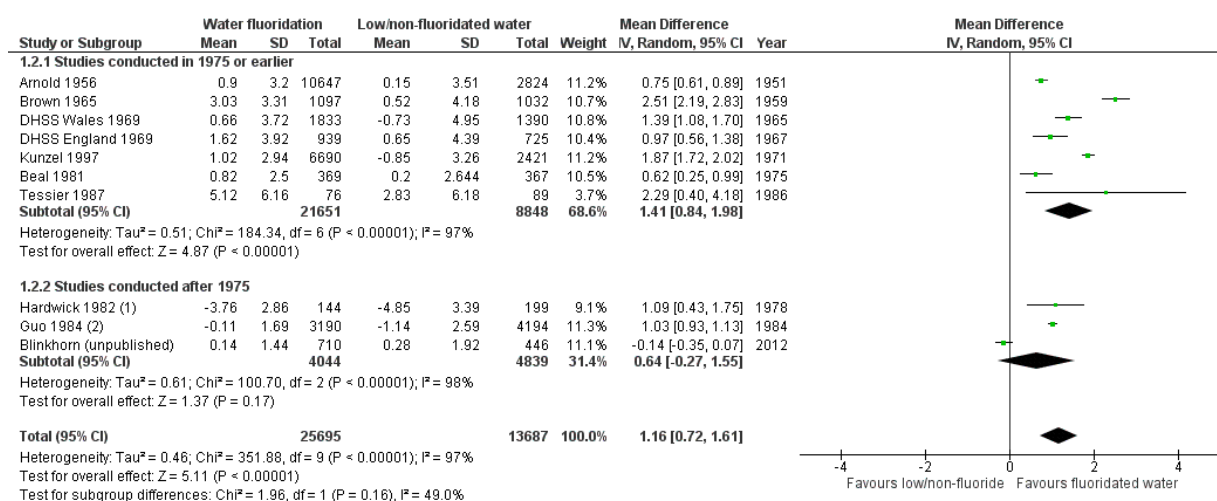
The McDonagh (2000) systematic review combined dmft and DMFT. The findings are discussed in the section on page 53. No further evidence on this outcome was identified in NHMRC (2007)

Literature search results for systematic reviews

The literature search identified three systematic reviews (Level IV evidence) which included studies that investigated the relationship between mean DMFT and fluoride levels in drinking water (Griffin et al 2007; Iheozor-Ejiofor et al 2015; Rugg-Gunn & Do 2012).

Results

Iheozor-Ejiofor et al (2015) included ten studies, with 78,764 participants that evaluated the change in DMFT. The pooled mean difference in DMFT was 1.16 lower (95%CI: 0.72 to 1.61 lower) in the fluoridation group. The mean DMFT at follow-up in the low/non-fluoridated areas ranged from 0.71 to 5.5 (median 4.4). This translates into a 26% reduction in DMFT for the water fluoridation groups over and above that for the control groups. The results were pooled, even in the presence of considerable heterogeneity ($I^2 = 97%$) as the direction of all the mean difference estimates was in the same direction and the authors considered that some of the heterogeneity was due to the large sample sizes in the studies. A slightly higher effect estimate was seen when studies with imputed data were excluded (1.32 lower, 95%CI: 0.53 to 2.11 lower; 4 studies). Please note that the unpublished study by Blinkhorn is reducing the pooled result and is inconsistent with the other studies findings. The direction of the effect also appears to be inconsistent with the findings for proportion caries-free (see Figure 9). The meta-analysis for DMFT is presented below in Figure 7. The GRADE assessment is presented in Table 43.



Footnotes
 (1) Hardwick 1982 commenced in 1974; possibility of fluoridated toothpaste being introduced during study period
 (2) Guo 1984 commenced in 1971; possibility of fluoridated toothpaste being introduced during study period

Figure 7 Initiation of water fluoridation compared with low/non-fluoridated water: change in DMFT

Rugg-Gunn and Do (2012) included thirty-seven primary studies that compared the mean DMFT in populations exposed to fluoridated water with groups not exposed. The median percentage reduction of caries in permanent teeth was 37% (range: 5%–85%) The results for each primary study are presented in Table 39. The GRADE assessment is presented in Table 44.

Table 39 Summary of results from primary studies in Rugg-Gunn (2012)

Author year	Age of subjects	Index	Mean DMFT in non-fluoride group	% Caries reduction	Study type
Armfield 2010	8–15	DMFT	1.04	32	X adj
Barros 1993 ⁵	12	DMFT	8.61	69	H
Basting 1997 ⁵	12	DMFT	8.60	44	H
Bastos et al 2005	12	DMFT	9.89	85	H
Brezina and Baranchuk 1991	10	DMFT	5.41	57	H
Cypriano et al 2003 ¹	12	DMFT	3.1	19	X
Dini et al 1998	11–12	DMFT	2.8	18	X
Evans et al 2009	11	DMFT	1.02	68	H
Ferreira 1999 ⁵	12	DMFT	9.3	84	H
Foster et al 2009	11	DMFT	0.67	33	X adj
Hopcraft and Morgan 2005	17–51	DMFT	3.91	24	X adj
Hopcraft et al 2008	17–35	DMFT	3.87	25	X adj
Jones et al 1997 ⁶	12	DMFT	1.46	43	X adj
Mahoney et al 2008	17–24	DMFT	4.5	24	X adj
Mahoney et al 2008	25–34	DMFT	7.8	39	X adj
Mahoney et al 2008	35–44	DMFT	11.3	35	X adj
Moreira 1996 ⁵	12	DMFT	3.4	53	H
Morgan et al 1992 ²	15–19	DMFT	5.02	27	X
Morgan et al 1992 ²	20–24	DMFT	8.32	49	X
National Ministry of Health 2010	18+	DMFT	15.7	10	X adj
O'Mullane et al 1996 ⁷	12	DMFT	2.2	27	X
O'Mullane et al 1996 ⁷	12	DMFT	1.6	19	X
O'Mullane et al 1996 ⁸	16–24	DMFT	7.6	5	X
Oliveira 1995 ⁵	12	DMFT	7.95	33	H
Park 2006	12	DMFT	4.13	41	X
Riordan 1991 ¹	12	DMFT	1.57	43	X adj
Sales Peres 2001 ⁵	12	DMFT	8.9	43	H
Sales-Peres and Bastos 2002 ⁹	12	DMFT	4.91	11	X
Saliba et al 2008	12	DMFT	3.38	54	X
Saliba et al 2008	15–19	DMFT	6.56	47	X
Saliba et al 2008	34–44	DMFT	20.12	31	X
Tagliaferro et al 2004	12	DMFT	4.4	25	X
Thomas and Kassab 1992 ²	18–32	DMFT	13.6	30	X
Treasure and Dever 1994	14	DMFT	6.20	49	X adj
1. Whelton et al 2004 ¹	15	DMFT	3.2	34	X adj
2. Whelton et al 2006 ¹	15	DMFT	3.6	42	X adj
3. Zadik et al 1992 / Kelman 1996	12	DMFT	4.39	40	X

Abbreviations: DMFT = number of decayed, missing & filled permanent teeth; X = cross-sectional study; H = historical (before-&-after) study; adj = results adjusted for confounders in multivariate analysis

¹ Included in Iheozor-Ejiogor et al (2015) Cochrane review

² Included in Griffin et al (2007) systematic review

³ Public schools

⁴ Private schools

⁵ Cited in single publication: Ramires & Buzalaf (2007)

⁶ Separate publications

⁷ Different Health Board regions

⁸ All of Ireland

⁹ Averaged over municipalities

The systematic review by Griffin et al (2007) aimed to examine the effectiveness of self- and professionally-applied fluoride and water fluoridation on adults aged 20 years and over. The review scored 6 of a possible 10 on the AMSTAR tool. Studies published in English, lasting for a year or more, and examining the association between fluoride and caries in adults with intact teeth were included. Cross-sectional studies were included if participants lived most of their lives in fluoridated or non-fluoridated communities or the authors estimated the effect of exposure to water fluoridation controlling for potential confounding factors. A total of nine studies were included—one prospective cohort study and eight cross-sectional studies. The combined results of the nine studies (7,853 participants) were significant at $p < 0.001$. Results for these studies are summarised in Table 40 below. The summary relative risk was 0.654 (95%CI: 0.490–0.874) from seven studies⁸ with 5,409 participants that included only lifetime residents of fluoridated or non-fluoridated communities (note that one study measured DFS). The forest plot of the individual studies is presented in Figure 8. The summary effect was equivalent to a prevented fraction of 34.6% (95%CI: 12.6%–51.0%). Heterogeneity was reported to be present but no other comments were made regarding this. When the authors pooled the 5 studies published after 1979 the summary prevented fraction was 27.2% (95%CI: 19.4%–34.3%). For this result the authors stated that heterogeneity “was not an issue.” The authors of this systematic review concluded that their findings suggest that fluoride prevents caries among adults of all ages.

One important limitation of the systematic review by Griffin et al (2007) should be noted. Three of the included studies reported fluoride levels above 1.5 ppm: one compared naturally occurring levels of 3.5 ppm with 0.7 ppm in New Mexico; another, levels of between 1.5 ppm and 2.0 ppm were compared with levels of 0.2 ppm in Great Britain; and the last one compared levels of 1.6 ppm with 0.2 ppm. Strictly speaking, these three studies do not meet the inclusion criteria for the overview, however a sensitivity analysis conducted by the evidence reviewers (which included only the four remaining studies) found a pooled RR of 0.64 (95%CI: 0.46–0.88) which is very close to the pooled estimate reported by Griffin et al (2007). In the interests of clarity and transparency and because including the three studies with >1.5 ppm levels of fluoride did not influence the pooled RR, it was therefore decided to report the findings of the systematic review as in the paper but use only the revised pooled estimate in the GRADE assessment. The GRADE assessment is presented in Table 45.

⁸ All studies in Table 36 except Grembowski et al 1992 and Hunt et al 1989

Table 40 Results primary studies of water fluoridation included in Griffin et al (2007)

Author year	Age of subjects	Number of subjects	Fluoride level comparisons	Outcome measure	Mean DMFT/S for fluoridation group	Mean DMFT/S for control group	Difference	p-value	Study type
Eklund et al 1986 / Burt et al 1986 ¹	27–65	315	3.5 ppm vs. 0.7 ppm	DMFT	7.00	8.70	1.70	0.01	Cross-sectional
Englander and Wallace 1962	18–59	1,831	1.2 ppm vs. 0.1 ppm	DMFS	21.84	43.24	21.40	0.01	Cross-sectional
Grembowski et al 1992 ²	20–34	595	NR	NR	NR	NR	NR	NR	Cross-sectional
Hunt et al 1989	NR	275	0.7–1.5 ppm vs. <0.5 ppm	NR	NR	NR	NR	NR	Prospective cohort
Morgan et al 1992 ²	20–24	104	NR	DMFT	4.27	8.32	4.05	0.00	Cross-sectional
Murray 1971	20–65	3,902	1.5–2.0 ppm vs. 0.2 ppm	DMFT	9.66	16.08	6.42	0.00	Cross-sectional
Stamm et al 1990	18–60+	967	1.6 ppm vs. 0.2 ppm	DMFT	10.90	15.10	4.02	0.00	Cross-sectional
Thomas and Kassab 1992 ²	20–32	649	0.9 ppm vs. NR	DMFT	9.48	13.62	4.14	0.00	Cross-sectional
Wiktorsson et al 1992	30–40	496	NR	DFS	36.10	45.61	9.51	0.00	Cross-sectional

Abbreviations: NR = not reported; DMFT/S = decayed, missing & filled permanent teeth or surfaces; ppm = parts per million

¹ Included in Iheozor-Ejiofor et al (2015) Cochrane review but not in their meta-analysis

² Included in Rugg-Gunn (2012) systematic review but not included in the meta-analysis in Griffin et al (2007)

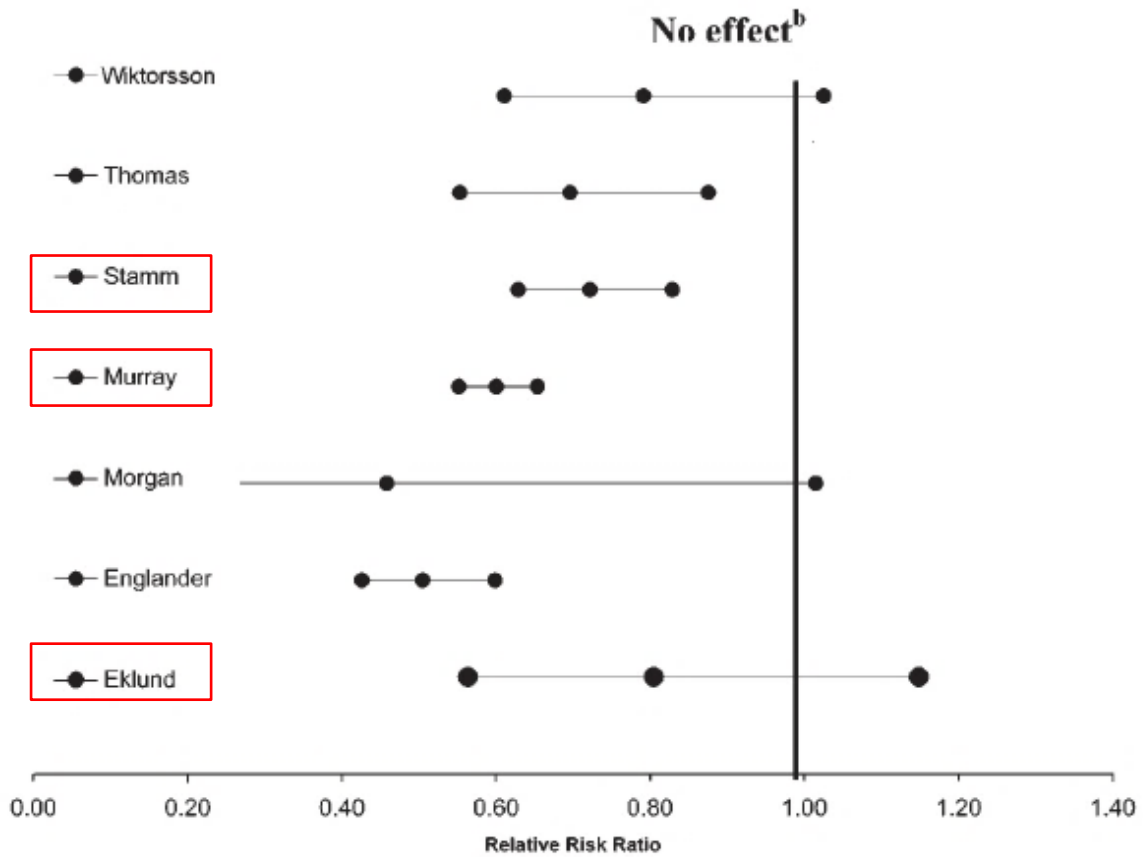


Figure 8 Relative risk ratio of carious teeth/surfaces by lifetime water fluoridation exposure^a.

^a Effect measure is for total study population.

^b Values to the left of the 'no effect' line (risk in fluoride group is less than risk in the control group) indicate fluoride effective, and values to the right indicate fluoride ineffective.

NB: The studies in red boxes have fluoride levels above 1.5 ppm

Literature search results for recent primary studies

The literature search identified six ecological studies (Level IV evidence) that investigated the relationship between mean DMFT and fluoride levels in drinking water (Armfield 2013; da Silva et al 2015; Haysom 2015; Public Health England 2014; Skinner et al 2014; Slade et al 2013). All six were assessed as being of acceptable quality.

Results

Armfield (2013) included 6,139 schoolchildren aged 11–16 years enrolled in the Australian School Dental Service from 2002 to 2005 in four Australian states. The participants' lifetime exposure to fluoridated water was calculated as previously described. Dental examinations were carried out by staff of the School Dental Service. 0–50% lifetime exposure was the reference and the linear model was adjusted for age, gender, household income, parental education, remoteness, tooth brushing frequency, & sugar-sweetened beverage consumption. The study found a statistically significant inverse association between percentage lifetime exposure to fluoridated water and mean DMFT score (β coefficient: -0.10 ; 95%CI: $-0.20, 0.00$; $p < 0.05$).

Da Silva et al (2015) selected those participants aged 12 years from the Brazilian Oral Health Study 2010. This was a household-based survey conducted by the Brazilian Ministry of Health in 177 cities, including the 27 state capitals. About 38,000 people divided into five age groups (5, 12, 15–

19, 35–44 and 65–74 years old) were interviewed and examined in their homes. Water fluoridation level data was based on the National Basic Sanitation Survey 2008. Actual numbers of 12-year-old participants was not reported. After adjustment for economic deprivation and ‘socio-sanitary’⁹ conditions, the study found that exposure to fluoridated water was associated with a reduction in mean DMFT (β coefficient: -0.613 ; 95%CI: $-1.030, -0.196$; $p=0.006$).

Slade (2013) analysed data from 3,779 people (aged ≥ 15 years) who had participated in the 2004–2006 Australian National Survey of Adult Oral Health. Participants in this survey had been selected randomly from all areas of Australia. Telephone interviews were conducted to establish eligibility and collect sociodemographic and dental care information. Those with natural teeth were asked to have a dental examination where the numbers of decayed, missing and filled permanent teeth were counted. Information of residential locations for each participant (from 1964 to 2003) was matched to water supply fluoride level data from the Australian Research Centre for Population Oral Health and the percentage lifetime exposure to fluoridated water was calculated. The participants were analysed in two cohorts: those born before 1960 (2,270 participants) and those born between 1960 and 1990 (1,509 participants). These represent the participants born before fluoridation was widespread and when fluoridation became more common. The results were reported as β coefficients and interpreted as those with $\geq 75\%$ lifetime exposure had 2.58 fewer DMFT (95%CI: $-2.09, -0.19$) in the pre-1960 cohort and 1.14 fewer DMFT (95%CI: $-4.05, -1.11$) in the 1960–1990 cohort compared to those with $<25\%$ lifetime exposure to water fluoridation.

Public Health England (2014) compared the weighted mean number of D3MFT¹⁰ of 12-year-olds in small local areas supplied with fluoridated drinking water with areas not supplied with fluoridated drinking water. These areas are standardised English small areas of 1000–3000 persons used for decennial census data. Small local residence areas located in drinking water supply zones classified as naturally fluoridated were excluded from the analysis. D3MFT data from 2009 was retrieved from the National Dental Epidemiology Programme surveys of 12-year-olds involving visual examination of school children for missing teeth, filled teeth, & teeth with obvious decay into dentine. When adjusted for deprivation and ethnicity, the mean D3MFT in the fluoridated areas was 0.10 less (95%CI: 0.20 less, 0.01 less) than in the unfluoridated areas. The results from this study are presented in Table 41.

Skinner et al (2014) randomly selected 1,199 students aged 14 and 15 years from attending schools in NSW under the jurisdiction of the NSW Department of Education and Training. Adjusting for all risk factors (i.e. income, mother’s education level, sugary drink consumption, dental visit last year, brushing frequency), age and gender, the study found that mean DMFT was significantly lower amongst the participants living in areas supplied with fluoridated water. The results from this study are presented in Table 42.

Haysom et al (2015) investigated the relationship between mean DMFT and water fluoridation in 361 young people (aged 13–21 years) who were in custody in juvenile justice centres in NSW between August and October 2009. Fluoridation exposure was assessed by matching location of past residence with fluoride levels in water supply obtained from the NSW Centre for Oral Health Strategy. The mean DMFT was significantly higher in those who had lived in areas not supplied with fluoridated water ($p=0.02$). This analysis was adjusted for aboriginality, age group, gender, history out-of-home care, socioeconomic disadvantage, remoteness, time incarcerated, snacks $>2x$ weekly, preferred sweetened drinks, tooth brushing frequency, toothache/problem with teeth/gums, self-reported status of teeth, dental service previous year, and location of the dental provider in the previous year. The results from this study are presented in Table 42. The GRADE assessment for these six studies is presented in Table 46.

⁹ A composite measure incorporating rates of urbanisation, proper sanitation and illiteracy.

¹⁰ The ‘3’ in D3MFT denotes obvious decay into dentine

Table 41 Results for mean D3MFT from Public Health England (2014)

Study Design Quality	Population	Exposur es		Outcome	Analysis	Results (95%CI)		Effect Estimate (95%CI)	Sig
		-	-			-	-		
Public Health England 2014 Ecological Acceptable -	Residents (aged 12 years) in areas with and without CWF in England -	CWF (0.8–1.0 ppm)	No CWF ¹	Weighted mean D3MFT ²	Unadjusted univariate model	0.65 (0.61,0.69)	0.76 (0.72,0.79)	Difference in mean D3MFT: –0.10 (–0.20, –0.01)	p<0.001
		-	-		-	Adjusted multivariate model ³	NR		

Abbreviations: CWF = community water fluoridation; D3MFT = number of decayed (obvious decay into dentine), missing & filled permanent teeth; NR = not reported; ppm = parts per million

¹ Areas classified as naturally fluoridated to 1 ppm were excluded

² Data from the National Dental Epidemiology Programme surveys of 12-year-olds (2009) involving visual examination of school children for missing teeth, filled teeth, & teeth with obvious decay into dentine (denoted by the '3' in d3mft/D3MFT)

³ Adjusted for deprivation & ethnicity

Table 42 Results for mean DMFT from Skinner et al (2014) and Haysom et al (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Effect Estimate (95%CI)	Sig
Skinner 2014 Ecological Acceptable -	Participants (14–15 years) in the NSW Teen Dental Survey 2010, Australia -	Fluoridated water (level NR)	Mean DMFT	Logistic regression ¹	Mean DMFT ratio ² =0.58 (0.44–0.75)	$p<0.001$
		Non-fluoridated water (level NR)	-	-	Reference	-
Haysom 2015 Ecological Acceptable -	Young people (aged 13–21 years) in New South Wales Juvenile Custodial Centres 2009 -	Fluoridated water supply (level NR)	Mean DMFT	Multivariate logistic regression ³	Reference	-
		Non-fluoridated water supply (level NR)	-	-	Mean DMFT ratio ⁴ =1.77(1.11–2.83)	$p=0.02$

Abbreviations: NR = not reported; DMFT = number of decayed, filled & missing permanent teeth; RR = rate ratio; IRR = incidence rate ratio

¹ Adjusted for all risk factors (i.e. income, mother’s education level, sugary drink consumption, dental visit last year & tooth brushing frequency), age, & gender

² Reported as ‘RR’

³ Adjusted for aboriginality, age group, gender, history out-of-home care, socioeconomic disadvantage, remoteness, time incarcerated, snacks >2x weekly, preferred sweetened drinks, tooth brushing frequency, toothache/problem with teeth/gums, self-reported status of teeth, dental service previous year, & location dental provider previous year

⁴ Reported as incident rate ratio (IRR)

Discussion

The systematic review by Iheozor-Ejiofor et al (2015) reported a significant reduction in mean DMFT with exposure to fluoridated water in children aged 8–11 years from 10 studies with over 70,000 participants. This was equivalent to a 36% reduction in DMFT for the water fluoridation groups over and above that for the control groups. The review was limited by the quality and quantity of primary studies and the highly restrictive inclusion criteria. The review by Rugg-Gunn and Do (2012) found a median percentage reduction of caries in permanent teeth of 37% (range: 5%–85%) with exposure to fluoridated water in participants aged 8–51 years from 37 studies. Even though this review did not score high on the AMSTAR tool due to poor reporting, the authors did not attempt to pool any results and simply reported the crude data from the primary studies. The final review by Griffin et al (2007) found that exposure to fluoridated water significantly reduced the risk of caries in adults aged 20 years and over by an estimated 30%. This review was also somewhat limited by poor reporting.

Even while taking into consideration the limitations of these systematic reviews, the findings are consistent and include participants from a wide range of age groups and settings and provide evidence that water fluoridation reduces caries in children and adults. In addition, the six ecological studies of acceptable quality and high applicability to the Australian context found a significant reduction in mean DMFT associated with exposure to water fluoridation. Therefore, there is consistent evidence from three systematic reviews and six additional primary studies that water fluoridation reduces caries in permanent teeth.

These findings contribute to the overall evidence statement on dental caries in permanent teeth on page 118.

Table 43 Caries score in permanent teeth from Ihezor-Ejiofor et al (2015) – GRADE Report (measured by mean DMFT)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
10	Observational studies	Serious ¹	Not serious ²	Serious ³	Not serious	Very strong association ⁴	78,764 ⁵	The pooled effect estimate was a reduction of 1.16 (95%CI: 0.72 lower to 1.61 lower) in mean DMFT in the areas with water fluoridation for children aged 8–11 years. This indicates a reduction in DMFT of 26% in the water fluoridation groups over and above that for the control groups ⁶ .	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: DMFT = number of decayed, missing & filled permanent teeth

¹ Studies at high risk of bias; quality of the evidence downgraded

² Substantial heterogeneity present, however, given that the direction of effect was the same in all but one of the studies/outcomes we did not downgrade due to heterogeneity

³ Indirectness of evidence due to lack of contemporary evidence; quality of the evidence downgraded. 71% of the studies conducted prior 1975; the use of fluoridated toothpaste, the availability of other caries prevention strategies, diet and tap water consumption are all likely to have changed in the populations in which the studies were conducted. No studies on the effect of water fluoridation in adults met the inclusion criteria

⁴ The authors of this systematic review judged that there was a very large effect size and upgraded the quality twice, however as this has been downgraded for risk of bias, there is no ability to upgrade in the GRADE approach

⁵ Total number of participants measured. Analysis undertaken on average number of participants measured at baseline and follow-up for each study

⁶ The mean DMFT at follow-up in the low/non-fluoridated areas ranged from 0.7 to 5.5 (median 4.4)

Table 44 Caries in permanent teeth from Rugg-Gunn and Do (2012) – GRADE Report (measured by mean DMFT)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
37	Observational studies	Serious ¹	Not serious ²	Serious ³	Very serious ⁴	None	NR	The median percentage reduction of caries in permanent teeth was 37% (range: 5%–85%) in participants aged 8–51 years.	⊕○○○ ○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth; NR = not reported

¹ Unclear risk of bias

² All report a reduction in caries

³ Unclear due to poor reporting of primary study details

⁴ Wide range of effects (5%–85%)

Table 45 Difference in mean DMFT score in adults for Griffin et al (2007) – GRADE Report

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
4	Observational studies ¹	Very serious ²	Not serious ³	Serious ⁴	Serious ⁵	None	3,080 ⁶	Significant reduction in mean DMFT in adults (18–65+years) with exposure to fluoridated water ⁷ .	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: DMFT = number of decayed, missing & filled permanent teeth; ppm = parts per million

¹ Cross-sectional studies

² Unclear—quality assessment was not reported—downgraded twice due to uncertainty of risk of bias

³ Results from all studies consistently favour water fluoridation

⁴ One study set in Australia, two in the UK, one in Canada, two in the USA and one in Sweden; however three studies included fluoride levels above 1.5 ppm

⁵ Wide confidence interval

⁶ As reported

⁷ Revised pooled estimate excluding three studies with fluoride levels >1.5 ppm: RR = 0.64 (95%CI: 0.46–0.88)

Table 46 Difference in mean DMFT score – GRADE Report

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
6	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	>12,700 ⁶	Significant reduction in mean DMFT in adolescents and adults (≥11 years) with exposure to community water fluoridation.	⊕⊕○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: DMFT = number of decayed, missing & filled permanent teeth

¹ Ecological studies

² All of acceptable quality with large representative sample size, good outcome measurement and adjustment for confounders

³ Results from all studies consistently favour water fluoridation

⁴ Five studies set in Australia, one in the UK and one in Brazil all in the context of community water fluoridation

⁵ Adequate confidence intervals

⁶ Number of subjects was not available for the da Silva et al (2015) and Public Health England (2014) studies

NUMBER OF DECAYED, MISSING AND FILLED PERMANENT TOOTH SURFACES

Evidence from prior reviews

No studies reporting DMFS were identified in McDonagh (2000) or NHMRC (2007).

Literature search results for systematic reviews

The literature search identified one systematic review (Level IV evidence) that scored low on the AMSTAR tool which included studies that investigated the association between a measure of caries on permanent tooth surfaces and exposure to differing levels of fluoride in drinking water (Rugg-Gunn & Do 2012).

Results

The review by Rugg-Gunn and Do (2012) included fourteen studies that measured DMFS and two that measured DFS in populations exposed to water fluoridation and compared these results with populations not exposed to water fluoridation. The authors found that the percentage of caries reduction ranged from 0% to 50% (median 29%). The results from the primary studies in this review are presented in Table 47 and the GRADE assessment is in Table 49.

Table 47 Summary of results from primary studies in Rugg-Gunn (2012)

Author year	Age of subjects	Index	Mean DMFS in non-fluoride group	% Caries reduction	Study type
Brunelle and Carlos 1990	12	DMFS	2.97	17	X
Brunelle and Carlos 1990	17	DMFS	8.59	18	X
Clark et al 1995	6–14	DMFS	2.53	35	X
Ellwood and O'Mullane 1995	14	DMFS	4.3	33	X adj
Gillcrist et al 2001	5–11	DMFS	1.0	25	X adj
Grembowski et al 1992 ²	20–34	DFS	27.9	44	X adj
Hopcraft and Morgan 2003	17–35	DMFS	10.49	23	X adj
Ismail et al 1990 ¹	15–17 ³	DMFS	12.8	24	X
Ismail et al 1990 ¹	15–17 ⁴	DMFS	9.0	5	X
Ismail et al 1993	11–12	DMFS	2.8	39	X
Lee and Dennison 2004	12	DMFS	2.37	41	X adj
Mackay and Thomson 2005 ¹	9	DMFS	1.22	50	X adj
Murray et al 1991	15	DMFS	6.1	43	X
Slade et al 1995	15	DMFS	2.70	0	X adj
Slade et al 1996	12	DMFS	1.80	48	X adj
Stockwell et al 1990	15	DFS	4.42	10	X adj

Abbreviations: DMFS= number of decayed, missing & filled permanent surfaces; DFS = number of decayed & filled permanent surfaces; X = cross-sectional study; H = historical (before-&-after) study; adj = results adjusted for confounders in multivariate analysis

¹ Included in Iheozor-Ejiogor et al (2015) Cochrane review

² Included in Griffin et al (2007) systematic review

³ Public schools

⁴ Private schools

⁵ Cited in single publication: Ramires & Buzalaf (2007)

⁶ Separate publications

⁷ Different Health Board regions

⁸ All of Ireland

⁹ Averaged over municipalities

Literature search results for recent primary studies

The literature search identified four ecological studies (Level IV evidence) that investigated the association between a measure of caries on permanent tooth surfaces and exposure to differing levels of fluoride in drinking water (Do & Spencer 2015; Do et al 2011; Do 2014; Slade et al 2013). Two studies of acceptable quality (Do & Spencer 2015; Do 2014) and one ecological study of low quality (Do et al 2011) investigated the association between the mean DMFS and exposure to fluoride in drinking water. The other acceptable quality study investigated the association between mean DFS score and the percentage lifetime exposure to fluoridated water (Slade et al 2013).

Results

Do (2014) studied a stratified random sample of 2,611 children aged 8–12 years from each randomly selected school in New South Wales based on age and gender distribution. Each participant's percentage exposure to water fluoridation from birth to three years of age was calculated from data collected via a parental questionnaire on time at residence during age period, public water fluoride level and public water use. Mean DMFS was significantly lower in the group exposed to fluoridated water for 100% of their lifetime from birth to 3 years of age compared to the group never been exposed to fluoridated water. This was adjusted for the following confounding factors: household income, parental education, dietary fluoride supplement use, age and gender. The results from this study are presented in Table 48.

Do and Spencer (2015) analysed the mean DMFS in 3,186 children aged 9–14 years from a stratified sample of 5 to 14-year-old schoolchildren attending school in Queensland, Australia. The mean DMFS score was significantly lower in the children resident in areas with fluoridated water compared to those with non-fluoridated water. The results for this study are presented in Table 48.

Do et al (2011) analysed the association between DMFS scores and water fluoridation using linear regression. There were 2,748 children aged 6–17 years from selected schools in Vietnam included in this analysis. The study reported a non-significant inverse relationship between DMFS count and fluoride naturally occurring in drinking water (β coefficient: -0.34 ; $p=0.330$) after adjustment for household income, parental education, dietary fluoride supplement use, age and gender.

Slade et al (2013), as described previously, also measured the mean DFS in 3,779 participants aged 15 years and older from the 2004–2006 Australian National Survey of Adult Oral Health. The study found, after adjusting for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age fluoride toothpaste first used, age of first dental visit, sugary drink consumption, and school type, that the β coefficient was -3.44 (95%CI: -15.47 , -6.72) for those with $\geq 75\%$ lifetime exposure in the pre-1960 cohort and -11.10 (95%CI: -5.28 , -1.60) in the 1960–1990 cohort compared to those with $<25\%$ lifetime exposure to water fluoridation.

The GRADE assessment for these four studies is presented in Table 50.

Discussion

One systematic review (Rugg-Gunn and Do 2012) using change in mean DMFS or DFS found that the median percentage caries reduction was 29% (range: 0% to 50%) with exposure to water fluoridation. As previously stated, this review was limited by poor reporting.

Four ecological studies investigated the association between mean DMFS or DFS count and fluoridated water (Do & Spencer 2015; Do et al 2011; Do 2014; Slade et al 2013). Three were of acceptable quality and one of low quality. Two studies found that mean DMFS was significantly reduced in participants living in areas supplied with fluoridated water. One found a significant inverse association between high lifetime exposure to water fluoridation and mean DMFS. Another did find an inverse association but it did not reach statistical significance; this study was assessed as being at high risk of bias.

Overall, these results provide consistent and applicable evidence that water fluoridation is associated with a reduction in caries in permanent teeth (as measured using a surface caries measure).

These findings contribute to the overall evidence statement on dental caries in permanent teeth on page 118.

Table 48 Results for mean DMFS from Do et al (2014) and Do and Spencer (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate (95%CI)
Do 2014 Ecological Acceptable - -	Children (8–12 years) who were participants in the NSW Child Dental Health Survey 2007	100% lifetime exposure to water fluoridation ¹	Mean DMFS	Multivariate regression analysis ²	0.59 (SE: 0.04)	Mean DMFS ratio ³ =0.76 (0.62–0.94)
		0–99% lifetime exposure to water fluoridation ¹	-	-	0.63 (SE: 0.09)	Mean DMFS ratio ³ =0.84 (0.66–1.07)
		0% lifetime exposure to water fluoridation ¹	-	-	0.91 (SE: 0.1)	Reference
Do & Spencer 2015 Ecological Acceptable -	Children (9–14 years) participating in the Queensland Child Oral Health Survey 2010–2011	Community water fluoridation	Mean DMFS	Multilevel multivariable analysis ³	0.82 (95%CI: 0.65–0.99)	Mean DMFS ratio ³ =0.63 (0.47–0.85)
		No community water fluoridation	-	-	1.51 (95%CI: 1.31–1.71)	Reference

Abbreviations: RR = rate ratio; DMFS = number of decayed, missing & filled permanent teeth surfaces; SE = standard error

¹ From birth to 3 years

² Adjusted for household income, parental education, dietary fluoride supplement use, age & gender

³ Reported as rate ratios (RR)

⁴ Adjusted for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age first used fluoride toothpaste, age of first dental visit, sugary drink consumption, & school type

Table 49 Caries in permanent teeth from Rugg-Gunn and Do (2012) – GRADE Report (measured by mean DMFS)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
16	Observational studies	Serious ¹	Not serious ²	Serious ³	Very serious ⁴	None	NR	The median percentage reduction of caries in permanent teeth was 29% (range: 0%–50%) in participants aged 5–35 years.	⊕○○○ ○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth; NR = not reported

¹ Unclear risk of bias

² All report a reduction in caries

³ Unclear due to poor reporting of primary study details

⁴ Wide range of effects (0%–50%)

Table 50 Difference in mean DMFS score – GRADE Report

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
4	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	12,344	<p>Significant reduction in mean DMFS in children and young people (8–14 years) with exposure to community water fluoridation in two studies.</p> <p>Significant inverse association between ≥75% lifetime exposure to water fluoridation and mean DFS (participants 15+ years) in one study.</p> <p>Non-significant inverse relationship between naturally occurring fluoride levels and mean DMFS (participants 6–17 years) in one study.</p>	⊕⊕○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: DMFS = number of decayed, missing & filled permanent tooth surfaces

¹ Ecological studies

² Three studies were of acceptable quality with good sample size, good outcome measurement and adjustment for confounders

³ Results from three studies consistently favour water fluoridation

⁴ Four studies set in Australia in the context of community water fluoridation; one in Vietnam with naturally occurring fluoride in water supplies

⁵ Good sample size and adequate confidence intervals

CARIES PREVALENCE AND PROPORTION CARIES-FREE: PERMANENT TEETH

As caries prevalence is closely related to caries prevalence (i.e. caries prevalence = 1–proportion caries-free) these two outcomes have been reported in one section.

Caries prevalence is the proportion of participants with a DMFT/S score of above zero (%DMFT/S>0) and proportion caries-free is the proportion of participants with a DMFT/S score of zero (%DMFT/S=0).

Evidence from prior reviews

No studies reporting caries prevalence or the proportion caries-free were identified in McDonagh (2000) or NHMRC (2007).

Literature search results of systematic reviews

The literature search identified one systematic review (Level IV evidence) was identified that reported on the proportion of participants whose permanent teeth were caries-free (Iheozor-Ejiofor et al 2015). No systematic reviews were identified which included studies looking at the association between water fluoridation and caries prevalence in the permanent dentition.

Results

Iheozor-Ejiofor et al (2015) included eight studies with 63,538 participants that measured the change in the proportion of caries-free children for permanent dentition. All studies were judged to be at high risk of bias. The pooled effect estimate found a 14% increase in the proportion of caries-free children in fluoridated areas (95%CI: 5% to 23% increase). The proportion of caries-free children at follow-up in the low/non-fluoridated areas ranged from 0.01 to 0.67 (median 0.14). There was considerable heterogeneity ($I^2=98%$) however the authors decided to pool the data because the measure of between-study variance (Tau^2) was low. The results of the meta-analysis are presented in Figure 9. The GRADE assessment can be found in Table 57.

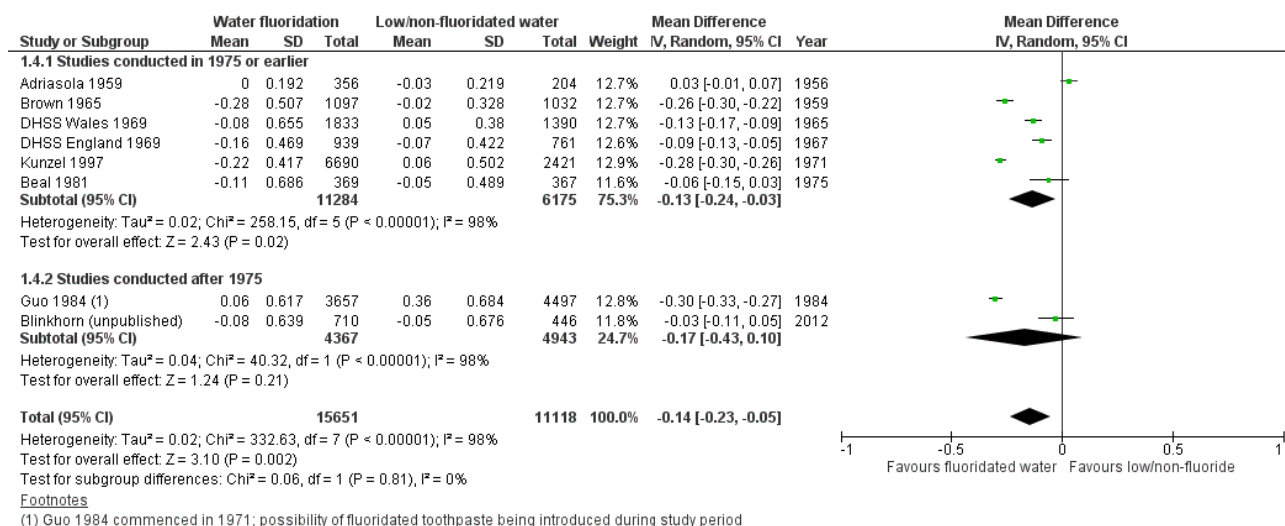


Figure 9 Initiation of water fluoridation compared with low/non-fluoridated water: change in proportion of caries-free children (permanent teeth)

Literature search results of recent primary studies

The literature search identified nine ecological studies (Level IV evidence) that investigated the effect of water fluoridation on caries prevalence in permanent teeth (Centers for Disease Control and Prevention 2011; Do et al 2015; Do 2014; Freire 2013; Haysom 2015; Lee & Han 2015; McGrady 2012; Public Health England 2014; Skinner et al 2014). Seven were assessed as being of

acceptable quality (Do et al 2015; Do 2014; Freire 2013; Haysom 2015; Lee & Han 2015; Public Health England 2014; Skinner et al 2014) and two were assessed as being of low quality (Centers for Disease Control and Prevention 2011; McGrady 2012).

Seven studies estimated the prevalence of caries on permanent teeth from the proportion of participants with a DMFT score greater than zero (Centers for Disease Control and Prevention 2011; Freire 2013; Haysom 2015; Lee & Han 2015; McGrady 2012; Public Health England 2014; Skinner et al 2014). Two studies calculated the proportion of participants with a DMFS score greater than zero as an estimate of caries prevalence (Do et al 2015; Do 2014).

The literature search identified two ecological studies (Level IV evidence) that reported on the proportion of caries-free permanent teeth (da Silva et al 2015; Laloo et al 2015). One was of acceptable quality (da Silva et al 2015) and the other low quality (Laloo et al 2015).

Results

Lee and Han (2015) investigated the prevalence of dental caries in permanent teeth of 8, 10 and 12-year-olds who participated in the South Korea National Oral Health Surveys in 2003, 2006 and 2010. This included a total of 23,059 participants. In the 2003 survey which was made up of 60 survey districts, a classroom for each age-group was randomly selected, and every fifth student was examined. In the 2006 survey 150 districts were included and every fifth student was examined. The 2010 survey 200 districts were included, a classroom for each age-group was randomly selected, and all the students in the classroom were examined. Adjusted for gender, fluoride sealant and region, five of the analyses showed a non-significant decrease in caries prevalence associated with water fluoridation and four showed a non-significant increase. It is likely these results are due to residual confounding as important known confounders (for example, sugary drink consumption, socioeconomic status and widespread fluoridated toothpaste use) were not included in the analysis. The results from this study are presented in Table 51.

Public Health England (2014) also compared the prevalence of D3MFT¹¹ of 12-year-olds in small local residence areas supplied with fluoridated drinking water with areas not supplied with fluoridated drinking water. The study has been described previously. When adjusted for deprivation and ethnicity, the odds of having any caries in the fluoridated areas was 21% less (95%CI: 29% less, 12% less) than in the unfluoridated areas. The results from this study are presented in Table 52.

Skinner et al (2014) as described before randomly selected 1,199 students aged 14 and 15 years from attending schools in NSW under the jurisdiction of the NSW Department of Education and Training. Adjusting for all risk factors (i.e. income, mother's education level, sugary drink consumption, dental visit last year, brushing frequency), age and gender, the study found that caries prevalence was significantly lower amongst the participants living in areas supplied with fluoridated water. The results from this study are presented in Table 53.

Freire et al (2013) analysed data from the 7,247 participants aged 12 years included in the Brazilian Oral Health Study 2010. Adjusting for gender, skin colour, household income, residences connected to water supply, and median income municipality, this study found that the prevalence of dental caries was significantly lower in those exposed to CWF (prevalence ratio = 0.78; 95%CI: 0.68–0.90). The results from this study are presented in Table 53.

Haysom et al (2015), as described before, included 361 young people (aged 13–21 years) who were in custody in juvenile justice centres in NSW between August and October 2009. This study found that the prevalence of dental caries was significantly lower in the participants exposed to water fluoridation. The results from this study are presented in Table 53.

¹¹ The '3' in D3MFT denotes obvious decay into dentine

McGrady et al (2012) included 1,783 students aged 11–13 years attending schools in Manchester (non-fluoridated water supply) and Newcastle (fluoridated water supply) in the UK in their low quality ecological study. Schools were selected based upon the percentage free school meals entitlement to provide a spectrum of socio-economic backgrounds and their willingness to participate. Students who were not lifetime residents were excluded from the study. The prevalence of caries lesions extending into dentine was significantly greater in the city with the non-fluoridated water supply (Manchester). The results from this study are presented in Table 53.

The Centers for Disease Control and Prevention (2011) low quality ecological study in Alaska (as described previously) also reported on caries prevalence in a convenience sample of 304 participants aged 6–16 years. The study found that the prevalence of caries in permanent teeth was significantly greater in the children from villages with a non-fluoridated water supply. These results were adjusted for soda pop consumption & frequency of tooth brushing. The results from this study are presented in Table 53.

Do et al (2015) found a significantly higher prevalence of caries among the 3,186 participants aged 9–14 years who were living in areas supplied with unfluoridated water. The population attributable fraction indicated that lack of water fluoridation attributed to 31% of the permanent dental caries. Moreover, 120 cases per 1000 population were estimated to be prevented should water fluoridation be implemented (given a prevalence of caries of 38.8%). The results for this study are presented in Table 54.

Do (2014) found that higher lifetime exposure to water fluoridation did not significantly reduce the prevalence of permanent dental caries in 2,611 participants aged 8–12 years. The results for this study are presented in Table 54.

The GRADE assessment for the prevalence of caries in permanent teeth is presented in Table 56.

Laloo et al (2015) investigated the proportion of children with caries-free permanent dentition and the effect that water fluoridation may have on this outcome. The authors found, after adjustment for age and gender, that the percentage of caries-free children was significantly higher in fluoridated areas than non-fluoridated areas for both Indigenous and non-Indigenous children. They also confirmed higher rates of caries-free children in non-Indigenous children compared to Indigenous children with the same exposure to water fluoridation (see Technical report for full details). The results from this study can be seen in Table 55.

Da Silva et al (2015) selected those participants aged 12 years from the Brazilian Oral Health Study (BOHS) 2010. The BOHS was a household-based survey conducted by the Brazilian Ministry of Health. Water fluoridation level data was based on national data. The actual numbers of 12-year-old participants was not reported. After adjustment for economic deprivation and 'socio-sanitary'¹² conditions, the study found that exposure to fluoridated water was not significantly associated with the proportion of participants who were caries-free (β coefficient: 6.750; 95%CI: -1.131, 14.63; $p=0.09$).

The GRADE assessment for these two studies is presented in Table 58.

¹² A composite measure incorporating rates of urbanisation, proper sanitation and illiteracy.

Table 51 Results for caries prevalence from Lee and Han (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Effect Estimate (95%CI)		
					2003	2006	2010
Lee & Han 2015 Ecological Acceptable	Participants (8 years) in the South Korea National Oral Health Surveys 2003, 2006 & 2010	CWF ¹ vs. no CWF (level NR)	Mean prevalence of dental caries (%DMFT>0)	Logistic regression ²	OR=1.30 (0.81–2.11)	OR=1.41 (0.47–4.25)	OR=0.80 (0.57–1.14)
-	Participants (10 years) in the South Korea National Oral Health Surveys 2003, 2006 & 2010	-	-	-	OR=0.92 (0.57–1.50)	OR=1.18 (0.64–2.20)	OR=1.04 (0.70–1.54)
-	Participants (12 years) in the South Korea National Oral Health Surveys 2003, 2006 & 2010	-	-	-	OR=0.74 (0.42–1.30)	OR=0.87 (0.44–1.74)	OR=0.92 (0.69–1.22)

Abbreviations: CWF = community water fluoridation; DT = number of decayed permanent teeth; OR = odds ratio; NR = not reported

¹ Defined as community that provided fluoridated tap water for more than three years at the time of the survey

² Adjusted for gender, region & use of fluoride sealant

Table 52 Results for caries prevalence from Public Health England (2014)

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results - (95%CI)		Effect Estimate (95%CI)	Sig
Public Health England 2014 Ecological Acceptable -	Residents (aged 12 years) in areas with and without CWF in England -	CWF (0.8–1.0 ppm)	No CWF ¹	Weighted caries prevalence (%D3MFT>0) ²	Unadjusted univariate model	31% (30, 33)	34% (33, 35)	% difference in odds: -11 (-20, -0.1)	NR
		-	-			-	Adjusted multivariate model ³		

Abbreviations: CWF = community water fluoridation; D3MFT = number of decayed (into dentine), filled & missing permanent teeth; NR = not reported; ppm = parts per million

¹ Areas classified as naturally fluoridated to 1 ppm were excluded

² Data from the National Dental Epidemiology Programme surveys of 5-year-olds (2012) & 12-year-olds (2009) involving visual examination of school children for missing teeth, filled teeth, & teeth with obvious decay into dentine (denoted by the '3' in d3mf/D3MFT)

³ Adjusted for deprivation & ethnicity

Table 53 Results for caries prevalence from Skinner et al (2014), Freire et al (2013), Haysom et al (2015), McGrady et al (2012), and Centers for Disease Control and Prevention (2011)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate (95%CI)	Sig
Skinner 2014 Ecological Acceptable -	Participants (14–15 years) in the NSW Teen Dental Survey 2010, Australia -	Fluoridated water (level NR)	Prevalence of dental caries (%DMFT>0)	Logistic regression ¹	NR	OR=0.59 (0.37–0.94)	$p<0.01$
		Non-fluoridated water (level NR)	-	-	NR	Reference	-
Freire 2013 Ecological Acceptable -	Participants (12 years) of the Brazilian Oral Health Study 2010 -	Fluoridated water supply	Prevalence of dental caries (%DMFT≥1)	Poisson multiple regression ²	53.9%	PR=0.90 (0.83–0.97)	NR
		Non-fluoridated water supply	-	-	67.8%	Reference	-
Haysom 2015 Ecological Acceptable -	Young people (aged 13–21 years) in NSW Juvenile Custodial Centres 2009 -	Fluoridated water supply	Prevalence of dental caries (%DMFT>0)	Multivariate logistic regression ³	NR	OR=0.30 (0.86–0.10)	$p=0.03$
		Non-fluoridated water supply	-	-	NR	Reference	-
McGrady 2012 Ecological Low -	Young people (11–13 years) attending school in two cities in the UK -	Water fluoridation (1 ppm)	Prevalence of dental caries (%D ₄₋₆ MFT>0) ⁴	Logistic regression ⁵	32%	OR=0.543 (0.667–0.443)	$p<0.001$
		No water fluoridation	-	-	46%	Reference	-
Centers for Disease Control and Prevention 2011 Ecological Low	Children (6–15 years) from 5 villages in Alaska, USA	Water fluoridation	Caries prevalence (%DMFT>0)	Multivariate analysis ⁶	6–8 years: 31% 9–11 years: 65% 12–15 years: 91%	OR=0.6 (0.7–0.5)	$p<0.001$

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate (95%CI)	Sig
-	-	No water fluoridation	-	-	6–8 years: 57% 9–11 years: 86% 12–15 years: 91%	Reference	-

Abbreviations: NSW = New South Wales; NR = not reported; DMFT = number of decayed, filled & missing permanent teeth; OR = odds ratio; PR=prevalence ratio; UK=United Kingdom; CDC=Centres for Disease Control and Prevention; ppm = parts per million

¹ Adjusted for all risk factors (i.e. Income, mother's education level, sugary drink consumption, dental visit last year & tooth brushing frequency), age, & gender

² Adjusted for gender, skin colour, household income, residences connected to water supply, & median income municipality

³ Adjusted for aboriginality, age group, gender, history out-of-home care, socioeconomic disadvantage, remoteness, time incarcerated, snacks >2x weekly, preferred sweetened drinks, tooth brushing frequency, toothache/problem with teeth/gums, self-reported status of teeth, dental service previous year, & location dental provider previous year

⁴ The '4-6' denotes visible caries into dentine

⁵ Adjusted for age at examination & IMD (index of multiple deprivation) score

⁶ Adjusted for soda pop consumption & frequency of tooth brushing

Table 54 Results for caries prevalence from Do et al (2014) and Do et al (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate (95%CI)
Do 2014 Ecological Acceptable	Children (8–12 years) who were participants in the NSW Child Dental Health Survey 2007	100% lifetime exposure to water fluoridation ¹	Caries prevalence (%DMFS>0)	Multivariate regression analysis ²	22.6% (SE: 1.2)	PR=0.84 (0.67–1.07)
-		0–99% lifetime exposure to water fluoridation ¹	-	-	22.6% (SE: 2.0)	PR=0.81 (0.62–1.06)
-		0% lifetime exposure to water fluoridation ¹	-	-	28.0% (SE: 2.3)	Reference
Do 2015 Ecological Acceptable	Children (9–14 years) participating in the Queensland Child Oral Health Survey 2010–2011	Community water fluoridation	Caries prevalence (%DMFS>0)	Complementary log-log regression ³	29.4% (95%CI: 26.1–32.9)	Reference
-		No community water fluoridation	-	-	39.3% (95%CI: 36.4–42.3)	PR=1.49 (1.01–2.21) PAF=31% N=120

Abbreviations: PR = prevalence ratio; DMFS = number of decayed, missing & filled permanent teeth surfaces; SE = standard error; PAF = population attributable fraction; N=number of cases for every 1,000 population to be prevented should community water fluoridation be introduced given a prevalence of caries of 47.1%; RR = rate ratio

¹ From birth to 3 years

² Adjusted for household income, parental education, dietary fluoride supplement use, age & gender

³ Adjusted for Indigenous status, household income, parental education, brushing frequency, fluoride supplement use, age first used fluoride toothpaste, age of first dental visit, sugary drink consumption, & school type

Table 55 Results for proportion caries-free permanent teeth from Laloo et al (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Sub-groups	Results (95%CI)	Effect Estimate (95%CI)
Laloo 2015 Ecological Low	Children (6–15 years) participating in the Child Dental Health Survey 2010 in Australia	Fluoride level in water supply ≥ 0.5 ppm	% caries-free permanent teeth ¹	Logistic regression ²	Indigenous	50.3% (45.1–55.4)	OR=1.30 (1.01–1.68)
-		-	Fluoride level in water supply <0.3 ppm	-	-	Indigenous	44.3% (40.2–48.6)

Abbreviations: OR = odds ratio; ppm = parts per million

¹ Measured using proportion with number of decayed, missing & filled permanent teeth (DMFT) = 0

² Adjusted for age & gender

Discussion

Seven ecological studies used the proportion of participants with a DMFT count greater than zero as a measure of caries prevalence (Centers for Disease Control and Prevention 2011; Freire 2013; Haysom 2015; Lee & Han 2015; McGrady 2012; Public Health England 2014; Skinner et al 2014). Five studies were assessed as being of acceptable quality, and two of low quality. Six studies reported a significant reduction in the prevalence of dental caries in permanent teeth.

Two ecological studies of acceptable quality measured caries prevalence in permanent teeth using the DMFS index (Do et al 2015; Do 2014). One reported a non-significant reduction in the prevalence of caries in permanent teeth associated with 100% lifetime exposure to CWF. The other, a statistically significant reduction in caries prevalence associated with CWF.

One systematic review (Iheozor-Ejiofor et al 2015) found a 14% increase in the proportion of caries-free children in permanent teeth. In both primary studies reporting proportion of caries-free permanent teeth the direction of effect was the same. One primary study (Lalloo et al 2015) found a significant increase in the proportion of caries-free 6 to 15-year-old Indigenous children in Australia for permanent teeth associated with water fluoridation and the other (da Silva et al 2015) reported a non-significant association between exposure to a fluoridated water supply and proportion of caries-free 12-year-olds for permanent teeth.

Consideration of this body of evidence indicates that water fluoridation is associated with a reduction in the prevalence of caries and an increase in the proportion of caries-free children for permanent teeth.

These findings contribute to the overall evidence statement on dental caries in permanent teeth on page 118.

Table 56 Caries prevalence in permanent teeth – GRADE Report (prevalence assessed with: %DMFT/S>0)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
9	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	>39,750 ⁶	Significant reduction in the prevalence of caries in children and young people (6–21 years) with exposure to community water fluoridation.	⊕⊕○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: DMFT = number of decayed, missing & filled permanent teeth

¹ Ecological studies

² Eight studies of acceptable quality with good sample size, outcome measurement and adjustment for confounders; two studies of low quality

³ Results from eight studies favour water fluoridation; one other study has an upper confidence interval just above no effect but the effect is in the same direction as the other studies; one has mixed results all crossing the line of no effect

⁴ Two studies set in the UK, three in Australia, one in the USA, one in Brazil and one in Korea in the context of community water fluoridation; the studies in Finland and Denmark are in the context of naturally-occurring fluoride

⁵ Wide confidence intervals in four studies but good sample sizes; all other studies have a good sample size and adequate confidence intervals

⁶ The number of subjects not available for the Public Health England (2014) study

Table 57 Change in proportion of caries-free children (permanent teeth) from Ihezor-Ejiofor et al (2015) – GRADE Report (assessed with %DMFT=0)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
8	Observational studies	Serious ¹	Not serious ²	Serious ³	Not serious	Very strong association ⁴	53,538 ⁵	The pooled effect estimate was an increase of 14% (95%CI: 5% to 23%) in the proportion of caries-free children (8–12 years) in areas with water fluoridation. ⁶	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth

¹ Studies at high risk of bias; quality of the evidence downgraded

² Substantial heterogeneity present, however, given that the direction of effect was the same in all but one of the studies/outcomes we did not downgrade due to heterogeneity

³ Indirectness of evidence due to lack of contemporary evidence; quality of the evidence downgraded. 71% of the studies conducted prior 1975; the use of fluoridated toothpaste, the availability of other caries prevention strategies, diet and tap water consumption are all likely to have changed in the populations in which the studies were conducted. No studies on the effect of water fluoridation in adults met the inclusion criteria

⁴ The authors of this systematic review judged that there was a very large effect size and upgraded the quality twice, however as this has been downgraded for risk of bias, there is no ability to upgrade in the GRADE approach

⁵ Total number of participants measured. Analysis undertaken on average number of participants measured at baseline and follow-up for each study

⁶ The proportion of caries-free children at follow-up in the low/non-fluoridated areas ranged from 1% to 67% (median 14%)

Table 58 Proportion of caries-free children (permanent teeth) – GRADE Report (prevalence assessed with: %DMFT=0)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
2	Observational study ¹	Not serious ²	Not serious	Not serious ³	Serious ⁴	None	>97,809 ⁵	Significant increase in proportion of caries-free 6 to 15-year-olds for permanent teeth with exposure to water fluoridation in one study. Non-significant positive association between water fluoridation and proportion of caries-free 12-year-olds in one study.	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: DMFT = number of decayed, missing & filled permanent teeth

¹ Ecological study

² One study of low quality and another of acceptable quality

³ Set in Australia and Brazil in the context of community water fluoridation

⁴ Wide confidence intervals

⁵ The number of participants was not available for the da Silva et al (2015) study

CARIES INCIDENCE: PERMANENT TEETH

Evidence from prior reviews

No studies reporting caries incidence in permanent teeth were identified in McDonagh (2000) or NHMRC (2007).

Literature search results for systematic reviews

No systematic reviews were identified which included studies looking at the association between water fluoridation and caries prevalence in the permanent dentition.

Literature search results for recent primary studies

The literature search identified one cohort study (Level III-2 evidence) of acceptable quality that measured the incidence of caries in the occlusal surface of permanent first molars.

Results

Broffitt (2013) measured first molar occlusal caries incidence from age 9 to 13 years (defined as any surface-level progression from sound, non-cavitated or questionable lesions at age 9 to cavitated lesion or filled or both at age 13) in 443 participants. This was a prospective cohort study (Level III-2 evidence) of acceptable quality. Participants in the Iowa Fluoride Study who participated in both the mixed (~9 years) & permanent dentition (~13 years) examinations were included. Those with inadequate responses for water fluoride levels, tooth-brushing frequency or beverage intake estimates were excluded. The study found that exposure to fluoride in drinking water reduced the odds of developing dental caries in permanent first molars but this was not statistically significant (at the 5% level). The results for this study are presented in Table 59. The GRADE assessment for this study is presented in Table 60.

Table 59 Results for caries incidence from Broffitt (2013)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate (95%CI)	Sig
Broffitt 2013 Cohort Acceptable	Participants (9 & 13 years) of the Iowa Fluoride Study in USA	Home tap water fluoride level (mean level 0.82 ppm)	Mean incidence of first molar occlusal caries from age 9 to 13 years ¹	Mixed effects logistic regression ²	16.9% (SD 0.34)	OR=0.32 (0.10–1.02)	$p=0.056$

Abbreviations: OR = odds ratio; SD = standard deviation; ppm = parts per million

¹ defined as progression to cavitated lesion (D₂,S) or filled (D₂,FS)

² adjusted for D₂,FS>0 at 9 years (vs. none), D₁ score at 9 years (vs. none), brushing frequency (AUC, age 9–13), D₁ * brushing frequency interaction, low income, & low income * fluoride level interaction

Discussion

One cohort study of acceptable quality assessed the effect of water fluoridation on the incidence of caries and found a non-significant reduction in the incidence of caries on first molar occlusal surfaces.

These findings contribute to the overall evidence statement on dental caries in permanent teeth on page 118.

Table 60 Incidence of first molar occlusal caries in permanent teeth – GRADE Report (prevalence assessed with: surface-level progression from sound, non-cavitated or questionable lesions at age 9 to cavitated lesion or filled or both at age 13)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Not serious ²	Not serious ³	Serious ⁴	Serious ⁵	None	93,622	Non-significant decrease in the incidence of first molar occlusal caries at age 13 with exposure to water fluoridation (OR=0.32; 95%CI: 0.10–1.02)	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: DMFT = number of decayed, missing & filled permanent teeth

¹ Cohort study

² Study of acceptable quality with good sample size, outcome measurement and adjustment for confounders

³ Only one study

⁴ Participants not representative of US population

⁵ Wide confidence interval

GRADE ASSESSMENTS (PERMANENT TEETH)

The summary of findings tables for the GRADE assessments of caries in permanent teeth are presented Table 61 below. The review authors decided to omit the GRADE terminology of 'very low, low, moderate, and high quality' and discuss the findings in terms of their confidence in the results. Instead they have included a comment on the extent of their confidence in the effect observed for each outcome.

Table 61 Summary of findings for dental caries in permanent teeth

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in permanent teeth assessed using DMFT	The pooled effect estimate was a reduction of 1.16 (95%CI: 0.72 lower to 1.61 lower) in mean DMFT in the areas with water fluoridation for children aged 8–11 years. This indicates a reduction in DMFT of 26% in the water fluoridation groups over and above that for the control groups ⁶ .	78,764 (10 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
	The median percentage reduction of caries in permanent teeth was 37% (range: 5%–85%) in participants aged 8–51 years.	NR (37 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
	Significant reduction in mean DMFT in adults (18–65+years) with exposure to fluoridated water	3,080 (4 observational studies)	⊕○○○	A single systematic review of reasonable methodological quality downgraded because of no clear reporting of assessment of risk of bias, and serious indirectness and imprecision
	Significant reduction in mean DMFT in adolescents and adults (≥11 years) with exposure to community water fluoridation (reduced by 0.19; 95%CI: 0.27 reduction, 0.11 reduction in one study)	>12,700 (7 observational studies)	⊕⊕○○	Five acceptable quality studies set in Australia in the context of CWF. Single large study of acceptable quality from England using a national database with adjustment for confounders in a setting of CWF.
Caries in permanent teeth assessed using DMFS	The median percentage reduction of caries in permanent teeth was 29% (range: 0%–50%) in participants aged 5–35 years.	NR (16 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
	Significant reduction in mean DMFS in children and adolescents (8–14 years) with exposure to community water fluoridation in two studies	12,344 (4 observational studies)	⊕⊕○○	Two studies of acceptable quality set in Australia in the context of CWF. One study set in Vietnam of limited applicability. One regression analysis from Australia.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
-	Significant inverse association between $\geq 75\%$ lifetime exposure to water fluoridation and mean DFS (participants 15+ years) in one study. Non-significant inverse relationship between naturally occurring fluoride levels and mean DMFS (participants 6–17 years) in one study.			
Caries prevalence (permanent teeth) assessed with %DMFT/S>0	Significant reduction in the prevalence of caries in children, adolescents and adults (6–21 years) with exposure to community water fluoridation	>39,750 (9 observational studies)	⊕⊕○○	Includes a single large study of acceptable quality from England using a national database with adjustment for confounders in a setting of CWF. Also six acceptable quality studies from Australia.
Proportion of caries-free children (permanent teeth) assessed with %DMFT/S =0	The pooled effect estimate was an increase of 14% (95%CI: 5% to 23%) in the proportion of caries-free children (8–12 years) in areas with water fluoridation.	53,538 (8 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
-	Significant increase in proportion of caries-free Indigenous children and adolescents (6–15 years) for permanent teeth with exposure to water fluoridation in one study (OR=1.30; 95%CI: 1.01–1.68). Non-significant positive association between water fluoridation and proportion of caries-free 12-year-olds in one study.	>97,809 (2 observational studies)	⊕○○○	One acceptable quality study from Australia of Indigenous children set in context of CWF. One acceptable study from Brazil using national data. Downgraded for imprecision.
Incidence of first molar occlusal caries in permanent teeth	Non-significant decrease in the incidence of first molar occlusal caries at age 13 with exposure to water fluoridation (OR=0.32; 95%CI: 0.10–1.02)	93,622 (1 observational study)	⊕○○○	A single study from US of acceptable quality. Downgraded for indirectness and imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Note: We have attempted as far as possible to use the following definitions: infants (0–4 years); children (5–11 years); adolescents (12–17 years); adults (18–64 years) and later adulthood (65+ years)

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States; NR = not reported

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Evidence Statement

The evidence evaluation identified three reviews and 10 ecological studies which found consistent evidence that water fluoridation at current Australian level is associated with a decreased prevalence of dental caries in the permanent teeth of children, adolescents and adults (assessed using DMFT, DMFS, proportion of caries-free permanent teeth and caries prevalence in permanent teeth).

COMBINED CARIES MEASURES

There are serious limitations in using a combined measure of caries (dmft/DMFT) in mixed dentition as the scores are dependent on the number of deciduous teeth remaining and the number of permanent teeth erupted. The score in deciduous teeth (dmft) tends to increase up to around 8 years of age and as decayed or filled deciduous teeth are lost, the combined caries score tends to drop as the newly erupted permanent teeth have no caries (and have a low DMFT score). In this way, combining dmft and DMFT measures does not necessarily reflect true caries experience. The results of this section should therefore be interpreted very cautiously.

Evidence from prior reviews

The McDonagh (2000) systematic review combined dmft and DMFT. The findings are discussed in the section on page 53. No further evidence on this outcome was identified in NHMRC (2007)

Literature search results for systematic reviews

No systematic reviews were identified from the literature search.

Literature search results for recent primary studies

The literature search identified three studies of acceptable quality that investigated the effect of water fluoridation on caries measures that included both permanent and deciduous teeth (Chankanka et al 2011; McLaren & Emery 2012; Zander et al 2013). Chankanka et al (2011) was a secondary analysis of a prospective cohort study (Level III-2 evidence). The other two studies (McLaren & Emery 2012; Zander et al 2013) were ecological studies (Level IV evidence).

Results

Zander et al (2013) was an ecological survey of acceptable quality from Australia which conducted a standardized dental examination and administered a questionnaire to measure the oral health of 434 children (32% were Aboriginal) aged 3–12 years in three small rural or regional areas. Caries prevalence was determined as the proportion of participants with any decayed, missing and filled deciduous and permanent teeth (dmft/DMFT). Fluoridation status was determined by whether the school's water was fluoridated or not. Fluoridation was not significantly associated with caries experience (OR=1.06; 95%CI: 0.67–1.67). When the participants who lived in both a fluoridated and non-fluoridated area during their lifetime were excluded, the odds of having any caries experience was reduced but did not reach statistical significance (OR=0.81; 95%CI: 0.46–1.43). The results of this study including the sensitivity analysis are presented in Table 62. The authors concluded that the study has shown that water fluoridation and Aboriginal status are less significantly associated with caries in these communities than socio-economic status, age and tooth-brushing.

Table 62 Results from Zander et al (2013)

	Baseline model ¹ (caries yes/no)	Model 1 ² (yes/mixed/no)	Model 2 ³ (yes/no—mixed excluded)
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Age group (years)	Significant	Significant	Significant
Concession card holder	2.07 (1.28–3.34)	1.93 (1.19–3.13)	2.20 (1.28–3.80)
Tooth brushing ≤1/day	1.91 (1.20–3.06)	1.93 (1.20–3.10)	1.72 (1.03–2.87)
Aboriginal	1.63 (0.94–2.84)	1.62 (0.93–2.81)	1.08 (0.58–1.99)
Fluoridation status	1.06 (0.67–1.67)	1.0	0.81 (0.46–1.43)
Mixed fluoride history	-	1.01 (0.59–1.71)	-
Unfluoridated	-	1.60 (0.88–2.92)	-

Abbreviations: OR = odds ratio; 95%CI = 95% confidence interval

¹ Participants with a mixed fluoridation history were included in the fluoridated group

² Three levels of fluoridation status: always lived in a fluoridated area; lived in both fluoridated and non-fluoridated areas ('mixed'), and; always lived in a non-fluoridated area

³ Participants with 'mixed' fluoridation status excluded

McLaren and Emery (2012) analysed data from the Canadian Health Measures Study (CHMS) to investigate the relationship between water fluoridation and dmft/DMFT counts. The CHMS recruited approximately 5,250 participants aged 6–79 years from 15 sites in Canada. McLaren and Emery (2012) looked at the data for 1,081 children aged 6–11 years old. Those participants with mixed fluoridation status were included in the no fluoridation group. Fluoridation was inversely related to mean dmft/DMFT counts (β coefficient was -1.6 ; 95%CI: $-3.4, 0.12$; $p < 0.10$). This was adjusted for variables, fluoridation x socioeconomic interaction terms, and sugary drink consumption, tooth brushing/flossing frequency, place of birth and dentist visits.

The GRADE report for these studies is presented in Table 63.

Chankanka et al (2011) used data from the Iowa Fluoride Study prospective cohort to investigate the relationship between water fluoride level exposure and the incidence of non-cavitated and cavitated caries. The Iowa Fluoride study is a prospective cohort study of mothers and newborns recruited from eight Iowa hospital postpartum units from 1992–1995 which has been collecting fluoride, dietary, and other related information associated with dental fluorosis and caries since children were 1.5 months old. Chankanka et al (2011) included 154 participants who had completed all examinations and questionnaires at each time point (i.e. at ages 5, 9 and 15 years). A composite water fluoride level was determined as weighted averages of main sources of water (i.e. home/school, bottled/filtered/tap water) at each time point. At the first examination (age 5) any cavitated or non-cavitated lesions were considered to be new cavitated or non-cavitated caries. Any transition from sound to non-cavitated or sound/non-cavitated to cavitated/filled between consecutive examinations was considered to be new non-cavitated or new cavitated caries. The analysis was on a per surface basis. The generalised linear mixed model analysis found that the β coefficient was -0.28 ($p=0.34$) for new non-cavitated caries and -0.18 ($p=0.57$) for new cavitated caries and was not carried over into the multivariate analysis.

The GRADE report for this study is presented in Table 64.

Discussion

One cohort study and two ecological studies reported on the effect of water fluoridation on caries in mixed dentition (deciduous and permanent teeth). All were of acceptable quality. The cohort study found a non-significant inverse association between water fluoride level and the incidence of cavitated and non-cavitated caries (Chankanka et al 2011). This study had limited generalisability due to the participants not being representative of the US population. One ecological study found a non-significant decrease in caries associated with exposure to fluoridated water (Zander et al 2013). The confidence intervals of the odds ratio were very wide suggesting that the study was underpowered. The final study found a non-significant inverse association between exposure to water fluoridation and mean dmft/DMFT (McLaren & Emery 2012).

As noted before, combining the dmft and DMFT scores does not necessarily truly reflect total caries experience due to the loss of deciduous teeth and the eruption of permanent teeth. The relationship between caries in deciduous teeth and permanent teeth during ages where there is mixed dentition (about 5–6 years to 12 years) is complex.

Therefore, considering the findings as a whole, these studies provide limited evidence of a relationship between water fluoridation and a decrease in caries in mixed dentition.

Table 63 Caries in mixed dentition – GRADE Report (assessed using mean dmft/DMFT)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
2	Observational studies	Not serious ¹	Not serious ²	Not serious ³	Serious ⁴	None	4,784	Non-significant reduction in caries in one study (OR=0.81; 95%CI: 0.46–1.43). Non-significant inverse association between dmft/DMFT and water fluoridation ($\beta = -1.6$; 95%CI: -3.4, 0.12; $p < 0.10$).	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: SES = socioeconomic status

¹ Studies all of acceptable quality

² All findings in favour of fluoridation

³ All in the setting of water fluoridation; one each in Australia & Canada

⁴ Wide confidence intervals

Table 64 Caries incidence in mixed dentition – GRADE Report (assessed using mean dmfs/DMFS)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational studies ¹	Not serious ²	Not serious ³	Serious ⁴	Serious ⁵	None	154	Non-significant inverse association between incidence of cavitated and non-cavitated caries in mixed dentition and water fluoridation ($\beta = -0.28$; $p=0.34$ & -0.18 ; $p=0.57$).	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: SES = socioeconomic status

¹ Cohort study

² Study of acceptable quality

³ Only one study

⁴ In the setting of water fluoridation in the US; highly selected population

⁵ Small sample size

GRADE ASSESSMENT (MIXED DENTITION)

The summary of findings tables for the GRADE assessments of caries in mixed dentition are presented Table 65 below. The review authors decided to omit the GRADE terminology of 'very low, low, moderate, and high quality' and discuss the findings in terms of their confidence in the results. Instead they have included a comment on the extent of their confidence in the effect observed for each outcome.

Table 65 Summary of findings for dental caries in mixed dentition

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in mixed dentition	Non-significant reduction in caries in one study in infants and children aged 3–12 years Non-significant inverse association between dmft/DMFT and water fluoridation in children aged 6–11 years	4,784 (2 observational studies)	⊕○○○	One study from Australia and another from Canada in the context of CWF. Downgraded for imprecision.
Caries incidence in mixed dentition	Non-significant inverse association between incidence of cavitated and non-cavitated caries in mixed dentition and water fluoridation (aged 3–13 years).	154 (1 observational study)	⊕○○○	Single study from the US using Iowa Fluoride Study data. Downgraded for indirectness and imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Note: We have attempted as far as possible to use the following definitions: infants (0–4 years); children (5–11 years); adolescents (12–17 years); adults (18–64 years) and later adulthood (65+ years)

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Evidence Statement

The evidence evaluation identified three studies (one cohort and two ecological) which provided insufficient evidence to reach a conclusion about any association between water fluoridation at current Australian levels and mixed dentition in children.

DISPARITIES

Evidence from prior reviews

The McDonagh et al (2000) review included fifteen studies that investigated the effect of water fluoridation on inequalities in dental health across social classes. As the authors considered this issue to be highly important, studies of any design that were conducted in the UK were included. Three studies were before-and-after studies and the rest were cross-sectional in design. Three were unpublished studies. The Registrar General’s classification of social class was used to define the social class groups (range: I–V)¹³

Six studies provided information about the proportion of caries-free children and young people aged 5–16 years. All studies except one (in 15 to 16-year-olds) show that for all age groups and social classes the proportion caries-free was greater in the areas with fluoridated water. With the exception of the same study, the proportion caries-free was higher in the higher social classes (social class I, II and III) than the lower social classes in both areas with and without fluoridated water. In all age groups and areas fluoridated and not fluoridated (except for the unfluoridated area in one study of 15 to 16-year-olds), there is a disparity between social classes in the proportion caries-free. This is illustrated in Figure 10 below for children aged 5 years (averaged data from four studies).

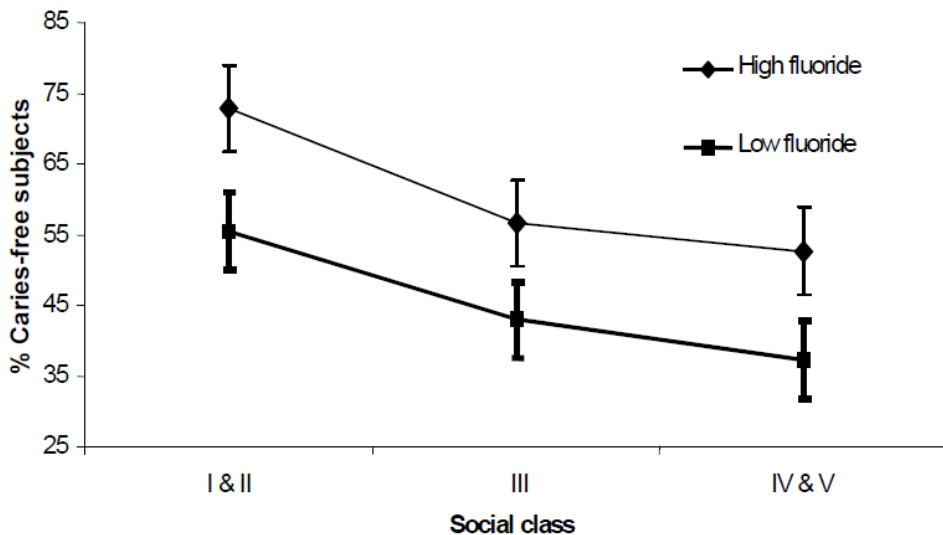


Figure 10 Proportion of (%) caries-free five-year-old children (95% CI) by social class in high and low fluoride areas

The absolute difference in the proportion caries-free between classes I and II and classes IV and V in the fluoridated area is 20% and 18% in the non-fluoridated areas. The authors of the review concluded that there was no evidence from these studies to suggest that water fluoridation reduces the disparity in proportion caries-free across social classes.

Seven studies provided information on the mean dmft/DMFT of participants aged 5–16 years. All studies demonstrated that for all age groups and social classes dmft/DMFT was lower in those living in areas with fluoridated water than non-fluoridated water. On average there is more dental caries in the lower social classes than the higher social classes. Again, in most age groups and areas fluoridated and not fluoridated, there is a disparity between social classes in mean dmft/DMFT scores. This is illustrated in Figure 11 below for children aged 5 years (averaged data from five studies).

¹³ Lower social classes indicated by higher number e.g. ‘IV’ & ‘V’

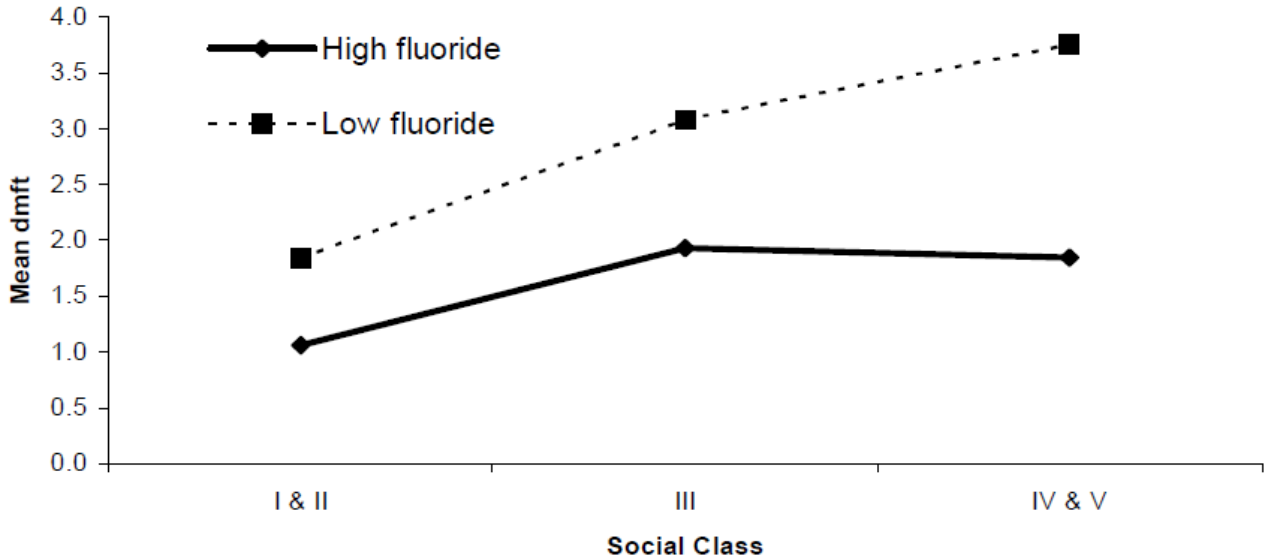


Figure 11 dmft by social class in high and low fluoride areas for children aged 5 years

The absolute difference in mean dmft between classes I and II and classes IV and V in the fluoridated area is 0.7 and 2.0 in the non-fluoridated areas. The authors of the review concluded that this data from 5-year-olds suggests that water fluoridation reduces dmft across social classes and reduces the disparity in dmft between social classes. This trend was not seen in the other age groups however.

Two other studies used regression analysis and found that water fluoridation had a greater effect in the most deprived groups. These studies used different measures of social deprivation (Townsend and Jarman indices).

Two other studies reported mixed results and another two provided insufficient data. The last one found that the effect of water fluoridation in reducing caries was greater in the lower social class groups.

Overall, the authors recommend caution in interpreting these findings due to the small number of studies, the differences between them and their low methodological quality. They concluded that there appeared to be some evidence that water fluoridation reduces the inequalities in dental health across social classes in five and 12 year-olds, using the dmft/DMFT measure but that this effect was not seen in the proportion of caries-free children among five year-olds. There was insufficient data for the effects in children of other ages to be investigated fully.

The NHMRC (2007) review did not report on the effect of water fluoridation on disparities in caries experience.

Literature search results for systematic reviews

The literature search identified one systematic review (Level IV evidence) that reported on the effect of water fluoridation on disparities in caries experience in deciduous teeth (Iheozor-Ejiofor et al 2015). No systematic reviews were identified which included studies of disparities in caries of permanent dentition.

Results

Iheozor-Ejiofor et al (2015) included three studies with a total number of 35,399 participants. All three studies were judged to be at high risk of bias. One study did not use a validated measure of deprivation and one did not contain sufficient information about fluoride levels or the number of participants measured at each time point. Therefore, the authors were unable to draw any robust

conclusion about the effect of the initiation of water fluoridation on disparities in caries across social class. The GRADE assessment is presented in Table 68.

Literature search results for recent primary studies

The literature search identified one ecological study (Level IV evidence) of acceptable quality that reported on the effect of water fluoridation on disparities in caries experience in deciduous and permanent dentition (Public Health England 2014) and two ecological studies of low quality (Lalloo et al 2015; McGrady et al 2012). Another cohort study (Level III-2) exploring the effect of exposure to water fluoridation and tooth loss also included analyses by ethnicity and education status (Neidell et al 2010). Public Health England (2014) also explored data regarding disparities in hospital admissions for caries in children aged 1–4 years.

Results

Lalloo et al (2015), as reported previously, was a low quality ecological study that investigated the effect of access to fluoride in the water supply on the disparity in dental caries between Indigenous and non-Indigenous children. The difference in the proportion of non-Indigenous and Indigenous caries-free children for deciduous dentition increased from 13.4% in the non-fluoridated areas to 25.2% in the fluoridated areas. The difference in the proportion of caries-free children for permanent dentition increased from 9.5% in the non-fluoridated areas to 20% in the fluoridated areas. The authors concluded that exposure to ≥ 0.5 ppm fluoride in the water supply did not reduce the gap in dental caries experience between Indigenous and non-Indigenous children. The results for this study are presented in Table 66. The GRADE assessment is presented in Table 69.

The other low quality ecological study by McGrady et al (2012) has been described before in the section on caries prevalence in permanent teeth. This study included 1,783 students aged 11–13 years attending schools in Manchester (non-fluoridated water supply) and Newcastle (fluoridated water supply) in the UK in their low quality ecological study. Postcode details for each participant enabled an individual level measure of social deprivation to be ascribed using the Index of Multiple Deprivation (IMD) by linking the postcode with the Local Super Output Area¹⁴ IMD score. Each comparison group were divided in five groups (quintiles) of increasing deprivation. The results for this study are presented in Table 67. The difference in the mean $D_{4-6}MFT$ ¹⁵ score between quintile 1 and quintile 6 was 0.54 in Newcastle and 0.97 in Manchester indicating that the disparity in $D_{4-6}MFT$ score between the most and least deprived participants was less in the city with fluoridated water. The findings between other levels of deprivation support this finding. The authors concluded that water fluoridation appears to reduce the disparity in caries experience by social deprivation. The GRADE assessment is presented in Table 70.

Public Health England (2014) conducted an exploratory analysis of data for mean d_3mft and found there was evidence that the association between fluoridation and mean d_3mft was stronger in the most deprived quintile of deprivation compared to the combined four least deprived quintiles: mean d_3mft was 0.16 lower (95% CI $-0.32, -0.01$; $p=0.04$) in fluoridated areas in the combined four least deprived quintiles compared to 0.51 lower (95% CI $-0.75, -0.27$; $p<0.001$) in the most deprived quintile. Similarly to the mean $dmft$ results, there was evidence that the association between fluoridation and prevalence of caries was stronger in the most deprived quintile of deprivation compared to the combined four least deprived quintiles: the prevalence of any d_3mft in the combined four least deprived quintiles was 17% lower (95% CI: 28% lower, 3.9% lower; $p<0.01$) in fluoridated areas compared to non-fluoridated areas whereas in the most deprived quintile the prevalence of any d_3mft was 32% lower (42% lower, 19% lower; $p<0.001$) in fluoridated areas.

The findings for permanent teeth were similar: the association between fluoridation and mean D_3MFT was stronger in the most deprived quintile of deprivation compared to the combined four least deprived quintiles: mean D_3MFT was 0.07 lower (95% CI $-0.17, 0.04$; $p=0.21$) in fluoridated

¹⁴ This is a set of geographical areas of consistent size of around 1,500 people

¹⁵ Denotes visible caries into dentine

areas in the combined four least deprived quintiles compared to 0.25 lower (95% CI -0.44, -0.07; $p < 0.01$) in the most deprived quintile. As for the difference in the prevalence of caries, there was some evidence that the association between fluoridation and prevalence D_3MFT was stronger in the most deprived quintile of deprivation with a 9% reduction in odds of having dental caries in the four least deprived quintiles (95%CI: 21% less, 5% more; $p = 0.21$) compared to a 26% reduction in odds in the most deprived quintile (95%CI: 40% less, 8% less; $p < 0.01$).

Public Health England (2014) also looked at disparities in the rate of hospital admissions for caries in children aged 1–4 years. The rate of admission was 27% lower (95% CI 62% lower, 39% higher; $p = 0.34$) in fluoridated areas compared to non-fluoridated areas in the combined four least deprived quintiles compared to 76% lower (95% CI 89% lower, 45% lower; $p = 0.001$) in the most deprived quintile. The GRADE assessment is presented in Table 70.

Lastly Neidell et al (2010) found that their results suggested that the effect of CWF exposure on reducing tooth loss appeared to be larger for individuals from lower socioeconomic status groups: the estimates for Blacks, high school dropouts, and high school graduates implied that exposure to CWF at birth was associated with having 0.37, 0.61, and 0.39 more teeth, respectively. The result for all participants was 0.26 more teeth. This study was not included in a GRADE assessment due to the results being a subgroup analysis and many other factors associated with tooth loss were not considered. The results of this study are presented in Table 72.

Discussion

The evidence from the single systematic review was insufficient for the authors to draw any conclusions regarding any effect of water fluoridation on disparities in caries experience between social classes.

There was evidence from a single large ecological study that water fluoridation did not reduce the gap in dental caries experience in deciduous or permanent teeth between Indigenous and non-Indigenous Australians aged 5–10 years. This finding is very likely due to residual confounding. The only confounding factors considered were age and gender; other known confounding factors were not included in the multivariate analysis e.g. use of fluoridated toothpaste and socioeconomic factors. It should be noted that water fluoridation was effective in increasing proportion of caries-free children in the deciduous and permanent teeth of Indigenous children even with an increase in disparity.

The low quality ecological study from the UK found evidence of a reduction in the disparity in caries experience by social deprivation.

Another single acceptable quality ecological study found evidence that water fluoridation had a greater effect in the most deprived subgroup of participants with respect to mean d_3mft/D_3MFT and caries prevalence in both deciduous and permanent teeth, and hospital admissions for caries of 1 to 4-year-olds compared to the four least deprived subgroups. In addition, a low quality study found evidence of a reduced difference in $D_{4-6}MFT$ between the most and least deprived groups in a UK city with fluoridated water.

The last study also found from their regression analysis that the effect of water fluoridation was greater in individuals from groups of lower socioeconomic status with respect to tooth loss.

On balance, these studies provide limited evidence that water fluoridation is associated with a reduction in the disparity in dental health across social class, levels of deprivation and socioeconomic status.

Table 66 Results for proportion caries-free deciduous/permanent teeth from Lalloo et al (2015)

Study Design Quality	Population	Exposures	Outcome	Analysis	Sub-groups	Results (95%CI)	Effect Estimate (95%CI)	
Lalloo 2015 Ecological Low	Children (5–10 years) participating in the Child Dental Health Survey 2010 in Australia	Fluoride level in water supply ≥ 0.5 ppm	% caries-free deciduous teeth ¹	Logistic regression ²	Non-Indigenous	52.5% (51.0–54.0)	OR=3.78 (3.17–4.50)	
					Indigenous	27.3% (23.7–31.2)	OR=1.27 (0.98–1.63)	
		Fluoride level in water supply < 0.3 ppm	-	-	-	Non-Indigenous	36.3% (35.3–37.3)	OR=1.93 (1.63–2.29)
						Indigenous	22.9% (20.2–25.9)	Reference
	Children (6–15 years) participating in the Child Dental Health Survey 2010 in Australia	Fluoride level in water supply ≥ 0.5 ppm	% caries-free permanent teeth ³	Logistic regression ²	Non-Indigenous	70.7% (69.3–72.0)	OR=3.72 (3.04–4.56)	
					Indigenous	50.3% (45.1–55.4)	OR=1.30 (1.01–1.68)	
		Fluoride level in water supply < 0.3 ppm	-	-	-	Non-Indigenous	53.8% (52.6–55.1)	OR=1.60 (1.32–1.95)
						Indigenous	44.3% (40.2–48.6)	Reference

Abbreviations: OR = odds ratio; ppm = parts per million

¹ Measured using number of decayed, missing & filled deciduous teeth (dmft) = 0

² Adjusted for age & gender

³ Measured using number of decayed, missing & filled permanent teeth (DMFT) = 0

Table 67 Results from McGrady (2012)

Quintile of deprivation	Newcastle (fluoridated water)		Manchester (unfluoridated water)		Sig
	N	Mean D4-6MFT caries into dentine (SD)	N	Mean D4-6MFT caries into dentine (SD)	
1	183	0.38 (0.86)	173	0.45 (0.88)	NS
2	197	0.47 (1.02)	160	0.84 (1.23)	p<0.001
3	213	0.62 (1.11)	148	1.07 (1.52)	p<0.05
4	127	0.87 (1.40)	226	1.37 (1.73)	p<0.05
5	190	0.99 (1.40)	166	1.52 (1.79)	p<0.001

Abbreviations: N = number of participants; Sig = statistical significance (p-value); D₄₋₆MFT = number of visible caries lesions into dentine, missing & filled permanent teeth; SD = standard deviation; NS = not significant

Table 68 Disparities in caries by SES status from Ihezor-Ejiofor et al (2015) – GRADE Report

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
3	Observational studies	Serious ¹	NR	NR	NR	NR	>35,399 ²	There is insufficient information to determine whether initiation of a water fluoridation programme results in a change in disparities in caries levels across SES	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: SES = socioeconomic status; NR = not reported in Ihezor-Ejiofor et al (2015)

¹ Studies at high risk of bias; quality of evidence downgraded

² Number of participants not reported in one study

Table 69 Disparities in caries by Indigenous status– GRADE Report (measured with proportion with dmft/DMFT=0)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Serious ²	Not serious ³	Not serious ⁴	Serious ⁵	None	97,809	Water fluoridation increased the gap in proportion caries-free children in deciduous and permanent teeth between Indigenous and non-Indigenous Australians aged 5–15 years	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft = number of decayed, missing & filled deciduous teeth

¹ Ecological study

² One study of low quality mainly due to limited measurement and control for known confounders i.e. only controlled and measured age & gender

³ Results consistent for subgroups within study

⁴ Set in Australia in the context of community water fluoridation

⁵ Wide confidence intervals

Table 70 Disparities in caries by deprivation – GRADE Report (measured with mean $D_{4-6}MFT$, proportion $d_3mft/D_3MFT=0$, mean d_3mft/D_3MFT , & rate of hospital admissions)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
2	Observational studies ¹	Serious ²	Not serious ³	Not serious ⁴	Serious ⁵	None	>1,783 ⁶	Water fluoridation had a greater effect in the most deprived subgroup of participants with respect to mean d_3mft and caries prevalence in 5-year-olds, mean D_3MFT and caries prevalence in 12-year-olds, and hospital admissions for caries of 1 to 4-year-olds compared to the four least deprived subgroups in one study. Difference in $D_{4-6}MFT$ between most and least deprived groups was reduced in areas with fluoridated water for 11 to 13-year-olds in one study.	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: $dmft/DMFT$ = number of decayed, missing & filled deciduous/permanent teeth; D_{4-6} denotes visible caries into dentine; d_3/D_3 denotes any caries into dentine

¹ Two ecological studies

² Exploratory analysis of subgroups with no adjustment for confounding in one study; the other study was assessed as being of low quality

³ Results consistent for subgroups and outcomes within studies

⁴ Both set in the UK in the context of community water fluoridation

⁵ Wide confidence intervals in one study

⁶ Number of participants were not reported in the Public Health England (2014) study

GRADE ASSESSMENT (DISPARITIES)

The summary of findings tables for the GRADE assessments of disparities in caries are presented Table 71 below. The review authors decided to omit the GRADE terminology of ‘very low, low, moderate, and high quality’ and discuss the findings in terms of their confidence in the results. Instead they have included a comment on the extent of their confidence in the effect observed for each outcome.

Table 71 Summary of findings for disparities in dental outcomes

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Disparities in caries by SES status	There is insufficient information to determine whether initiation of a water fluoridation programme results in a change in disparities in caries levels (deciduous teeth) across SES	>35,399 (3 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded once for high risk of bias. The authors reported the quality of evidence as being ⊕⊕○○ and provided no reason why they upgraded. GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
Disparities in caries by Indigenous status	Water fluoridation increased the gap in proportion caries-free children in deciduous and permanent teeth between Indigenous and non-Indigenous Australians aged 5–15 years	97,809 (1 observational study)	⊕○○○	A single Australian study of low quality in the context of CWF. Downgraded for risk of bias and imprecision.
Disparities in caries by deprivation	Water fluoridation had a greater effect in the most deprived subgroup of participants with respect to mean d ₃ mft and caries prevalence in 5-year-olds, mean D ₃ MFT and caries prevalence in 12-year-olds, and hospital admissions for caries of 1 to 4-year-olds compared to the four least deprived subgroups in one study. Difference in D ₄₋₆ MFT between most and least deprived groups was reduced in areas with fluoridated water for 11 to 13-year-olds in one study.	>1,783 (2 observational studies)	⊕○○○	A single large study of acceptable quality from England using a national database setting of CWF. Exploratory analysis of subgroups. No adjustment for confounding. Downgraded for risk of bias and imprecision. Another single large study from the UK downgraded for risk of bias.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Note: We have attempted as far as possible to use the following definitions: infants (0–4 years); children (5–11 years); adolescents (12–17 years); adults (18–64 years) and later adulthood (65+ years)

Abbreviations: d₃mft/ D₃MFT = number of decayed (into dentine), missing and filled deciduous/permanent teeth; CWF = community water fluoridation; SES = socioeconomic status

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Evidence Statement

The evidence evaluation identified one review and three ecological studies which provided insufficient evidence to reach a conclusion about any association between water fluoridation at current Australian levels and disparities in dental caries experience.

OTHER DENTAL OUTCOMES

Studies identified as reporting dental outcomes other than caries were located from both the search for primary studies on caries (da Silva et al 2015; Crocombe et al 2013; Public Health England 2014) and the search for other health outcomes (Barbato & Peres 2009; Burke et al 2010; Jolaoso et al 2014; Koltermann et al 2011; Neidell et al 2010; Public Health England 2014; Singh et al 2014). The evidence identified in the search for other health outcomes are presented based on the applicability of the included studies. Study applicability was based on how similar the water fluoride levels reported within each study were to those experienced in Australia.

TOOTH LOSS

Dental caries is an important cause of tooth loss. The Australian National Survey of Adult Oral Health (AIHW 2007) reported that almost 19% of adults had at least one tooth lost, and 15 to 24-year-olds had on average 0.6 number of teeth lost due to pathology.

Both the NHMRC (2007a) and McDonagh (2000) et al systematic reviews did not include tooth loss *per se* as an outcome in their systematic reviews. They did include dmft/DMFT (decayed, missing, or filled primary or permanent teeth) counts as an outcome which is a composite measure that includes missing teeth; however, the absolute number of missing teeth cannot be determined from these scores.

Literature search results for systematic reviews

No systematic reviews were identified from the literature search.

Literature search results for recent primary studies and other health effects

The literature search for the systematic review of recent primary studies of caries identified two studies (Level IV evidence) that included missing teeth as an outcome (da Silva et al 2015; Crocombe et al 2013). Both were ecological studies (Level IV evidence) of acceptable quality. In addition, the literature search for the systematic review of other health effects identified three studies that included tooth loss as an outcome. One was a retrospective cohort study (Level III-2 evidence) of acceptable quality (Neidell et al 2010) and the other two were ecological studies (Level IV evidence) of acceptable quality (Barbato & Peres 2009; Koltermann et al 2011).

Results

Da Silva et al (2015) selected those participants aged 12 years from the Brazilian Oral Health Study 2010. This was a household-based survey conducted by the Brazilian Ministry of Health. Water fluoridation level data was based on national data. The actual numbers of 12-year-old participants was not reported. After adjustment for economic deprivation and 'socio-sanitary'¹⁶ conditions, the study found that exposure to fluoridated water was associated with a reduction in the mean number of missing permanent teeth (β coefficient: -0.330 ; 95%CI: $-0.602, -0.058$; $p=0.019$).

Crocombe et al (2013) analysed data of 466 participants aged 15–45 years from the 2004–2006 Australian National Survey of Adult Oral Health. This cohort was born between 1960 and 1990 and all resided outside Australia's capital cities. The mean number of missing permanent teeth in those exposed to fluoridated water for over 50% of their lifetime was compared to those with 50% or less lifetime exposure. Confounding factors included in the linear regression were age, annual income, education, diabetes and access to dental care. The study found that a higher level of lifetime fluoridation exposure was not significantly associated with a reduction in missing teeth in younger rural adults (β coefficient: -0.03 ; $p=0.92$).

The cohort study by Neidell et al (2010) investigated the relationship between exposure to CWF and tooth loss in individuals born between 1950 and 1969 living in the communities described in the 1992 U.S. Water Fluoridation Census. Optimal fluoride levels recommended by the U.S. Public

¹⁶ A composite measure incorporating rates of urbanisation, proper sanitation and illiteracy.

Health Service and Centers for Disease Control and Prevention (CDC) for drinking water range from 0.7 ppm for warmer climates to 1.2 ppm for cooler climates. Tooth loss data from the Behavioural Risk Factor Surveillance System (BRFSS) survey for 1995 through to 1999 was matched to CWF status as measured by the proportion of the population in each county exposed to fluoridated water. Interval regression models were constructed to explore any correlation between CWF exposure and tooth loss.

The authors initially found a significant correlation between current CWF exposure and tooth loss ($\beta = 0.162$; $p < 0.01$), however this correlation disappeared once CWF from earlier years are added to the model (see 'all participants' column in Table 72). In the final model, only CWF exposure at birth was related significantly to tooth loss ($\beta = -0.255$; $p < 0.01$). Interpreting the beta coefficient as the change in the number of teeth lost when CWF exposure increases from 0% to 100% in an area being fluoridated, the results suggest that 0.26 fewer teeth were lost when a person was exposed to CWF at birth. The results also suggested that the effect of CWF exposure appeared to be larger for individuals from lower socioeconomic status groups: the estimates for Blacks, high school dropouts, and high school graduates implied that exposure to CWF at birth was associated with having 0.37, 0.61, and 0.39 more teeth, respectively. The results for this study are presented in Table 72.

Barbato & Peres (2009) conducted an ecological study that investigated the factors associated with tooth loss among adolescents aged 15 to 19 years by analysing secondary data from the 2003 Brazilian Oral Health Survey. In total 16,833 participants underwent an oral examination to identify missing teeth. Optimum CWF levels in Brazil are set at 0.8 ppm. Of those living in cities with CWF, 30% had missing teeth compared to 46% of those living in areas without CWF. After adjusting for type of dental service, education gap, income, age, skin colour, gender, and locality, it was found that the prevalence of missing teeth was significantly greater in areas without CWF compared to areas with CWF (Prevalence ratio: 1.40 (95%CI: 1.34, 1.46)).

Kolterman et al (2011) evaluated factors associated with the presence of functional dentition (defined here as having 20 or more teeth present in the mouth) in 10,407 adults aged 35 to 44 years in the Rio Grande do Sul State, Brazil. Individual data was taken from a population-based cross-sectional study conducted in 2003 and contextual data from participating municipalities. After adjusting for confounding variables the odds of still having functional dentition in an area which had had CWF present for 10 or more years was 78% higher than in an area which had CWF for less than 5 years (OR: 1.78 (95%CI: 1.32–2.40)). Moreover, the odds of having functional dentition was significantly higher in area with CWF for 5 to 9 years compared to an area which had CWF for less than 5 years (OR: 1.88 (95%CI: 1.20–2.95)).

The results for Barbato & Peres (2009) and Kolterman et al (2011) are presented in Table 73. The GRADE assessment for all five studies is summarised in Table 74.

Table 72 Results from interval regression analysis from Neidell et al (2010)

Exposure	All participants, b (SE)	White, b (SE)	Black, b (SE)	< High-school degree, b (SE)	High-school degree, b (SE)	College degree, b (SE)
Current CWF	0.061 (0.123)	0.013 (0.114)	0.118 (0.349)	-0.113 (0.611)	0.079 (0.151)	0.048 (0.107)
CWF 20y ago	-0.083 (0.123)	-0.007 (0.119)	-0.556 (0.341)	-0.216 (0.584)	-0.052 (0.155)	-0.073 (0.113)
Birth CWF	-0.255 (0.066)*	-0.186 (0.075)**	-0.372 (0.179)**	-0.609 (0.404)	-0.389 (0.086)*	-0.057 (0.060)

Abbreviations: CWF = community water fluoridation; b = beta coefficient; SE = standard error

* $p < 0.01$; ** $p < 0.05$

Note: All regressions include separate indicator variables for year of birth, survey year, state of residence, and age; individual-level controls for gender, race, education, marital status, employment status, number of not good mental health days in past month, diabetic status, number of children, household income, and insurance status; and 2000 county-level controls for population, population per square mile, percentage of

population White, percentage of population aged older than 65 years, percentage of population aged younger than 5 years, median age, median household income, and death rate.

Table 73 Results for missing teeth and functional dentition from Barbato and Peres 2009 and Kolterman et al (2011)

Study Quality	Population	Exposures -		Outcome	Analysis	Results -		Effect Estimate	Sig
Barbato 2009 Ecological Acceptable	15 to 19-year-olds in Brazil	No CWF	CWF	Missing teeth ¹	Poisson regression ²	4,281 / 9,304 (46.0%)	2,272 / 7,529 (30.2%)	Prevalence ratio: 1.40 (1.34, 1.46)	$p < 0.01$
Kolterman 2011 Ecological Acceptable	Adults (35–44 years) in Brazil	≥10 years CWF	≤5 years CWF	Functional dentition ³	Logistic regression ⁴	NR	NR	OR: 1.78 (1.32–2.40)	$p < 0.01$
	-	5–9 years CWF	≤5 years CWF	-	-	NR	NR	OR: 1.88 (1.20–2.95)	$p < 0.01$

Abbreviations: CWF = community water fluoridation; NOF = naturally occurring fluoride; OR = odds ratio; NR = not reported

¹ Determined by oral examination

² Adjusted for type of service, education gap, income, age, skin colour, gender, & locality

³ Defined as having ≥20 teeth present as assessed by trained dentists

⁴ Adjusted for contextual (lifespan, income, education, location, fluoridation, population/dentist), individual demographic (age, gender, family income, schooling) and individual health-system variables (dentist visits, treatment facility, info on prevention)

Discussion

The cohort study Neidell et al (2010) found a positive association between exposure to CWF at birth and reduced tooth loss in adults aged 40–60 years. Current exposure and exposure 20 years previous were not significantly associated. The only ecological study set in Australia found no significant association between water fluoridation and tooth loss in 15 to 45-year-olds. Two studies from Brazil reported a positive association between number of missing teeth and water fluoridation in 12-year-olds and 15 to 19-year-olds. The final Brazilian study found that fluoridation was positively associated with the odds of having 'functional dentition'. All were of acceptable quality and were based upon good sample sizes, however it is difficult to make any firm conclusions due to concerns regarding the applicability of the evidence, the heterogeneity of populations and outcomes, and lack of consideration of other causes of tooth loss e.g. trauma, periodontitis.

Evidence statement

The evidence evaluation identified five studies (one retrospective cohort and four ecological) which provided insufficient evidence to reach a conclusion about any association between tooth loss and water fluoridation at current Australian levels.

Table 74 Difference in number of missing permanent teeth - GRADE Report

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
5	Observational studies ¹	Not serious ²	Serious ³	Not serious ⁴	Not serious ⁵	None	>120,625 ⁶	Four of five studies show lower prevalence of tooth loss with fluoridation of water	⊕○○○	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ One cohort and three ecological studies

² All of acceptable quality with good sample size and adjustment for confounders

³ The Australian study showed no effect; one other showed an effect due to exposure from birth but not over lifetime; two studies favoured fluoridation; one study used the outcome 'functional dentition'

⁴ One study set in the US, one in Australia and three in Brazil in the context of community water fluoridation; one study measured functional dentition rather than tooth loss

⁵ Some wide confidence intervals but large sample sizes

⁶ The da Silva et al (2015) study did not report number of participants

DELAYED TOOTH ERUPTION

Several studies have suggested that exposure to fluoride may delay the eruption of permanent teeth (Kunzel 1976; Leroy et al 2003; Virtanen et al 1994). Proposed mechanisms for this effect include prolonged retention of deciduous teeth due to caries prevention or thickening of the bone around the emerging teeth.

The NHMRC (2007a) and McDonagh et al (2000) systematic reviews did not include any studies that reported on delayed tooth eruption as an outcome.

Literature Search Results

The literature search for other health effects identified two ecological studies that reported delayed tooth eruption as an outcome (Jolaoso et al 2014; Singh et al 2014). One was of acceptable quality and had highly applicable fluoride comparisons (Jolaoso et al 2014) and the other was of low quality and included partially applicable comparisons (Singh et al 2014).

Highly Applicable Comparison

Jolaoso et al (2014) measured the number of erupted permanent teeth in a group of 13,348 school children aged between 5 and 17 years with a history of a single continuous residence. The sample was selected from the 1986–1987 National Survey of Oral Health in the US. Children who were receiving fluoride tablets and/or drops or whose school water fluoride was >1.2 ppm were excluded from participation. Participants were divided into three groups: those exposed to fluoride levels of <0.3 ppm, 0.3 ppm to <0.7 ppm, and 0.7 ppm to 1.2 ppm in their school drinking water. Teeth missing for orthodontic or non-disease reasons were excluded from the analysis.

There was no significant difference in the mean number of erupted permanent teeth between the three groups ($p=0.12$). This was adjusted for age, gender, ethnicity, metropolitan status, and school region. Analysis of the mean number of erupted 1st molars in 7-year-olds found a greater number in the group exposed to fluoride of 0.7–1.2 ppm compared to the group exposed to between 0.3 and <0.7 ppm. No other pairwise comparison was statistically significant. The results and GRADE assessment are summarised in Table 75 and Table 77, respectively.

Partially Applicable Comparison

Singh et al (2014) measured the occurrence of delayed tooth eruption in 10 school children aged 8 to 15 years from one village with a drinking water fluoride level of 1.0 ppm and 60 children from five other villages with higher water fluoride levels (mean 2.7 ppm). Of the 60 children in the high fluoride group, half were specifically selected with dental fluorosis and the other half without. The authors found that 56% of the children in the high fluoride group reported delayed eruption of teeth, whereas there were none in the low fluoride group. No statistical analysis was performed. The results and GRADE assessment are summarised in Table 76 and Table 78, respectively.

Discussion

The Jolaoso et al (2014) study found no consistent association between water fluoride levels and delays in permanent tooth eruption. This study is of acceptable methodological quality with a large sample size, good recruitment methods and adjustment for confounding factors. The setting is highly comparable to the Australian setting, with similar water fluoride levels and healthcare systems.

The small ecological study by Singh et al (2014) provides very limited evidence of any relationship between delayed tooth eruption and water fluoride level. This study has significant methodological limitations: poor reporting of recruitment methods and outcome ascertainment, no control for known confounders, and no statistical analysis. In addition, the setting is unlikely to be generalisable to the Australian context due to a higher fluoride level in the comparator group and probable significant differences in healthcare provision and socioeconomic conditions.

Evidence statement

The evidence evaluation identified two ecological studies which found no association between delayed tooth eruption and water fluoridation at current Australian levels.

Table 75 Number of permanent teeth erupted – Results for Highly Applicable Comparison

Study Design Quality	Population	Outcome	Analysis	Results			Sig
				F <0.3 ppm	F 0.3 to <0.7 ppm	F 0.7–1.2 ppm	
Jolaoso 2014 Ecological Acceptable	Children (5–17 years) from the 1986–1987 National Survey of Oral Health in the US ¹	Mean number of permanent teeth erupted (SE) ²	Generalised linear regression ³	19.03 (0.07)	18.96 (0.09)	18.89 (0.07)	<i>p</i> =0.12
-	-	Mean number of erupted 1 st molars in 7-year-olds (SE) ²		3.82 (0.06)	3.67 (0.09)*	3.92 (0.06)*	* <i>p</i> <0.01 for 0.3 to <0.7 ppm compared to 0.7–1.2 ppm Other pairwise comparisons not significant

Abbreviations: SE = standard error; F = fluoride level; ppm = parts per million

¹ The original survey used a stratified, multistage probability sampling method

² Measured by clinical examination by trained dentists

³ Adjusted for age, gender, ethnicity, metropolitan status, and school region

Table 76 Delayed Tooth Eruption – Results for Partially Applicable Comparison

Study Design Quality	Population	Exposures		Outcome	Results	
		2.7 ppm	1.0 ppm		2.7 ppm	1.0 ppm
Singh 2014 Ecological Low	Children (8–15 years) recruited from schools in India ¹	NOF mean 2.7 ppm (1.6–5.5)	NOF mean 1.0 ppm (0.98–1.0)	No. of children with delayed tooth eruption ²	32/60 (53.3%)	0/10 (0.0%)

Abbreviations: NOF = naturally occurring fluoride

¹ Unclear recruitment method; ppm = parts per million

² Unclear how this was measured

Table 77 Number of permanent teeth erupted - GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
1	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious	None	13,348	No significant difference in mean number of permanent teeth erupted	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Good recruitment method, outcome ascertainment, and adjustment for confounding

³ Results for number erupted permanent teeth and erupted 1st molar in 7-year-olds is consistent

⁴ Fluoride comparator levels <0.3 ppm to 1.2 ppm range; socioeconomic & healthcare system factors similar to Australian context

Table 78 Delayed Tooth Eruption - GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
1	Observational studies ¹	Very serious ²	Not serious ³	Serious ⁴	Very serious ⁵	None	70	Prevalence of delayed eruption was 53% in 2.7 ppm fluoride area and 0% in 1.0 ppm area	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Poor reporting of recruitment method and outcome ascertainment, no adjustment for confounding, no statistical analysis, small sample size, half of intervention group selected for dental fluorosis status

³ Single study

⁴ Upper fluoride comparator levels above 0.4–1.5 ppm range; socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data supplied

TOOTH WEAR

The presence of fluoride in saliva and plaque favours remineralisation of demineralised enamel hydroxyapatite with the more stable fluorapatite. Fluorapatite is less prone to demineralisation and may result in the teeth being less prone to wear. However, fluoridation of water is associated with dental fluorosis in some of the population. This is characterised by areas of hypomineralisation and increased porosity in the outer layers of enamel. The net impact of these two processes is unknown (Burke et al 2010).

Tooth wear was not included as an outcome in either the NHMRC (2007a) or the McDonagh et al (2000) systematic reviews.

Literature Search Results

The literature search for other health outcomes identified one cross-sectional study of acceptable quality in which tooth wear was an outcome (Burke et al 2010). This was set in the context of CWF in the Republic of Ireland and so the comparisons were highly applicable.

Highly Applicable Comparison

Burke et al (2010) compared the severity of tooth wear in:

- 1,047 adults exposed to CWF for either a lifetime or at least 35 years
- 920 adults with some exposure to CWF
- 557 adults with no exposure to CWF

The participants were a stratified random sample from the electoral roll of the Republic of Ireland. Tooth wear was determined using a partial mouth examination assessing the upper and lower anterior teeth. Exposure status was determined by using details and history of the source of participants' water supplies recorded on the consent form. Fluoride levels were in the range 0.8 to 1.0 ppm since 1964 then reduced to between 0.6 and 0.8 ppm in 1970. An analysis of variance found that increased age, being male, and partial exposure to fluoridated water were associated with 'any' wear. Brushing twice or more a day was associated with less wear. A detailed examination of the table of distribution showed that the association between tooth wear and some exposure to CWF was not consistent across each category of wear. The authors concluded that there was no significant relationship between fluoridation and tooth wear. The results of Burke et al (2010) and the GRADE assessment are presented in Table 79 and Table 80, respectively.

Discussion

This study was assessed as being of acceptable quality with good participant selection methods and outcome measurement. There were some limitations of the categorisation of fluoride exposure with the participants having 'some exposure' being a heterogeneous group with exposure durations varying between 1 and 34 years. The analysis was a simple analysis of variance. Because of this and the nature of cross-sectional study design, the findings should be considered to be suggestive evidence of no association between CWF and tooth wear.

Evidence statement

The evidence evaluation identified a single cross-sectional study which found no association between the prevalence of tooth wear in adults and adolescents and water fluoridation at current Australian levels.

Table 79 Tooth Wear – Results for Highly Applicable Comparison

Study Design Quality	Population	Outcome ¹	Results		
			Full CWF ²	Part CWF ³	No CWF ⁴
Burke 2010 Cross-sectional Acceptable - -	Irish population 16–24 years	Mild tooth wear Moderate tooth wear Severe tooth wear	33.9% 3.3% 0.4%	40.8% 0.7% 0.0%	33.4% 2.5% 0.0%
	Irish population 35–44 years	Mild tooth wear Moderate tooth wear Severe tooth wear	71.3% 10.5% 0.7%	60.1% 9.2% 1.0%	60.4% 16.3% 3.5%
	Irish population 65+ years	Mild tooth wear Moderate tooth wear Severe tooth wear	51.2% 31.5% 10.3%	54.2% 36.3% 2.5%	62.4% 19.3% 11.6%

Abbreviations: CWF = community water fluoridation

¹ Measured using a modified version of the Smith and Knight index

² Exposure to CWF for either lifetime or ≥35 years

³ Some exposure to CWF

⁴ No exposure to CWF at any residence

Table 80 Tooth Wear – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational studies ¹	Not serious ²	Serious ³	Not serious ⁴	Very serious ⁵	None	2,456	No consistent association with water fluoridation	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Cross-sectional study

² Acceptable quality

³ Degree of wear not consistent across each category of fluoride exposure

⁴ Populations and fluoride comparisons applicable to Australian context: CWF in the Republic of Ireland

⁵ No variance data reported

HOSPITAL ADMISSIONS

Dental caries can be a common cause of hospital admissions in children (Public Health England 2014) and is therefore an important outcome to include. Admission is mostly for extraction of decayed teeth under a general anaesthetic (Public Health England 2014).

Both the NHMRC (2007a) and McDonagh et al (2000) systematic reviews did not include hospital admissions for dental caries as an outcome in their systematic reviews. No other systematic reviews were identified from the literature search for systematic reviews.

Literature search results for recent primary studies

One acceptable quality ecological study included the rate of hospital admissions as an outcome (Public Health England 2014).

Results

Public Health England (2014) compared the rate of hospital admissions for caries in children aged 1–4 years (per 1000,000 children) in upper-tier local authority areas supplied with fluoridated drinking water with areas not supplied with fluoridated drinking water. Upper-tier local authorities include unitary authority councils, county councils, metropolitan borough councils, London borough councils, City of London and Isles of Scilly. Hospital admission data for the period 2009–2012 was obtained from the Annual Report of the Chief Medical Officers (2012) by upper-tier local authority. When adjusted for deprivation, the admission rate in the fluoridated areas was 55% less than in the unfluoridated areas ($p=0.001$). These results from this study are presented in Table 81 below and the GRADE assessment is presented in Table 82.

Discussion

One single population-wide ecological study in England of acceptable quality provided evidence that hospital admissions for dental caries in 1 to 4-year-olds is lower in areas supplied with fluoridated water. There is also evidence suggesting that this effect is greater in participants experiencing more deprivation.

Evidence statement

The evidence evaluation identified one ecological study which provided insufficient evidence to reach a conclusion about any association between hospital admissions for dental caries in children and water fluoridation at current Australian levels.

Table 81 Results for rate of hospital admissions from Public Health England (2014)

Study Design Quality	Population	Exposures	Outcome	Analysis	Results (median, range, SD)	Effect Estimate (95%CI)	Sig	
Public Health England 2014 Ecological Acceptable	Residents in areas with and without CWF in England	CWF (0.8–1.0 ppm)	Rate of hospital admissions for caries (1–4 years) per 100,000 pyar ²	Unadjusted univariate model	221 (42; 13–773; 257)	400 (370; 7–1550; 311)	% difference in rate: –45% (–68, –6)	<i>p</i> =0.03
		No CWF ¹		Adjusted multivariate model ³	NR	NR	% difference in rate: –55% (–73, –27)	<i>p</i> =0.001

Abbreviations: SD = standard deviation; 95%CI = 95% confidence interval; CWF = community water fluoridation; pyar = person-years at risk; NR = not reported; ppm = parts per million

¹ areas classified as naturally fluoridated to 1 ppm were excluded

² data from the Annual Report of the Chief Medical Officers 2012 of hospital admission rate for dental caries in children aged 1–4 years per 1000,000 children aged 1–4 years by upper-tier local authority 2009–2012.

³ adjusted for deprivation

Table 82 Difference in rate of hospital admissions in 1 to 4-year-olds - GRADE Report

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
1	Observational study ¹	Not serious ²	Not serious ³	Not serious ⁴	Serious ⁵	None	NR	The rate of hospital admissions for 1 to 4-year-olds was 55% lower in fluoridated areas (-73, -27)	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations

Abbreviations: NR = not reported.

¹ One ecological study

² Acceptable quality with good sample size and adjustment for confounders

³ Only single study

⁴ Set in England in the context of community water fluoridation

⁵ Wide confidence intervals

⁶ Number of participants not reported

GRADE ASSESSMENTS (OTHER DENTAL OUTCOMES)

The summary of findings tables from the GRADE assessments for other dental effects performed for the review are reproduced in Table 83 below. The review authors decided to omit the GRADE terminology of 'very low, low, moderate, and high quality' and discuss the findings in terms of their confidence in the results. Instead they have included a comment on the extent of their confidence in the effect observed for each outcome.

Table 83 Summary of findings for other dental effects

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Number of missing permanent teeth	Four of five studies show lower prevalence of tooth loss with fluoridation of water	>120,625 (5 observational studies)	⊕○○○	Downgraded for inconsistency and indirectness.
Erupted permanent teeth assessed by clinical examination	No significant difference in mean number of permanent teeth erupted	13,348 (1 observational study)	⊕⊕○○	A single study of acceptable quality from the US with representative sample and adjustment for confounding factors.
Delayed eruption of permanent teeth (assessment method NR)	Prevalence of delayed eruption was 53% in 2.7 ppm fluoride area and 0% in 1.0 ppm area	70 (1 observational study)	⊕○○○	A single small, low quality study from India in school children aged 8–15 years with poor reporting of recruitment method and outcome ascertainment, no adjustment for confounding, and no statistical analysis. Set in the context of naturally occurring fluoride in water of up to 2.7 ppm
Tooth Wear assessed with modified version of the Smith and Knight index	No consistent association with water fluoridation	2,456 (1 observational study)	⊕○○○	A single study of acceptable quality from the Republic of Ireland. Downgraded in the GRADE assessment for imprecision and inconsistency.
Hospital admissions	The rate of hospital admissions for 1 to 4-year-olds was 55% lower in fluoridated areas (95%CI: 73% lower, 27% lower)	NR (1 observational study)	⊕○○○	A single population-based study using national admission data from England of acceptable quality in a setting of CWF. Downgraded for imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States; NR = not reported; ppm = parts per million

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

RESULTS OF THE REVIEW OF DENTAL FLUOROSIS

A systematic review was not undertaken on the role of water fluoridation in the development of dental fluorosis as the review of Ihezor-Ejiofor, 2015 is recent, scored well on the AMSTAR tool (11/11) and included all applicable studies reporting this outcome. The findings from this report are therefore reported along with those of McDonagh (2000) and NHMRC (2007) for context. Further review activity was considered a duplication of effort.

DENTAL FLUOROSIS

Dental fluorosis occurs due to hypomineralisation of the dental enamel. In mild forms there are faint white lines or streaks visible only clinically and in more severe cases there may be brown staining or pitting of the tooth enamel. There are a number of measures of dental fluorosis, the most common are:

- Dean's Fluorosis Index,
- Tooth Surface Index of Fluorosis (TSIF),
- Thylstrup-Fejerskov index (TFI), and
- Modified Developmental Defects of Enamel (DDE).

For review purposes, any score >0 on these indices (or 'questionable' on the Dean's index) are considered to have fluorosis. Cut offs for fluorosis of aesthetic concern are 'mild' or worse on Dean's index, ≥ 2 on TFI (total possible score of 9), and ≥ 3 on TSIF (total possible score of 7). DDE was not included for analysis of fluorosis of aesthetic concern.

Evidence from prior reviews

The McDonagh (2000) systematic review included 88 studies looking at the association of dental fluorosis with water fluoridation. Overall, the authors considered the studies to be of low quality. The review identified a significant dose-response relationship, using both measures of fluorosis, through a regression analysis. Based on this regression analysis, the proportion of the population affected by dental fluorosis at a water fluoride concentration of 1.0ppm was estimated to be 48% (95% CI 40–57%) and at the same concentration, those with fluorosis of aesthetic concern was estimated to be 12.5% (95% CI 7.0–21.5%).

The NHMRC review (2007) identified an additional ten studies published after the McDonagh (2000) review and undertook a meta-analysis of these comparing fluorosis rates in sub-optimally (≤ 0.4 ppm fluoride) and optimally (0.8–1.2 ppm fluoride) fluoridated water. They concluded that while there is a fourfold risk of developing 'fluorosis of aesthetic concern' with optimal water fluoridation, the absolute increase in prevalence is small, increasing by approximately 4–5%.

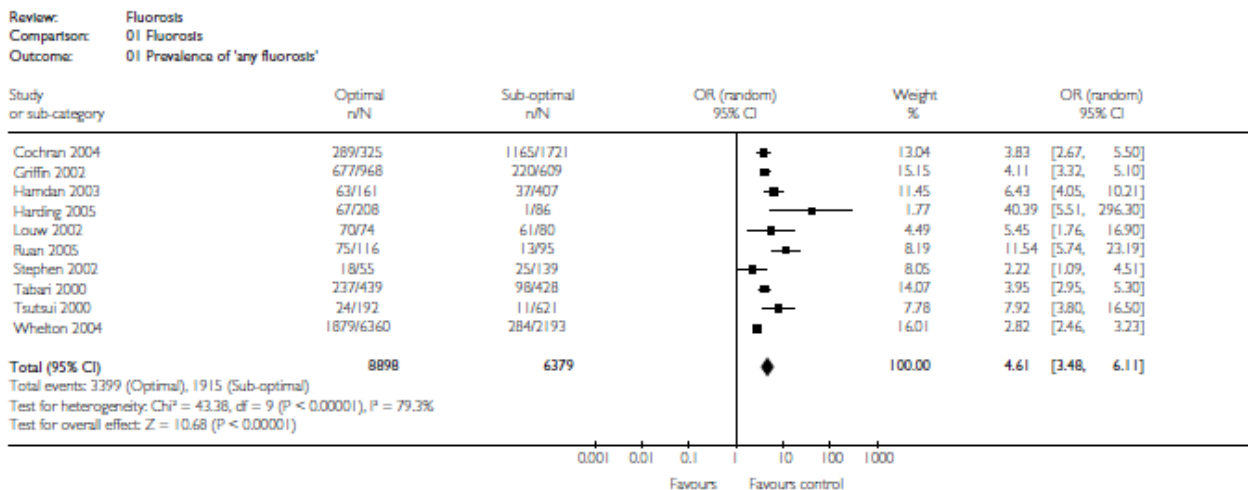


Figure 12 Meta-analysis of the odds ratio of the prevalence of 'any fluorosis' in areas with optimal vs sub-optimal water fluoridation, from NHMRC 2007

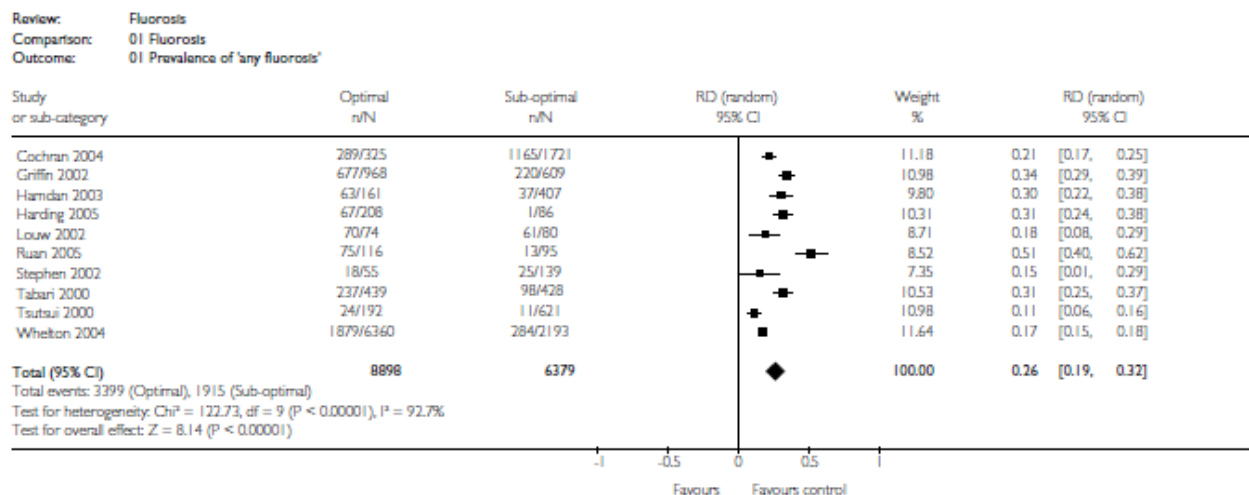


Figure 13 Meta-analysis of the risk difference of the prevalence of 'any fluorosis' in areas with optimal vs sub-optimal water fluoridation, from NHMRC 2007

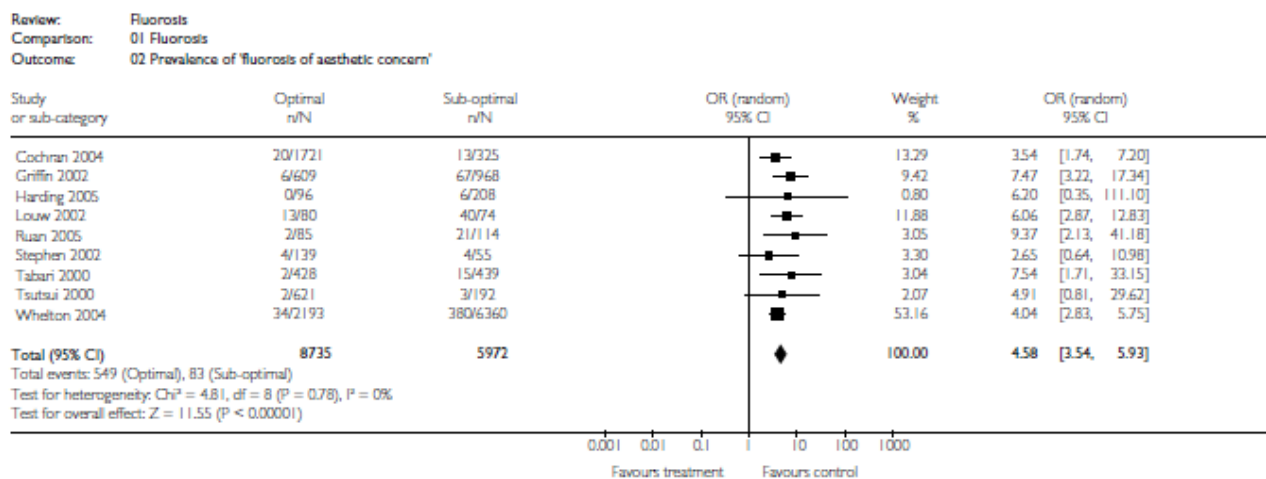


Figure 14 Meta-analysis of the odds ratio of the prevalence of 'fluorosis of aesthetic concern' in areas with optimal vs sub-optimal water fluoridation, from NHMRC 2007

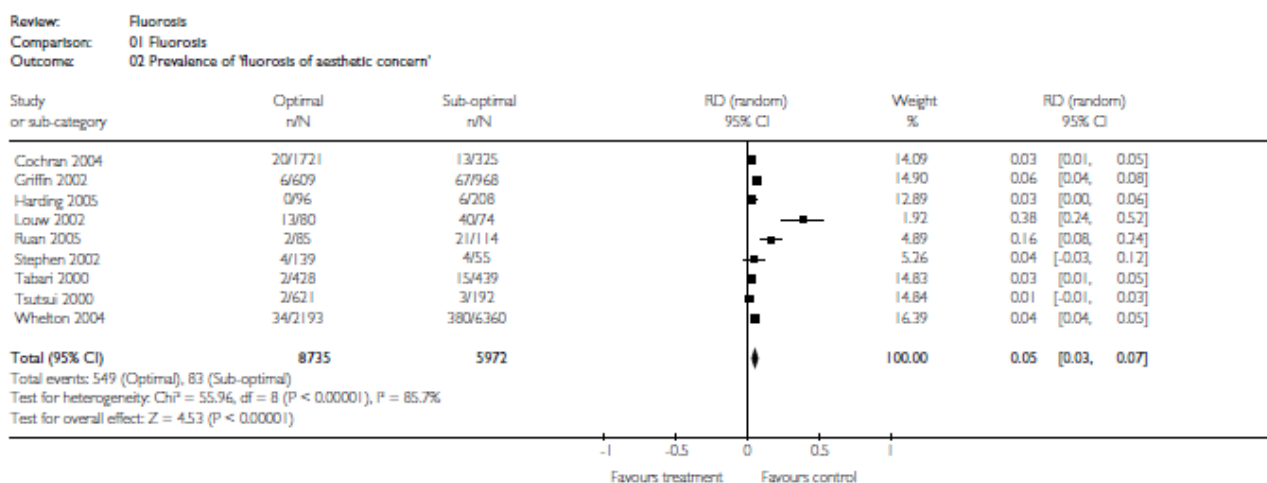


Figure 15 Meta-analysis of the risk difference of the prevalence of 'fluorosis of aesthetic concern' in areas with optimal vs sub-optimal water fluoridation, from NHMRC 2007

Evidence from Iheozor-Ejirofor 2015

Inclusion and exclusion criteria for fluorosis studies

Studies of any design, with concurrent controls, that compared populations exposed to different water fluoride levels were included for the dental fluorosis question. Fluoride could be at any level present in drinking water. Outcomes included percentage of children with fluorosis of any level or of aesthetic concern. Non-fluoridated water was defined as water with a fluoride concentration of 0.4 ppm or less.

Risk of bias in the included studies

All included studies were assessed for risk of bias using a modified Cochrane 'Risk of Bias' assessment tool adapted for non-randomised studies. The following factors were identified by the review authors to be important confounders: sugar consumption/dietary habits, socioeconomic status, ethnicity and use of other fluoride sources. For each study an assessment of the overall risk of bias was undertaken.

Analyses performed

Random-effects models with random intercept and random slope were used to model the log odds of fluorosis as a function of fluoride exposure. The intercept and slope were allowed to vary from study to study. The results were presented as probabilities. The primary analysis was carried out on fluoride levels of 5 ppm or less for both dental fluorosis of aesthetic concern and any degree of fluorosis.

If data was missing and could not be calculated from the available data, the authors were contacted. If the number of participants was not reported, then the data was not included in the analyses. If standard deviations were missing then they were estimated using a standard equation for both before-and-after mean caries values. A sensitivity analysis was conducted to determine the effect of the imputed standard deviations. Due to the lack of clarity of reporting and the limited data, heterogeneity in fluoridation technique, fluoride level, outcome measure and technique was not assessed for caries data. Fluoride level was explored as part of the fluorosis analysis. Publication bias was not investigated because there were not enough studies for a robust analysis.

A post hoc subgroup analysis of studies conducted prior to 1975 was done to investigate any potential effect of the widespread use of fluoride toothpaste on outcomes. The planned sensitivity analyses based on risk of bias and timing of baseline measurement were not undertaken because of insufficient numbers of trials. Due to the small number of studies and lack of clear reporting, sources of heterogeneity were not explored using meta-regression or subgroup analysis by study design.

GRADE assessment

The GRADE approach was used to assess the quality of the evidence within the review. Due to concerns about its use in the context of a public health intervention, the review authors decided to omit the GRADE terminology of 'very low, low, moderate, and high quality' and discuss the findings in terms of their confidence in the results.

All studies were observational and quality was downgraded for an overall high risk of bias and inconsistency due to substantial between-study variation. Hence their confidence in the effect estimate was limited.

Results

Ninety studies provided sufficient data for the analysis of dental fluorosis of any degree, and 40 studies for fluorosis of aesthetic concern. All of the studies were assessed as being at high risk of bias.

Forty studies, with 59,630 participants, were included in the analysis of dental fluorosis of aesthetic concern for fluoride levels of 5 ppm or less. The mean fluoride exposure was 0.80 ppm with a range of 0 to 4.9 ppm. A higher prevalence of dental fluorosis was associated with increased fluoride exposure (OR = 2.90, 95%CI: 2.05 to 4.10). The marginal probabilities of dental fluorosis of aesthetic concern at different fluoride levels are presented in Table 84 below:

The analysis of fluorosis of aesthetic concern including all fluoride levels was based on 40 studies with 180,530 participants. The mean level of fluoride was 0.85 ppm with a range of 0 to 7.6 ppm. As with the analysis restricted to fluoride \leq 5 ppm, a higher prevalence of dental fluorosis was positively associated with increased fluoride exposure (OR = 2.84, 95%CI: 2.00 to 4.03).

For dental fluorosis of any degree for water fluoride levels of 5 ppm or below, ninety studies, at high risk of bias, were included with 180,530 participants. The mean fluoride level was 1.22 ppm with a range of 0 to 5 ppm. The effect of fluoride exposure was positive and statistically significant: controlling for study effects, the odds of dental fluorosis would increase by 3.6 times for each 1 ppm increase in fluoride level (OR = 3.60, 95%CI: 2.86 to 4.53). The marginal probabilities of any dental fluorosis at different fluoride levels are presented in Table 84.

Table 84 Probability of dental fluorosis at different fluoride levels

Fluoride exposure (ppm)	Probability of dental fluorosis of aesthetic concern (95% CI)	Probability of any dental fluorosis (95% CI)
0.1	0.08 (0.05 to 0.12)	0.28 (0.23 to 0.33)
0.2	0.09 (0.06 to 0.13)	0.30 (0.25 to 0.34)
0.4	0.10 (0.06 to 0.15)	0.33 (0.28 to 0.38)
0.7	0.12 (0.08 to 0.17)	0.40 (0.35 to 0.44)
1.0	0.15 (0.11 to 0.21)	0.47 (0.42 to 0.52)
1.2	0.18 (0.13 to 0.24)	0.52 (0.47 to 0.56)
2.0	0.31 (0.23 to 0.40)	0.68 (0.62 to 0.73)
4.0	0.59 (0.46 to 0.71)	0.83 (0.77 to 0.88)

Abbreviations: ppm = parts per million; 95%CI = 95% confidence interval

For all water fluoride levels, ninety studies were included in this analysis with 182,233 participants. Fluoride levels ranged from 0 to 14 ppm with a mean of 1.28 ppm. Pooled estimates were similar to that seen above, with an OR of 3.13 (95%CI: 2.55 to 3.85).

Possible sources of heterogeneity were investigated using a multivariate analysis. When controlling for source of fluoride (artificial or natural) and its interaction with fluoride concentration the OR for fluorosis of aesthetic concern at all concentration becomes 3.16 (95%CI: 2.12 to 4.71) and 3.22 (95%CI: 2.16 to 4.79) for levels 5 ppm or less. For the outcome of fluorosis of any degree, the additional covariates do not contribute significantly to the model. Note that these results are not directly comparable to ones with fluoride concentration as the only covariate, as there are different numbers of studies in each analysis.

Discussion

Iheozor-Ejiofor et al (2015), and prior reviews, conclude that there is a significant relationship between the level of fluoride in drinking water and dental fluorosis, but that the evidence was limited due to the high risk of bias and between-study variation. Iheozor-Ejiofor et al (2015) noted that the studies examining dental fluorosis had generally been from areas with high naturally occurring fluoride levels, and had not accounted for other sources of fluoride. Finally, the authors commented that there was very little contemporary evidence, with most data coming from studies conducted pre-1975.

Iheozor-Ejiofor et al (2015) was generally a well-conducted systematic review with good score on the AMSTAR instrument however there are some major limitations relating to the body of literature on fluorosis.

The McDonagh (2000) review noted that measures of fluorosis do not distinguish between fluoride related opacity in the enamel and other opacities not caused by fluoride, therefore the level of fluorosis may be overestimated. Similarly, NHMRC (2007) noted the wide variation in fluorosis prevalence both across studies and across different populations within studies, with many studies reporting much higher levels of fluorosis than found in Australia. This may result from both methodological and environmental factors. With regards to environmental factors, there was a lack of consideration of confounding from other sources of fluoride in the included studies but fluoride supplements and fluoride toothpaste are known confounders. Iheozor-Ejiofor et al (2015) did not undertake a pre- and post-1975 analysis of fluorosis as they did with caries.

The thresholds used in the reviews of 'any fluorosis' and 'fluorosis of aesthetic concern' potentially overestimates the 'harm' of fluorosis. A review of perceptions of dental appearance and oral health-related quality of life associated with fluorosis found that mild fluorosis was not a concern and had little impact of quality of life, and was sometimes associated with improved oral health related quality

of life (Chanakanka et al 2009). In the Australian context, a recent prospective study of 8 to 13-year-old children in South Australia found a 30% rate of any fluorosis with the majority being mild and diminishing with time. The highest fluorosis score in the sample was TF3 (moderate fluorosis). Perceptions of poor oral health were significantly associated with the number of untreated decayed tooth surfaces but not with fluorosis (Do et al, 2016).

Both McDonagh (2000) and Ihezor-Ejiofor et al (2015) undertook regression analyses to pool data on fluorosis and evaluate the dose-response relationship. This analyses makes the assumption of linearity, but there is no discussion regarding whether this assumption is likely to hold. The degree to which this analysis is relevant to the Australian context in which water is fluoridated at low levels is difficult to assess.

Therefore, although existing reviews have demonstrated a significant association between level of water fluoridation and dental fluorosis these findings should be considered in light of the limitations discussed, their limited applicability to the Australian context and the low observed prevalence and impact of dental fluorosis in Australia (Do et al 2016).

Table 85 Dental fluorosis of aesthetic concern¹ – GRADE Report (measured by Dean's Index, TFI, TSIF)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
40	Observational studies	Serious ²	Serious ³	Serious ⁴	Not serious ⁵	None	59,630	For a fluoride level of 0.7 ppm the percentage of participants with dental fluorosis of aesthetic concern was estimated to be 12% (95% CI 8% to 17%).	⊕○○○ ⁵	CRITICAL

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: TFI = Thylstrup-Fejerskov Index; TSIF = Tooth Surface Index of Fluorosis; ppm = parts per million

¹ Data come from studies of both naturally occurring and artificially fluoridated areas (i.e. not just areas where water fluoridation has been initiated). Dental fluorosis of aesthetic concern only with levels of reported fluoride exposure of 5 ppm or less

² Studies at high risk of bias; quality of the evidence downgraded

³ Substantial heterogeneity; quality of the evidence downgraded

⁴ Levels of fluoride up to 5 times greater than used for community water fluoridation in Australian context

⁵ The quality assessment has been revised—the Iheozor-Ejiofor et al (2015) review reported the quality as ⊕○○○ but this should have been downgraded for high risk of bias and inconsistency

GRADE ASSESSMENT (DENTAL FLUOROSIS)

The summary of findings table for the GRADE assessment for dental fluorosis is presented in Table 86 below. The review authors decided to omit the GRADE terminology of ‘very low, low, moderate, and high quality’ and discuss the findings in terms of their confidence in the results. Instead they have included a comment on the extent of their confidence in the effect observed for each outcome.

Table 86 Summary of findings for dental fluorosis

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Dental fluorosis of aesthetic concern (measured by Dean’s Index, TFI, TSIF)	For a fluoride level of 0.7 ppm the percentage of participants with dental fluorosis of aesthetic concern was estimated to be 12% (95% CI 8% to 17%).	59,630 (40 observational studies)	⊕○○○ ²	Single well-conducted systematic review. The estimate for any level of dental fluorosis at 0.7 ppm was 40% (95% CI 35% to 44%; 90 studies). This includes dental fluorosis that can only be detected under clinical conditions and other enamel defects. The GRADE assessment has been revised and downgraded for high risk of bias, indirectness and inconsistency.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: CI = confidence interval; TFI = Thylstrup-Fejerskov Index; TSIF = Tooth Surface Index of Fluorosis; ppm = parts per million

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

² The quality assessment has been revised—the Iheozor-Ejiofor et al (2015) review reported the quality as ⊕⊕○○ but this should have been downgraded for high risk of bias and inconsistency

Evidence Statement

The evidence evaluation identified one review which provided consistent evidence that an increase in the fluoride concentration in water supplies is associated with an increase in the prevalence of dental fluorosis. However, the majority of the evidence is derived from countries where naturally occurring fluoride levels are up to five times greater than the levels of fluoride in artificially fluoridated water in Australia. This evidence has limited applicability in the Australian context and is of insufficient quality to predict the prevalence of any dental fluorosis or dental fluorosis of aesthetic concern associated with the current levels of water fluoridation in Australia. This is due to a lack of control for other fluoride sources and marked between-study variation across non-comparable populations. There is also some uncertainty as to what level of dental fluorosis is perceived to be of aesthetic concern.

RESULTS OF THE SYSTEMATIC LITERATURE REVIEW OF OTHER HEALTH EFFECTS

RESULTS OF THE LITERATURE SEARCH

The systematic literature search identified 2,166 citations and the searching of other resources identified 8 citations. After the removal of duplicates, a total of 1,708 unique citations were eligible for review. A summary of the citation review process is presented in Figure 16 and the stages of the review process are described in detail below.

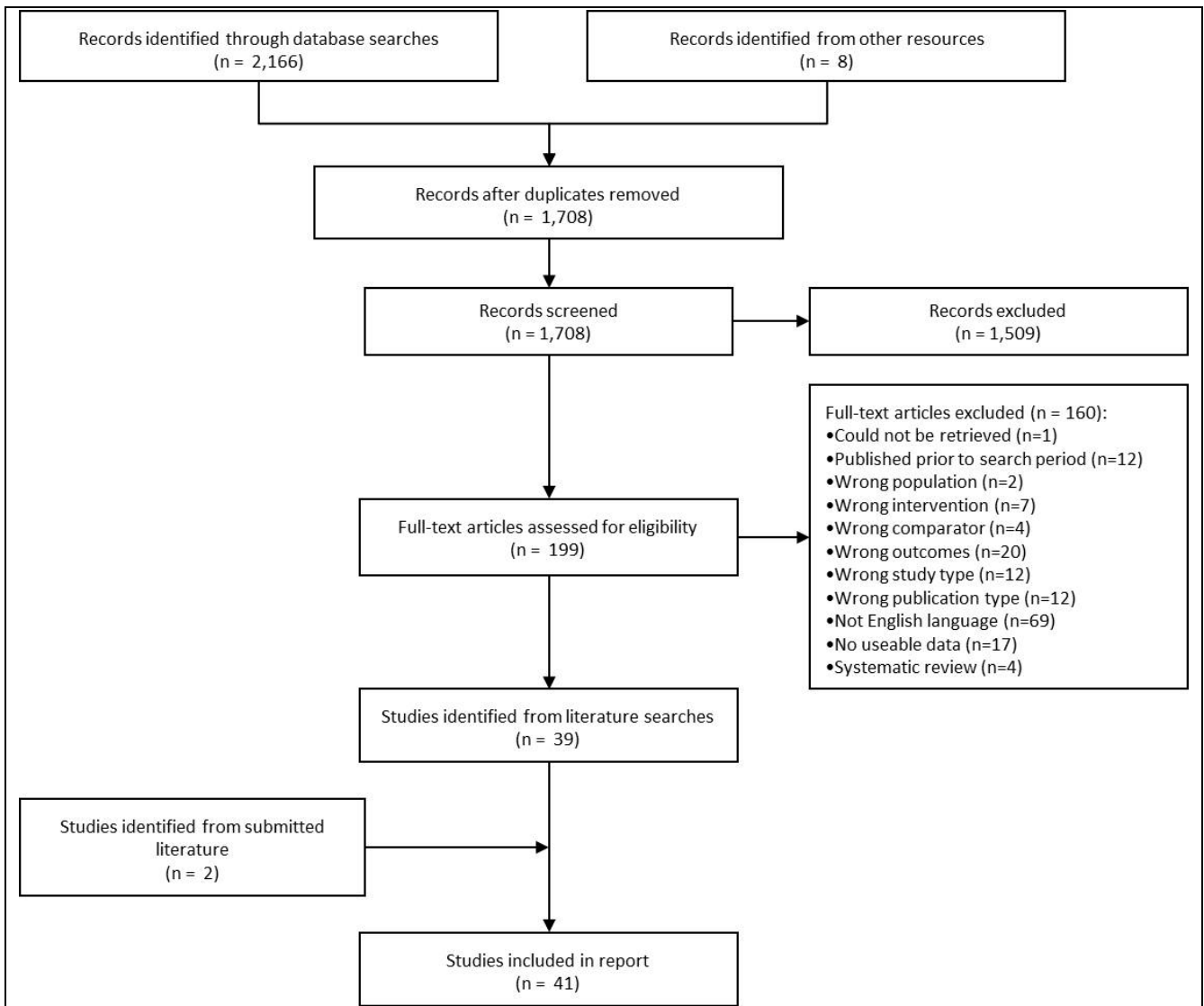


Figure 16 Summary of review of citations

Review of titles and abstracts

Application of the PICOS criteria to the retrieved citations resulted in the exclusion of 1,509 citations. A list of the studies excluded at this stage is included in the Technical Report. For the remaining 199 citations, the full text of the publication was retrieved for further review.

Review of full text

The 199 studies were assessed using the full text of the publication. For one study (Sharma & Sharma 2010) the full text of the publication could not be retrieved and the study was excluded. A further 12 studies had been published prior to the specified start date of 1st October, 2006 and were excluded.

The remaining studies were assessed against the PICOS inclusion criteria used in the review of titles and abstracts (see Table 17), leading to the exclusion of 57 studies. For full details of this process see the Technical Report.

A total of 12 studies were excluded due to study type because the selection methods used in these studies confounded the assessment of the study outcomes. These studies purported to compare subjects from areas with differing water fluoride levels, but actually compared people with fluorosis in one region to those without fluorosis in another region. In all studies the subjects from the “high” fluoride area were only included if they had dental fluorosis and subjects in the “low” fluoride area were only included if they had no dental fluorosis. Consequently, the subjects in the “high” and “low” fluoride groups were not representative of all the people living in that area and exposed to that level of fluoride. As a result of this flawed design, it was impossible to assess the independent effect of water fluoride levels on the study outcomes. The findings of these studies were considered irretrievably confounded and the studies were excluded with the approval of the NHMRC and the Fluoride Reference Group.

A total of 69 studies were excluded due to being published in a language other than English. Of these, 68 were published in Chinese and one was published in Korean. Based on the abstracts, all of these 69 studies met at least one exclusion criteria. Of the remaining studies, 17 were excluded as they did not report any outcome data that could be used in the current review. Four studies did not report the water fluoride levels for the populations compared in the study, twelve studies did not report outcomes by water fluoride level, and one study was a before-and-after study that only reported outcome data from after the intervention was implemented.

After the full text review 39 eligible studies were included. For further information about the review process and a list of the studies excluded at this stage please see the Technical Report.

Systematic reviews

The literature search identified four relevant systematic reviews (Choi et al 2012; Ludlow et al 2007; Ortega Garcia et al 2006; Parnell et al 2009). These reviews were not eligible for inclusion in the current review, but were considered sources for eligible primary studies. The list of included studies from each of the systematic reviews was checked against the citations identified in the literature search. This checking did not identify any additional studies that met the criteria for inclusion in the current review.

The review by Parnell et al (2009) investigated the effectiveness and safety of water fluoridation and is discussed on page 28. The review by Choi et al (2012) investigated the association between fluoride and children’s IQ. This review is discussed in the results section related to IQ and cognitive function (page 215) and in the discussion section (page 225). The review by Ludlow et al (2007) investigated the association between water fluoridation and chronic kidney disease (CKD). This review is discussed in the results section related to CKD (page 236) and in the discussion section (page 236). The review by Ortega Garcia et al (2006) investigated the effects of a number of known and suspected environmental neurotoxins, including fluoride. The review was published in the Spanish language and was not assessed further.

RESULTS OF THE PUBLIC CALL FOR EVIDENCE

A total of 379 citations were received by NHMRC from the public. These were reviewed for eligibility and a total of 99 studies conducted in humans were considered potentially eligible for inclusion in the review and these were passed to the University of Sydney team for further assessment.

The University of Sydney assessed these studies against the results of the systematic literature search. Of the 99 potentially eligible studies, 62 had been identified in the literature search and were not considered further. The remaining 37 studies were assessed for eligibility and 35 were not eligible for inclusion. The main reasons for exclusion were that the study was not a comparative clinical study, that the participant selection methods used in the study confounded the assessment of the study outcomes, and that the study did not report on an eligible health effect. The remaining two studies were considered eligible for inclusion in the review and were added to the list of included studies (Singh et al 2013; Xiang et al 2009). For full details of this review process please see the Technical Report.

STUDIES INCLUDED IN THE REVIEW

In total, 41 primary studies were included in the current review, 39 from the literature search and 2 from the public call for evidence. A full listing of the citations for the included studies is provided in the references section of this report and in the Technical Report.

The literature search identified only one Level II study, which was a prospective cohort study by Broadbent et al (2014). Four Level III studies were identified, including two retrospective cohort studies (Level III-1) and two case-control studies (Level III-2). All of the remaining 36 included studies were Level IV evidence. This included 8 cross-sectional studies and 28 ecological studies.

Quality of the included studies

Only one of the included studies was assessed as being of high quality, and this was the prospective cohort study by Broadbent et al (2014). In total, 14 studies were of acceptable quality, including the 2 retrospective cohort studies, 4 cross-sectional studies and 8 ecological studies. The remaining studies were all assessed as low quality, including the 2 case-control studies, 4 cross-sectional studies and 20 ecological studies.

Overall, the quality of the evidence identified through the literature search was considered to be low. This was largely due to poor reporting, high risk of residual confounding, and lack of blinding of outcome assessors. Information about participant selection methods and participant characteristics was often inadequate making the assessment of the representativeness and comparability of the exposed and non-exposed groups very difficult. As a substantial number of studies did not measure or adjust for any potential confounding factors, the results found in the studies could not be confidently ascribed to the exposure. There was also a risk of measurement bias in many studies because outcome assessors were not blinded to participant exposure status. The quality of the individual studies is discussed further under each of the presented outcomes.

ALL-CAUSE MORTALITY

There were five studies, all of low quality, included in the McDonagh et al (2000) review that had all-cause mortality as an outcome. Three studies found an increase in mortality associated with water fluoridation, one found a decrease in mortality and one found no association. No measures of the statistical significance of these associations were provided. However, for two of the studies that found an increase in mortality, the adjusted rate-ratio was 1.01, and the review authors considered these results unlikely to have reflected a statistically significant effect. The review concluded that because of the small number of studies, the study designs used and the low quality of studies that there was insufficient evidence to reach a conclusion. The review concluded that because of the small number of studies, the study designs used and the low quality of studies that there was insufficient evidence to reach a conclusion. The NHMRC (2007a) systematic review of the efficacy and safety of fluoridation included the studies from McDonagh et al (2000) and did not identify any additional studies. The conclusion of the NHMRC (2007a) review was: "The authors of previous systematic reviews concluded that the studies examining other possible negative effects of water fluoridation provide insufficient evidence to reach a conclusion."¹⁷

Literature Search Results

The literature search identified one acceptable quality ecological study (Level IV evidence) that included all-cause mortality as an outcome (Public Health England 2014). As the study compared areas with CWF schemes aiming to achieve a fluoride concentration of 1.0 ppm with areas without CWF the analysis is highly applicable to the Australian context.

Highly Applicable Comparison

The authors estimated the exposure to fluoridated water at the lower super output area level. These areas are standardised English small areas of 1000–3000 persons used for decennial census data. The Drinking Water Inspectorate provided boundaries of English water zones with a binary variable indicating whether each zone was subject to fluoridation schemes in 2012. The number of deaths was also obtained at local super output area level from the Office for National Statistics for January 2009 to January 2012. These years were used because mortality was relatively stable following reductions over the preceding years (Public Health England, 2014).

After the initial unadjusted analysis, the authors examined the following confounding variables in multivariate analyses: age (proportion of population above 65 years), gender (proportion of the population male), deprivation (measured by Index of Multiple Deprivation, 2010) and ethnicity (proportion of the population white). The results were presented as number of deaths per person-years at risk. Consequently the denominator is the cumulative population of England over four years.

The crude rate of all-cause mortality was 5.2% higher (95% CI: 3.4%, 7.0%; $p < 0.001$) in areas with CWF schemes. After adjusting the multivariate model for age, gender, deprivation and ethnicity, the incidence rate was 1.3% lower (95% CI: -2.5%, -0.1%; $p = 0.04$) in communities receiving fluoridated water. The results of this study and the GRADE assessment are presented in Table 87 and Table 88, respectively.

Discussion

The authors of the single study concluded that while there was some evidence of a lower rate of deaths in fluoridated areas, the size of the effect estimate in their analysis was small, and this was likely to have been due to chance, or possibly confounding.

Despite the high applicability and methodological quality of the identified study, it is difficult to form a robust conclusion about an association between all-cause mortality and water fluoridation.

¹⁷ p 106 NHMRC (2007a)

Evidence statement

The evidence evaluation identified a single ecological study suggesting a small association between reduced all-cause mortality and water fluoridation at current Australian levels; however, the size of the effect estimate was small and may be due to chance.

Table 87 All-cause Mortality – Results for Highly Applicable Comparison

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results -		Effect Estimate (95%CI)	Sig
Public Health England 2014 Ecological Acceptable	Residents in areas with and without CWF in England	CWF (0.8–1.0 ppm)	No CWF ¹	All-cause mortality per 100,000 person-years at risk ²	Unadjusted univariate model	924 (233,922 deaths in 25,314,612 person-years at risk)	874 (1,602,206 deaths in 183,256,350 person-years at risk)	Difference in incidence: 5.2% (3.4, 7.0)	<i>p</i> <0.001
-	-	-	-	-	Adjusted multivariate model ³	NR	NR	Difference in incidence: -4% (-2.6, -0.3)	<i>p</i> =0.02
-	-	-	-	-	Adjusted multivariate model ⁴	NR	NR	Difference in incidence: -1.3% (-2.5, -0.1)	<i>p</i> =0.04

Note: Effect estimate expressed as percentage difference in incidence, e.g. 5.2% (95%CI: 3.4, 7.0) equates to an incidence rate ratio of 1.052 (95%CI: 1.034, 1.070)

Abbreviations: CWF = community water fluoridation; pyar = person-years at risk; 95%CI = 95% confidence interval; NR = not reported; ppm = parts per million

¹ Areas classified as naturally fluoridated to 1 ppm were excluded

² All deaths registered with the Office of National Statistics from 2009 to 2012

³ Adjusted for age, gender, deprivation

⁴ Adjusted for age, gender, deprivation, and ethnicity

Table 88 All-cause Mortality – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (N)	Comparator (N)	Effect	Quality	Importance
1	Observational study ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious	None	25,314,612 person-years at risk	183,256,350 person-years at risk	Adjusted incidence was 1.3% lower in areas with CWF (95%CI: 2.5% lower to 0.1% lower)	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Good sample size, adjustment for confounders

³ Not applicable, single study

⁴ Community water fluoridation scheme applicable to Australian context

ATHEROSCLEROSIS

Atherosclerosis was not included as an outcome in either the NHMRC (2007a) or McDonagh et al (2000) systematic reviews of CWF. There does not appear to be any plausible biological rationale for an association between fluoride exposure and atherosclerosis.

Literature Search Results

The literature search identified one cross-sectional study (Level IV evidence) of acceptable quality that assessed the relationship between exposure to water fluoride and the development of carotid artery atherosclerosis in 585 adults in China (Liu et al 2014). The study selected eight villages in Zhaozhou County in the Heilongjiang Province based on a previous endemic fluoride survey. Drinking water samples were collected from wells of all study subjects' households. Households were categorised based on their water sample's fluoride concentration into ≤ 1.20 ppm, 1.21–2.00 ppm, 2.01–3.00 ppm or ≥ 3.01 ppm. Subjects were excluded if they had a history of diabetes, stroke, coronary heart disease, kidney disease, liver disease, respiratory disease, emaciation, or long-term use of drugs.

As the lowest fluoride group is less than 1.5 ppm, these comparisons were classified as partially applicable to the Australian context. The comparisons made between higher fluoride concentration groups (all > 1.5 ppm) were classified as having limited applicability to the Australian context.

The authors used carotid ultrasound examinations and an imaging probe to determine the prevalence of atherosclerosis—defined as either intima pathological changes (intima-media thickness of carotid artery between 1.0 mm and 1.5 mm) or carotid plaque (intima-media thickness of carotid artery over 1.5 mm).

Partially Applicable Comparisons

The unadjusted prevalence of carotid artery atherosclerosis was lowest in the low fluoride group (≤ 1.2 ppm), which is comparable to CWF levels in Australia. The logistic regression analysis found that the odds of having carotid artery atherosclerosis when exposed to the three highest fluoride levels were all statistically significant greater compared to the odds of having atherosclerosis when exposed to a fluoride level of ≤ 1.2 ppm fluoride:

- OR = 1.93 (95% CI: 1.11, 3.35) for 1.21–2.00 ppm vs. ≤ 1.20 ppm
- OR = 2.02 (95% CI: 1.13, 3.60) for 2.01–3.00 ppm vs. ≤ 1.20 ppm
- OR = 2.33 (95% CI: 1.12, 4.85) for ≥ 3.01 ppm vs. ≤ 1.20 ppm.

The odds ratios are adjusted for gender, age, systolic and diastolic blood pressure, total cholesterol, and high density lipoprotein-cholesterol levels. The results of the partially applicable comparisons for atherosclerosis and the GRADE assessment are presented in Table 89 and Table 91.

Comparisons with Limited Applicability

No statistically significant differences were observed when comparing the two highest fluoride concentration groups (NOF 2.01–3.00 ppm and ≥ 3.01 ppm) with the second lowest group, 1.21–2.00 ppm or when comparing the highest group (≥ 3.01 ppm) with the second highest (2.01–3.00 ppm). The results of these analyses and the GRADE assessment are presented in

Table 90 and Table 92, respectively.

Table 89 Atherosclerosis – Results for Partially Applicable Comparisons

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results -		Effect Estimate	Sig
Liu 2014 Cross-sectional	Adults (>40 years) in China	NOF 1.21–2.00 ppm	NOF ≤1.20 ppm	Prevalence of carotid artery atherosclerosis ¹	Chi-squared test	49/180 (27.2%)	30/186 (16.1%)	NR	p=0.009
Acceptable	-	NOF 2.01–3.00 ppm	-	-	-	42/155 (27.1%)	-	NR	p=0.013
-	-	NOF ≥3.01 ppm	-	-	-	19/64 (29.7%)	-	NR	p=0.018
-	-	NOF 1.21–2.00 ppm	NOF ≤1.20 ppm	-	Adjusted logistic regression ²	NA	NA	OR=1.93 (1.11–3.35)	p<0.05
-	-	NOF 2.01–3.00 ppm	-	-	-	NA	-	OR=2.02 (1.13–3.60)	p<0.05
-	-	NOF ≥3.01 ppm	-	-	-	NA	-	OR=2.33 (1.12–4.82)	p<0.05

Abbreviations: NOF = naturally occurring fluoride; OR = odds ratio; NR = not reported; NA = not applicable; ppm = parts per million

¹ Presence of intima pathological changes or carotid plaque determined by carotid ultrasound + imaging probe

² Adjusted for sex, age, systolic & diastolic blood pressure, total cholesterol, & high density lipoprotein-cholesterol

Table 90 Atherosclerosis – Results for Comparisons with Limited Applicability

Study Design Quality	Population	Exposures		Outcome	Analysis	Results		Effect Estimate	Sig		
		-	-			-	-				
Liu 2014 Cross-sectional Acceptable -	Adults (>40 years) in China -	NOF 2.01–3.00 ppm	NOF 1.21–2.00 ppm	Prevalence of carotid artery atherosclerosis ¹ -	Chi-squared test -	42/155 (27.1%)	49/180 (27.2%)	NR	p=0.979		
		NOF ≥3.01 ppm	-			19/64 (29.7%)	-			NR	p=0.705
		NOF ≥3.01 ppm	NOF 2.01–3.00 ppm			19/64 (29.7%)	42/155 (27.1%)			NR	p=0.697

Abbreviations: NOF = naturally occurring fluoride; NR = not reported; ppm = parts per million

¹ Presence of intima pathological changes or carotid plaque determined by carotid ultrasound + imaging probe

Discussion

While the authors did adjust for a variety of biological characteristics in their regression analysis they failed to capture known significant lifestyle factors associated with the development of atherosclerosis, including smoking, alcohol consumption and physical activity.

Given the incomplete adjustment for confounding variables highlighted above, the association between exposure to water fluoride and the presence of carotid artery atherosclerosis found by Liu et al (2014) is not sufficient to form a conclusion.

Evidence statements

The evidence evaluation identified a single cross-sectional study which provided insufficient evidence to draw a conclusion about any association between water fluoridation and carotid artery atherosclerosis, due to lack of adjustment for confounding and limited applicability to fluoride exposure at current Australian levels.

Table 91 Atherosclerosis – GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Serious ²	Not serious ³	Very serious ⁴	Not serious ⁵	None	585	Higher prevalence in areas with greater exposure	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Cross-sectional study

² Unclear level of representativeness, known important confounders not included in analysis

³ Not relevant - only one study

⁴ Low applicability to the Australian context due to socioeconomic & healthcare system differences

⁵ Narrow 95% CIs around adjusted OR from logistic regression

Table 92 Atherosclerosis– GRADE Report for Comparison with Limited Applicability

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Serious ²	Not serious ³	Very serious ⁴	Very serious ⁵	None	399	No significant difference in prevalence	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Cross-sectional study

² Unclear level of representativeness, no adjusted analysis

³ Not relevant - only one study

⁴ Low applicability to the Australian context due to socioeconomic & healthcare system differences

⁵ No variance data supplied

HYPERTENSION

Neither the NHMRC (2007a) report nor the McDonagh et al (2000) systematic review on water fluoridation included any studies evaluating the effects of water fluoridation on hypertension. There appears to be no plausible biological rationale for an association between fluoride exposure and hypertension.

Literature Search Results

The literature review identified three low quality ecological studies and one acceptable quality cross-sectional study (all Level IV Evidence) that assessed the relationship between fluoride exposure and hypertension (Amini et al 2011; Chandrajith et al 2011; Ostovar et al 2013; Sun et al 2013). All of the studies included a fluoride level comparison less than 1.5 ppm and so were considered to be partially applicable to the Australian context of CWF.

Partially Applicable Comparisons

Ostovar et al (2013) and Amini et al (2011) were both ecological studies conducted in Iran.

Amini et al (2011) used the mean fluoride content of ground water resources from a previously conducted study as a surrogate for the fluoride concentration in drinking water. All provinces in Iran were included in the analysis; however, the number of communities considered was not reported. Hypertension prevalence was determined from the 2007 provincial report of non-communicable disease risk factor surveillance. An unadjusted regression model found a weak positive correlation between exposure to fluoride in drinking water and the prevalence of hypertension ($r=0.495$; $p<0.001$).

Ostovar et al (2013) sampled water from 91 villages in Bushehr Province in southern Iran to determine fluoride exposure. Data from the provincial health centre surveillance system was used to establish the prevalence of hypertension in the region. The unadjusted regression model found a weak negative correlation between water fluoride level and the prevalence of hypertension (Spearman's $\rho = -0.578$; $p=0.005$).

The results for both these low quality studies are presented in Table 93.

Sun et al (2013) conducted a cross-sectional study on adults in eight Chinese villages with varying water fluoride concentrations. Water samples were collected from the household well of each participant. Participant's blood pressure was measured three times in the morning using a mercury sphygmomanometer. Hypertension was deemed to be present when the systolic blood pressure (SBP) >140 mm Hg, or diastolic blood pressure (DBP) was >90 mm Hg, or when the adult had a history of hypertension or took medication(s) for hypertension. Villages were grouped into fluoride concentration categories and the relationship with hypertension assessed using a logistic regression model adjusted for sex, age, smoking, alcohol consumption, body mass index (BMI), and endothelin-1 levels. The authors made three comparisons based on water fluoride concentration groups. The adjusted odds ratios (aOR) increased as the comparator fluoride concentration increased:

- 1.02 (95% CI: 0.56–1.86) for 1.21–2.00 ppm vs. ≤ 1.20 ppm
- 1.73 (95% CI: 0.94–3.19) for 2.01–3.00 ppm vs. ≤ 1.20 ppm
- 2.84 (95% CI: 1.38–5.83) for ≥ 3.01 ppm vs. ≤ 1.20 ppm

Note that the odds were only significantly greater in one comparison: ≥ 3.01 ppm vs. ≤ 1.20 ppm. The results of this study are presented in Table 94.

The GRADE assessment for Ostovar et al (2013), Amini et al (2011), and Sun et al (2013) is presented in Table 95.

The fourth identified study, Chandrajith et al (2011) primarily assessed the geographic distribution and environmental implications of chronic kidney disease in Sri Lanka. The results for the chronic kidney disease primary outcome are reported elsewhere (page 236). The authors also collected data on the prevalence of diabetes and hypertension. However, the study was of particularly low quality, with incomplete outcome data and no statistical analyses. As such, no data were extracted from this study and a GRADE assessment was not performed.

Table 93 Hypertension – Results of Partially Applicable Continuous Analyses

Study Design Quality	Population	Exposures	Outcome	Analysis	Effect Estimate	Sig
Ostovar 2013 Ecological Low	Residents of villages in Iran	NOF range 0.2–2.2 ppm	Prevalence of hypertension ¹	Weighted least squares linear regression ²	Spearman's rho = – 0.578	p<0.001
Amini 2011 Ecological Low	Population of Iran	NOF range 0.23–1.86 ppm	Prevalence of hypertension ³	Simple regression ²	r = 0.495	p=0.005

Abbreviations: NOF = naturally occurring fluoride; ppm = parts per million

¹ Determined by provincial health centre surveillance system; prevalence of hypertension defined as % percentage of individuals with blood pressure ≥140/90 mm Hg

² Determined using the provincial report of non-communicable disease risk factor surveillance of the Islamic Republic of Iran; definition of hypertension was not reported

³ No adjustment for any confounding factors

Table 94 Hypertension – Results of Partially Applicable Comparison

Study Design Quality	Population	Exposures	Outcome	Analysis	Results	Effect Estimate	Sig		
Sun 2013 Cross-sectional Acceptable	Adults (40–75 years) in China	NOF 1.21–2.00 ppm	NOF ≤1.20 ppm	Prevalence of hypertension ¹	Adjusted logistic regression ²	40/163 (24.5%)	26/129 (20.2%)	OR = 1.02 (0.56–1.86)	p=0.401
-	-	NOF 2.01–3.00 ppm	-	-	-	42/130 (32.3%)	-	OR = 1.73 (0.94–3.19)	p=0.018
-	-	NOF ≥3.01 ppm	-	-	-	32/65 (49.2%)	-	OR = 2.84 (1.38–5.83)	p<0.001

Abbreviations: NOF = naturally occurring fluoride; OR = odds ratio; ppm = parts per million

¹ Defined as having a SBP >140 mm Hg or DBP >90 mm Hg, or the participant had a history of hypertension or took medication(s) for hypertension

² Adjusted for sex, age, smoking, alcohol consumption, BMI & endothelin-1

Discussion

The two regression models in Ostovar et al (2013) and Amini et al (2011) produced conflicting results: one, a positive correlation and the other a negative correlation between water fluoride concentration and the prevalence of hypertension. These studies were also of low methodological quality, and neither model included any adjustment for confounding variables.

Despite the lack of statistical analysis, Chandrajith et al (2011) concluded that hypertension was found commonly in patients with advanced chronic kidney disease which is, in turn, somewhat associated with residency in areas with drinking water containing medium to high levels of fluoride.

Evidence of a relationship between exposure to water fluoride and the prevalence of hypertension is very limited. The two low quality ecological studies conducted in Iran revealed conflicting results and did not adjust for demographic or lifestyle factors likely to confound the correlation. In the other study of acceptable quality (Sun et al 2013), the comparison between the group exposed to water fluoride concentrations comparable to the Australian setting (≤ 1.20 ppm) and high fluoride (1.21–2.00 ppm) also did not generate a statistically significant *p*-value. There was no consideration of other known confounders including salt intake, family history or poor physical activity. Taken overall, there is insufficient evidence to make any conclusion about any relationship between water fluoridation and the incidence of hypertension.

Evidence statement

The evidence evaluation found three ecological studies and one cross-sectional study which provided insufficient evidence to draw a conclusion about any association between water fluoridation and hypertension, due to lack of adjustment for confounding, limited applicability to fluoride exposure at current Australian levels and poor measurement of fluoride exposure and hypertension.

Table 95 Hypertension – GRADE Report for Partially Applicable Comparisons

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
3	Observational studies ¹	Very serious ²	Not serious ³	Serious ⁴	Very serious ⁵	None	487 ⁶	<p>Conflicting results from the two continuous analyses</p> <p>Significantly higher odds of hypertension for ≥3.01 ppm fluoride compared to ≤1.20 ppm fluoride exposure only (all other comparisons between intermediate levels and lowest level not significant)</p>	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Two ecological studies and one cross-sectional study

² Unclear quality of outcome data capture methods; no consideration of confounding in two studies

³ Reasonable agreement between the studies

⁴ Socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data supplied for continuous analyses and wide confidence intervals in Sun et al (2012)

⁶ From Sun et al (2012) only

OSTEOSARCOMA

An association between fluoride ingestion and an increased risk of osteosarcoma has been suggested due to the deposition of fluoride in bone (Public Health England, 2014). The McDonagh et al (2000) and NHMRC (2007a) systematic reviews included a total of eight studies that investigated the relationship between water fluoridation and osteosarcoma.

Evidence from prior reviews

McDonagh et al (2000) included seven studies with mixed results. Five studies reported no significant association between water fluoridation and the development of osteosarcoma (Gelberg et al 1995; Hoover et al 1976; Hrudey et al 1990; McGuire et al 1991; Moss et al 1995). One study reported a reduction in osteosarcoma risk with water fluoridation (Mahoney et al 1991), and the final study (Cohn 1992) reported a significantly increased risk of osteosarcoma with water fluoridation for men (RR = 3.4, 95%CI: 1.4–8.1), but not for women (RR = 1.0, 95%CI: 0.3–3.5). Overall, McDonagh et al (2000) concluded that there was no clear association between water fluoridation and the incidence of osteosarcoma.

Four other studies that investigated unspecified bone-related cancer were also included in McDonagh et al (2000). Out of 8 analyses from these studies, there was a negative association (fewer cancers) between bone-related cancers and water fluoridation in three, a positive association (more cancers) in four, and no association in one. The authors of the review concluded that there was no clear association between water fluoridation and bone cancer.

The NHMRC (2007a) systematic review identified one additional case-control study by Bassin et al (2006). This was an exploratory analysis of a sub-set of patients from a larger hospital-based case-control study that had yet to report its findings. The average fluoride level and percent of CDC-recommended climate-specific target level in drinking water from all sources (public supply, well water and bottled water) was estimated at each age for cases and controls. The odds ratios of osteosarcoma were estimated for those exposed to 30–99%, or >99% of the drinking water target level of fluoride compared to <30% of drinking water target. The authors limited the analysis to those less than 20 years, which excluded around 24% of the participants. Median family income for area of residence was lower for cases than controls and a larger proportion of controls used bottled water. The odds ratio of osteosarcoma of maximum exposure (>99% of target) compared to minimum exposure (<30% of target) at age 7 years, adjusted for income of residence area, county population, ever use of bottled water, age, and any use of fluoride products, was 5.46 (95%CI: 1.50 to 19.90) for males and 1.75 (95%CI: 0.48 to 6.35) for females. The odds ratios for medium exposure (30–99% of target) compared to minimum exposure (<30%) for males and females were 3.36 (0.99 to 11.42) and 1.39 (0.41 to 4.76), respectively.

The authors concluded that their exploratory analysis found an association between fluoride exposure in drinking water during childhood and the incidence of osteosarcoma among males, but not consistently among females, and recommended that further research be performed to confirm or refute this observation. The NHMRC (2007a) report authors commented on a Letter to the Editor by co-investigators of Bassin et al (2006). The letter authors pointed out that they had not been able to replicate these findings in the broader study, which included prospective cases from the same 11 hospitals (Douglass & Joshipura 2006). The NHMRC (2007a) authors concluded that, due to shortcomings in the methodology and reporting, the results of this study should be interpreted with caution pending publication of the larger study results.

The final publication of the study described in the publication by Bassin et al (2006) was published in 2011 (Kim et al 2011). Kim et al (2011) was not eligible for inclusion in the current review as it did not specifically measure exposure to water fluoride; however, it is of considerable interest. The study measured the fluoride content of bone adjacent to tumours and iliac crests of 137 incident cases of osteosarcoma and 51 control subjects. The odds ratio of osteosarcoma for a 1-unit increase in the natural log of fluoride concentration in bone was 1.23 (95%CI: 0.51 to 2.97) i.e. no

significant association between bone fluoride levels and osteosarcoma risk was detected. This was adjusted for history of broken bones, other cancers, other bone diagnoses, having received radiation prior to illness, age, and gender. This finding was consistent in a risk adjusted model, and a subgroup of patients aged less than 45 years old.

The 2007 NHMRC review concluded that there was no clear association between water fluoridation and the incidence of osteosarcoma.

Literature Search Results

The literature search identified six studies that met the inclusion criteria. Five were ecological studies (Blakey et al 2014; Comber et al 2011; Levy & Leclerc 2012; National Fluoride Information Service 2013; Public Health England 2014) (Level IV evidence) that compared unfluoridated water with fluoride levels from CWF schemes within the 0.4 to 1.5 ppm range. Four of these were assessed as being of acceptable quality (Blakey et al 2014; Comber et al 2011; Levy & Leclerc 2012; Public Health England 2014) and the other low quality (National Fluoridation Information Service, 2013). The final study was a low quality case-control study (Level III-3 evidence) in which the measured fluoride levels were also equivalent to the range of water fluoridation levels seen in Australia (Kharb et al 2012). Therefore, all six studies were considered to include highly applicable fluoride comparisons.

Highly Applicable Comparisons

Four ecological studies from the UK (Public Health England, 2014; Blakey et al, 2014), US (Levy and Leclerc, 2012), and the Republic of Ireland (Comber et al, 2010) explored the relationship between the incidence of osteosarcoma and CWF at levels comparable to that used in Australia.

An acceptable quality ecological study from England (Public Health England, 2014) compared the age-standardised incidence of osteosarcoma of small local residence areas supplied with fluoridated drinking water with areas not supplied with fluoridated drinking water. These areas are standardised English small areas of 1000–3000 persons used for decennial census data. Small local residence areas located in drinking water supply zones classified as naturally fluoridated were excluded from the analysis. Osteosarcoma case data from 1995 to 2010 was retrieved from the National Cancer Registration Service. Around 5.8 million people (9.5% of the total population) in different parts of England are supplied with artificially fluoridated water with the aim to bring the fluoride content in the water up to 1.0 ppm.

Two separate populations were included in the analysis, the population under 25 years and the population aged 50 years and over. They were selected to reflect the clear bimodal age distribution of the incidence of osteosarcoma, with the first peak being in older children and adolescents, and the second peak in older men and women. A subgroup analyses for women and men in the population under 25 years was also performed. The authors found that after adjusting for age, gender, ethnicity and deprivation the age-standardised incidence of osteosarcoma in areas with fluoridated water was not significantly different from the incidence in areas without fluoridated water in both people under 25 years (incidence was 8.2% higher in areas with fluoridated water with a 95%CI between 9.3% lower and 29% higher; $p=0.38$) and those aged 50 years or over (incidence was 15% lower with a 95%CI between 34% lower and 9.6% higher; $p=0.21$). This finding was consistent for men and women aged less than 25 years and all aged 50 years and over. The authors concluded that there was no evidence of a difference in the rate of osteosarcoma between fluoridated and non-fluoridated areas.

The ecological study by Levy and Leclerc (2012) from the US was of acceptable quality and compared the incidence of osteosarcoma in children and adolescents in states where $\geq 85\%$ of the population received fluoridated water (14 states) with the incidence in states where $\leq 30\%$ of the population received fluoridated water (4 states). All cases of osteosarcoma registered with the CDC for the period 1999 to 2006 were extracted. State CWF status from 1992–2006 was sourced from the National Oral Health Surveillance System of the CDC. The level of fluoride is adjusted to

between 0.7 and 1.2 ppm by CWF schemes. There were no significant differences in incidence rates between the two fluoridation categories for males aged 15 to 19 years (IRR = 1.01; 95%CI: 0.83–1.23; p=0.93) or females of the same age range (IRR = 1.08; 95%CI: 0.82–1.43; p=0.60). This finding was consistent for males and females in the other age ranges: 5 to 9 years, and 10 to 14 years. The authors concluded that these findings were consistent with the hypothesis that CWF has no influence on the development of osteosarcoma in either sex during childhood or adolescence.

The acceptable quality study by Comber et al (2010) used data from the Northern Ireland Cancer Registry and the National Cancer Registry of Ireland between 1994 and 2006 to compare the incidence of osteosarcoma in areas with CWF (level required to be 0.8–1.0 ppm) and without community fluoridation (level not reported). Approximately 70% of the Republic of Ireland's population are in receipt of fluoridated drinking water, mainly in urban areas. All areas labelled as 'rural' were considered non-fluoridated and all other areas were considered to be fluoridated. There is no intentional water fluoridation in Northern Ireland.

Again, no significant differences were observed between fluoridated and non-fluoridated areas in the age-standardised incidence rates of osteosarcoma (IRR = 1.17; 95%CI: 0.87–1.58). Subgroup analysis of males and females under 25 years, both separately and together, found no significant difference in incidence rates, neither did the comparison of the fluoridated and non-fluoridated areas in the Republic of Ireland alone. The authors concluded that the results of this study did not support the hypothesis that osteosarcoma incidence in the island of Ireland was significantly related to public water fluoridation. The results of these studies are presented in Table 96.

Table 96 Osteosarcoma – Results for Highly Applicable Comparisons

Study Design Quality	Population	Exposures -		Outcome	Analysis	Subpopulation	Results -		Effect Estimate (95%CI)	Sig
		CWF	No CWF				CWF	No CWF		
Public Health England 2014 Ecological Acceptable	Residents aged <25 years or ≥50 years in England	CWF (0.8–1.0 ppm)	No CWF ¹	Age-standardised osteosarcoma incidence per 100,000 pyar (95%CI) ²	Adjusted multivariate model ³	All participants: <25 years	0.45 (0.38–0.52) <i>(148 cases per 31,313,151 person-years at risk)</i>	0.42 (0.40–0.45) <i>(949 cases per 216,921,400 person-years at risk)</i>	Difference in incidence: 8.2% (–9.3, 29)	p=0.38
						Males: <25 years	0.55 (0.45–0.68) <i>(92 cases per 15,981,438 person-years at risk)</i>	0.47 (0.43–0.51) <i>(540 cases per 110,831,320 person-years at risk)</i>	Difference in incidence: 17% (–7.1, 46)	p=0.19
						Females: <25 years	0.35 (0.26–0.46) <i>(56 cases per 15,331,713 person-years at risk)</i>	0.37 (0.34–0.41) <i>(409 cases per 106,090,080 person-years at risk)</i>	Difference in incidence: –2.5% (–27, 30)	p=0.86
						All participants: ≥50 years	0.20 (0.15–0.25) <i>(73 cases per 33,080,465 person-years at risk)</i>	0.23 (0.21–0.25) <i>(587 cases per 232,282,090 person-years at risk)</i>	Difference in incidence: –15% (–34, 9.6)	p=0.21

Study Design Quality	Population	Exposures		Outcome	Analysis	Subpopulation	Results		Effect Estimate (95%CI)	Sig		
		≥85% population receives CWF (0.7–1.2 ppm)	≤30% population receives CWF				CWF	No CWF				
Levy 2012 Ecological Acceptable	All children (5–19 years) resident in the continental US states where ≥85% or ≤30% of the population received CWF	≥85% population receives CWF (0.7–1.2 ppm)	≤30% population receives CWF	Osteosarcoma incidence per 1,000,000 ⁴ (95%CI)	Incidence rate ratio (95%CI)	Males: 5–9 year	3.0 (2.3–3.9)	3.1 (2.2–4.1)	IRR = 0.99 (0.67–1.45)	p=0.95		
						Males: 10–14 years	7.8 (6.7–9.1)	8.2 (6.8–9.8)			IRR = 0.96 (0.76–1.21)	p=0.70
						Males: 15–19 year	11.6 (10.2–13.1)	11.5 (9.8–13.4)			IRR = 1.01 (0.83–1.23)	p=0.93
						Females: 5–9 years	3.1 (2.4–4.0)	2.9 (2.1–4.0)			IRR = 1.05 (0.71–1.65)	p=0.81
						Females:10–14 years	8.4 (7.2–9.7)	9.9 (8.3–11.7)			IRR = 0.85 (0.68–1.06)	p=0.15
						Females: 15–19 years	6.3 (5.3–7.5)	5.9 (4.6–7.3)			IRR = 1.08 (0.82–1.43)	p=0.60
Comber 2010 Ecological Acceptable	Residents of the Republic of Ireland & Northern Ireland	Areas with CWF (0.8–1.0 ppm)	Areas without CWF	Age-standardised incidence of osteosarcoma per 100,000 ⁵ (95%CI)	Age-standardised IRR (95%CI)	All participants: all ages	0.26 (0.21–0.32) <i>(92 cases in a population of 2,588,482)</i>	0.22 (0.18–0.27) <i>(91 cases in a population of 2,943,353)</i>	IRR = 1.17 (0.87–1.58)	NR		
						All participants: 0–24 years	0.40 (0.36–0.43)	0.39 (0.36–0.43)			IRR = 1.01 (0.88–1.15)	NR
						Males: 0–24 years	0.52 (0.46–0.58)	0.52 (0.46–0.57)			IRR = 1.00 (0.85–1.17)	NR
						Females: 0–24 years	0.27 (0.23–0.32)	0.26 (0.22–0.30)			IRR = 1.05 (0.83–1.33)	NR
						Republic of Ireland: all participants	0.26 (0.21–0.32)	0.25 (0.17–0.32)			IRR = 1.07 (0.75–1.54)	NR

Study Design Quality	Population	Exposures		Outcome	Analysis	Subpopulation	Results		Effect Estimate (95%CI)	Sig
		-	-				CWF	No CWF		
-	-	-	-	-	-	Republic of Ireland: 0-24 years	0.40 (0.36-0.43)	0.43 (0.37-0.48)	IRR = 0.92 (0.78-1.09)	NR

Note: Effect estimate in Public Health England (2014) is expressed as percentage difference in incidence, e.g. 8.2% (-9.3, 29) equates to an incidence rate ratio of 1.082 (0.907, 1.290)

Abbreviations: CWF = community water fluoridation; IRR = incidence rate ratio; pyar = person-years at risk; 95%CI = 95% confidence interval; ppm = parts per million

¹ Areas classified as naturally fluoridated to 1 ppm were excluded

² All cases of osteosarcoma (n=1757) registered with the National Cancer Registration Service between 1995 & 2010

³ Adjusted for age, gender, deprivation, & ethnicity

⁴ All cases of osteosarcoma registered with the Centers for Disease Control (CDC) between 1999 & 2006

⁵ All cases of osteosarcoma (n=183) registered with the Northern Ireland Cancer Registry & the National Cancer Registry of Ireland between 1994 & 2006

The other study from the UK was an ecological study (Level IV evidence) of acceptable quality by Blakey et al (2014). The authors examined the relationship between the incidence of osteosarcoma in those aged less than 50 years with the level of fluoride in drinking water in small local residence areas in Great Britain. Routine fluoride monitoring data was used from the relevant authorities for the period 2004–2006, with the mean fluoride levels ranging between 0.00 ppm to 1.27 ppm. Case data was extracted from 10 regional cancer registries for the period 1980 to 2005. Negative binomial regression analysis adjusted for age, gender, and deprivation found a non-significant association between drinking water fluoride level and the incidence of osteosarcoma. The results of this study are presented in Table 97.

Table 97 Osteosarcoma - Results for Highly Applicable Continuous Analysis in Blakey et al (2014)

Study Design Quality	Population	Exposure	Outcome	Analysis	Results	Effect Estimate
Blakey 2014 Ecological Acceptable	Residents aged 0–49 years in England, Scotland and Wales	Mean water fluoride level (0.00–1.27 ppm)	Crude incidence of osteosarcoma per 1,000,000 person-years at risk ¹	Negative binomial regression ²	2.59 (2,566 / 992,213 person-years at risk) ³	Adjusted RR ⁴ = 1.001 (90% CI: 0.871–1.151)

Abbreviations: CI = confidence interval; CWF = community water fluoridation; RR = relative risk; ppm = parts per million

¹ All cases of osteosarcoma (n=2,566) registered in 10 regional cancer registries between 1980 to 2005

² Adjusted for age-group, gender, the interaction age-group*gender, the Townsend score & the interaction Townsend score*female

³ From McNally et al (2012)

⁴ Relative risk of osteosarcoma per 1 ppm increase in fluoride level

The last ecological study (Level IV evidence) of low quality from New Zealand investigated whether the incidence of osteosarcoma is different in areas with CWF than areas without CWF (National Fluoridation Information Service, 2013). Levels of fluoride in the CWF areas ranged between 0.8 and 1.0 ppm, and were between ~0.1 ppm to 0.2 ppm in areas without CWF. This was a preliminary analysis of the rates of osteosarcoma recorded by the NZ Cancer Registry for the period 2000 to 2008. National rates were calculated for each sex and age group in the fluoridated and non-fluoridated areas using 2006 census estimates. The authors concluded that their results indicated that there was no difference in the rates of osteosarcoma cases between areas with CWF and areas without CWF for both males and females. The results of this study are presented in Table 98.

The GRADE assessment of the above five studies is reported in Table 100.

Table 98 Comparison of crude incidence rates of osteosarcoma per 100,000 per year

Population	All					Male					Female				
	0–9	10–19	20–39	40–64	65+	0–9	10–19	20–39	40–64	65+	0–9	10–19	20–39	40–64	65+
CWF	1.7	10.4	1.7	2.5	1.7	1.3	10.6	2.6	2.3	4.0	2.1	10.2	0.9	2.8	0.0
no CWF	2.7	11.1	2.3	0.9	4.8	4.3	12.7	3.6	1.8	6.6	0.9	9.3	1.0	0.0	3.2

Abbreviations: CWF = community water fluoridation

Kharg et al (2012) was a case-control study from India that measured the fluoride level in the drinking water from the homes of 10 participants with osteosarcoma and compared it with the fluoride level in the drinking water from 10 healthy volunteers' homes. The authors found that the

mean fluoride from the homes of the participants was significantly higher than in the water from the healthy volunteers' homes (1.30 vs. 0.48 ppm; $p < 0.001$). However, the publication contains no information about the participants' characteristics, how they were recruited, how disease status was assessed, or the measurement of potential confounding factors. Sample size is also small. Consequently, the study was assessed as having a very high risk of bias and the results should be interpreted with extreme caution. The results of this study and the GRADE assessment are presented in Table 99 and Table 101, respectively.

Table 99 Osteosarcoma - Results from Highly Applicable Case-Control Comparison

Study Design Quality	Population	Cases	Controls	Exposure	Analysis	Results	Sig
Kharb 2012 Case-control Low	India ¹	Osteosarcoma cases (n=10)	Healthy volunteers (n=10)	Mean fluoride level from water in participants residences	Student's t-test	Mean fluoride level (\pm SD): 1.30 \pm 0.76 ppm Mean fluoride level (\pm SD): 0.48 \pm 0.24 ppm	$p < 0.001$

Abbreviations: SD = standard deviation; ppm = parts per million

¹ No other information supplied

Summary of the available evidence

The effect estimates from the McDonagh et al (2000), NHMRC (2007) reviews have been plotted with estimates from the current review to illustrate the body of evidence for osteosarcoma. Separate forest plots have been created for each type of effect estimate: odds ratios (OR) and incidence rate ratios (IRR). The results from Blakey et al (2014) were not plotted as it was the only study reporting a relative risk (RR) and the results from Mahoney et al (1991) were not plotted as no variance data was reported. The results were not pooled due to high clinical and statistical heterogeneity.

Studies reporting odds ratios

The current review did not identify any new studies reporting odds ratios for osteosarcoma. Four studies identified in the earlier reviews reported odds ratios for osteosarcoma and are presented in Figure 17 below. Taken together, the studies do not present any clear evidence for a specific relationship between water fluoride levels and osteosarcoma.

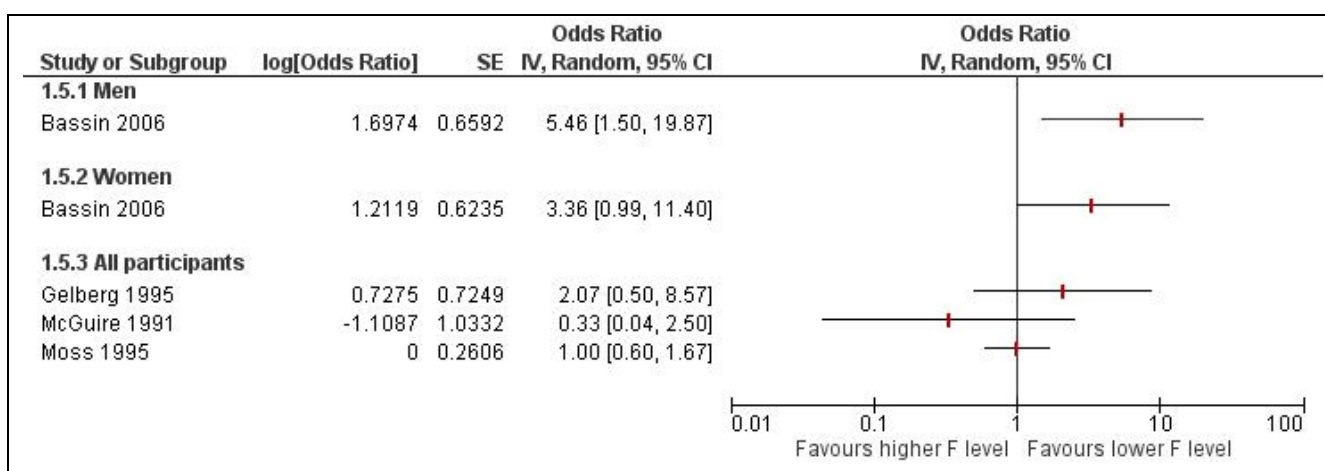


Figure 17 Osteosarcoma OR: Higher fluoride level vs. lower fluoride level

Abbreviations: CI = confidence interval; F = fluoride; SE = standard error; IV = inverse variance

Studies reporting incidence rate ratios

Two studies identified in the McDonagh et al (2000) review were described as reporting relative risks for osteosarcoma, but on inspection these studies actually reported incidence rate ratios (Cohn et al, 1992 and Hrudey et al, 1990). A further three studies from the current review also reported the risk of osteosarcoma with different water fluoride levels using incidence rate ratios (Comber et al, 2010; Levy et al, 2012 and Public Health England, 2014). The results from all five are presented in Figure 18. Overall, these studies do not support any association between water fluoride levels and the risk of osteosarcoma.

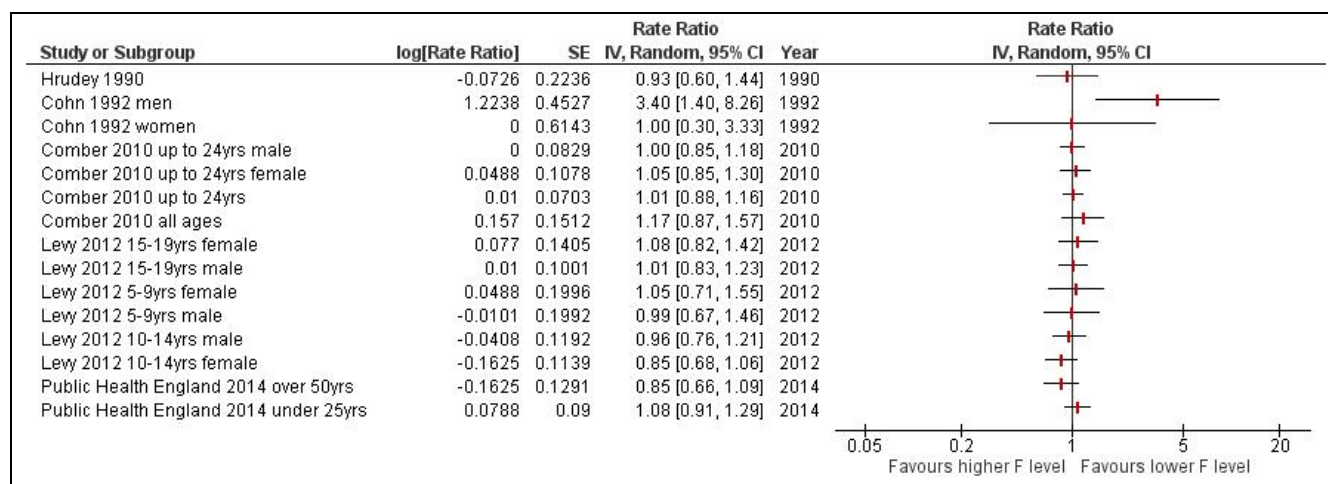


Figure 18 Osteosarcoma IRR: Higher fluoride level vs. lower fluoride level

Abbreviations: CI = confidence interval; F = fluoride; SE = standard error; IV = inverse variance

Discussion

The best and most applicable evidence identified by the current review comes from the four acceptable quality ecological studies by Blakey et al (2014), Comber et al (2011), Levy & Leclerc (2012) and Public Health England (2014). All were from countries that have CWF schemes at levels similar to that used in Australia and have similar healthcare provision and socioeconomic parameters. All of these studies used routine cancer incidence data from national registries and found no significant difference in the incidence of osteosarcoma in areas supplied with fluoridated water and areas not supplied. The low quality study from New Zealand used similar data sources and was highly applicable, but only reported crude incidence rates stratified by age and gender. The single small case-control study by Kharb et al (2012), in contrast, had serious methodological limitations and the results of this study are very likely highly biased. It also has poor applicability to the Australian context due to differences in socioeconomic factors, healthcare provision and health services access.

All of this evidence, when taken in conjunction with the evidence identified in the earlier reviews, indicates that water fluoridation at levels used in the Australian context is unlikely to be associated with an increased risk of developing osteosarcoma.

Evidence statement

The evidence evaluation identified six studies (five ecological and one case-control) which found no association between the incidence of osteosarcoma and water fluoridation at current Australian levels.

Table 100 Osteosarcoma - GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
5	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	519,128,941 person-years at risk ⁶	No statistically significant difference in incidence of osteosarcoma between areas with water fluoridation and those without ⁷	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological studies

² Four studies of acceptable quality

³ All estimates are similar in magnitude

⁴ Populations and fluoride comparisons applicable to Australian context

⁵ Confidence intervals within an effect size of ±0.5

⁶ From Public Health England (2014) and Comber (2010) only

⁷ From 4 studies; Blakey et al (2014) reported an adjusted non-significant RR of 1.00 (95%CI: 0.87–1.15) for every increase of 1 ppm fluoride in water

Table 101 Osteosarcoma - GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
1	Observational studies ¹	Very serious ²	Not serious ³	Serious ⁴	Not serious	None	10 cases 10 controls	Participants with osteosarcoma were more likely to live in areas with higher fluoride water levels than people without osteosarcoma (1.30 ppm vs. 0.48 ppm)	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Case-control study

² No information about participant demographics, recruitment, assessment of disease status, or the presence of potential confounding factors; and small numbers of participants

³ Only one study

⁴ Applicability to Australian context unlikely due to socioeconomic & healthcare system differences

EWING SARCOMA

Concerns have been raised about an association between fluoride ingestion and an increased risk of bone cancers, including Ewing sarcoma, due to the deposition of fluoride in bone (Public Health England, 2014). The McDonagh et al. (2000) and NHMRC (2007a) systematic reviews included four studies that looked at bone cancer generally (see page 173), but none that investigated the relationship between water fluoridation and Ewing sarcoma specifically.

Literature Search Results

The literature search identified one ecological study (Level IV evidence) by Blakey et al (2014) that included the incidence of Ewing sarcoma as an outcome. This study evaluated fluoride levels that were in the range considered to be highly applicable to the Australian context.

Highly Applicable Comparisons

The single ecological study (Level IV evidence) from the UK was of acceptable quality (Blakey et al 2014). The authors examined the relationship between the incidence of Ewing sarcoma in those aged less than 50 years and the level of fluoride in drinking water in small local residence areas in Great Britain. These areas are standardised small areas of 1000–3000 persons used for decennial census data. Routine fluoride monitoring data from the relevant authorities for the period 2004–2006 was utilised to estimate fluoride exposure. The mean fluoride levels in drinking water were between 0.00 ppm and 1.27 ppm. Case data was extracted from 10 regional cancer registries for the period 1980 to 2005. Negative binomial regression analysis adjusted for age, gender, population density, and non-car ownership found no evidence of an association between drinking water fluoride level and the incidence of osteosarcoma. The results of this study and the GRADE assessment are presented in Table 102 and Table 103, respectively.

Table 102 Ewing sarcoma - Results for Highly Applicable Continuous Analysis in Blakey et al (2014)

Study Design Quality	Population	Exposure	Outcome	Analysis	Result	Effect Estimate
Blakey 2014 Ecological Acceptable	Residents aged 0–49 years in England, Scotland and Wales	Mean water fluoride level (0.00–1.27 ppm)	Crude incidence per 1,000,000 person-years at risk ¹	Negative binomial regression ²	1.66 (1650 / 992213 person-years at risk) ³	Adjusted RR = 0.929 (90% CI: 0.773–1.115) ⁴

Abbreviations: CI = confidence interval; RR = relative risk; ppm = parts per million

¹ Registered in 10 regional cancer registries between 1980 and 2005

² Adjusted for age-group, gender, the interaction age-group*gender, Scotland, East Midlands, population density and non-car ownership

³ From McNally et al (2012)

⁴ Relative risk of Ewing sarcoma per 1 ppm increase in fluoride level

Discussion

This was a population-based study of acceptable methodological quality from Great Britain that used national cancer registries and fluoride levels that were based on regular testing of water supplied by regional water companies and the Drinking Water Inspectorate. In addition, it adjusted for important confounders like age and gender. These findings are consistent with the findings for osteosarcoma, i.e. there was no significant increase in the incidence of osteosarcoma with increasing water fluoride levels. Moreover, they are

consistent with the conclusions of the McDonagh et al (2000)—that there was no clear association between water fluoridation and the incidence of any bone cancer.

Evidence statement

The evidence evaluation identified a single ecological study which found no evidence of an association between incidence of Ewing Sarcoma and water fluoridation at current Australian levels.

Table 103 Ewing sarcoma – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	992,213 person-years at risk	No significant increase in the risk of Ewing sarcoma with increasing fluoride level	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Of acceptable methodological quality

³ Only one study

⁴ Populations and fluoride comparisons applicable to Australian context

⁵ Confidence intervals within an effect size of ±0.5

TOTAL CANCER INCIDENCE

The possibility that fluoridation might increase the risk of cancer has been suggested in a population-based study in the mid-seventies, but these findings have largely not been supported by subsequent reviews (Medical Research Council 2002). The same report concluded that even though the available evidence had not established that fluoride was carcinogenic in humans, and most of the studies suggest that it is not, the possibility of some effect could not be excluded.

The McDonagh et al (2000) systematic review concluded that there was no clear association between water fluoridation and overall cancer incidence or mortality for “all cause” cancer from ten studies (Chilvers 1982; Cook-Mozaffari et al 1981; Goodall et al 1980; Hoover et al 1976; Lynch 1985; Raman 1977; Richards & Ford 1979; Schlesinger 1956; Smith 1980). The evidence relating fluoridation to cancer incidence or mortality was mixed, with small variations on either side of no effect. There were also two studies included that found no association between water fluoride levels and thyroid cancer (Hoover et al 1976; Kinlen 1975).

The NHMRC (2007a) systematic review included three ecological studies: one poor quality study with major limitations which reported mixed results (Takahashi et al 2001) and another poor quality study that reported an inverse correlation between cancer incidence and fluoride concentration (Steiner 2002). The last study of fair quality reported that the results did not support an association between cancer mortality and fluoridation (Yang et al 2000). The 2007 NHMRC review concluded that there was no clear association between water fluoridation and overall cancer incidence or mortality.

Literature Search Results

The literature search identified two ecological studies of acceptable quality that investigated the relationship between water fluoridation and cancer incidence (Public Health England 2014; Schwartz 2014). Both studies were set in the context of CWF and so were highly applicable to the Australian context.

Highly Applicable Comparison

The acceptable quality study by Public Health England (2014) sought to investigate water fluoridation and the incidence of all cancer and invasive bladder cancer alone. The authors investigated bladder cancer separately because of a theoretical possibility of an increase in incidence. Since fluoride is excreted in the urine the bladder lining is exposed to relatively high concentrations. Information from the National Cancer Registration Service was matched to both demographic and water fluoridation scheme location data (sourced from various national databases). Incidence rate ratios were calculated, adjusted for age, gender, deprivation and ethnicity.

There was no evidence of a difference in the rate for all cancer between fluoridated and non-fluoridated areas with the adjusted incidence being 0.4% lower in fluoridated areas (95%CI: -1.2%, +0.4%). In contrast, the incidence of invasive bladder cancer was 8.0% lower (95%CI: -9.9%, -6.0%) in fluoridated areas. The results from this study are presented in Table 104 and the GRADE assessment for all cancer is reported in Table 106 and for bladder cancer in Table 107

Schwartz (2014) investigated the correlation between the age-adjusted incidence of eye and orbit cancers with the proportion of the population receiving fluoridated water in 44 states in the US. Eye and orbit cancer rate was used as a surrogate for uveal melanoma rate (90% of adult eye cancers are melanomas and the majority involve the uveal tract). In the final model, including latitude, eye cancer incidence was found to be inversely correlated with the percentage of the population receiving fluoridated water ($r=0.45$, $p=0.002$)¹⁸. The results from this study and then GRADE assessment are presented in Table 105 and Table 108, respectively.

¹⁸ Note that the correlation coefficient, r , was reported in the original publication without a negative sign

Discussion

The population-based study from England found no significant difference in the overall incidence of cancer between areas with or without water fluoridation. In contrast, there was a finding that the incidence of bladder cancer was significantly lower in the fluoridated areas, but the effect was small. This analysis was adjusted for age, gender, deprivation, and ethnicity, but not for smoking; a strong risk factor for bladder cancer. The authors concluded that it was possible that the finding could be a result of residual confounding, bias, and/or reverse causation, rather than a true association. The second study found an inverse correlation between fluoridation and eye cancer incidence. The authors concluded that the results should be considered to be an interesting hypothesis and should be investigated further. Both studies were highly applicable to the Australian context and, considered together, provide evidence that CWF is not associated with an increase in cancer incidence.

Evidence statement

The evidence evaluation identified a single, large ecological study that found no association between the overall incidence of cancer and water fluoridation at current Australian levels.

Table 104 All Cancer and Bladder Cancer – Results for Highly Applicable Comparison

Study Design Quality	Population	Exposures		Outcome	Analysis	Results		Effect Estimate (95%CI)	Sig
Public Health England 2014 Ecological Acceptable	Residents in areas with and without CWF in England	CWF (0.8–1.0 ppm)	No CWF ¹	Age-standardised incidence of any cancer per 100,000 pyar (95%CI) ²	Multivariate model ⁴	402 (399–404) <i>(131,288 cases per 25,314,612 person-years at risk)</i>	396 (395–397) <i>(921,583 cases per 183,256,350 person-years at risk)</i>	Difference in incidence: –0.4% (–1.2, 0.4)	<i>p</i> =0.29
				Age-standardised incidence of bladder cancer per 100,000 pyar (95%CI) ³		12.4 (12.2–12.6) <i>(11,327 cases per 67,978,298 person-years at risk)</i>	13.0 (12.9–13.1) <i>(84,780 cases per 487,149,150 person-years at risk)</i>		

Note: Effect estimate in Public Health England (2014) is expressed as percentage difference in incidence, e.g. 8.2% (–9.3, 29) equates to an incidence rate ratio of 1.082 (0.907, 1.290)

Abbreviations: CWF = community water fluoridation; pyar = per-years at risk; 95%CI = 95% confidence interval; ppm = parts per million

¹ Areas classified as naturally fluoridated to 1 ppm were excluded

² All cancers registered with the National Cancer Registration Service from 2007 to 2010

³ All bladder cancers registered with the National Cancer Registration Service from 2000 to 2010

⁴ Adjusted for age, gender, deprivation, and ethnicity

Table 105 Eye Cancer – Results for Highly Applicable Comparison

Study Design Quality	Population	Exposure	Outcome	Analysis	Effect Estimate	Sig
Schwartz 2014 Ecological Acceptable	Non-Hispanic whites in the U.S.	Proportion of population in each state exposed to CWF	Age-adjusted incidence of eye cancer ¹	Multivariable linear regression ²	<i>r</i> = 0.45 ³	<i>p</i> =0.002

Abbreviations: CWF = community water fluoridation

¹ All eye cancer registrations from the North American Association of Central Cancer Registries for 2006 to 2010

² Adjusted for latitude

³ As recorded in the paper even though the text reports an inverse correlation

Table 106 All Cancer – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious	None	208,570,962 person-years at risk	Incidence was 0.4% lower in the fluoridated areas (95%CI: 1.2% lower to 0.4% higher)	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Acceptable quality; population-based; good data capture; adjustment for confounders

³ Single study

⁴ Community water fluoridation setting in the US and England

Table 107 Bladder Cancer – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious	None	555,127,448 person-years at risk	Incidence was 8.0% lower in the fluoridated areas (95%CI: 9.9% lower to 6.0% lower)	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Acceptable quality; acceptable quality; population-based; good data capture; adjustment for some confounders

³ Single study

⁴ Populations and fluoride comparisons applicable to Australian context

Table 108 Eye Cancer – GRADE Report for Highly Applicable Continuous Analysis and Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious	None	NR	Negative correlation between incidence of eye cancer and water fluoride level (r=0.38 ⁵ , p=0.01)	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: NR = not reported

¹ Ecological study

² Acceptable quality; acceptable quality; population-based; good data capture; adjustment for some confounders

³ Single study

⁴ Populations and fluoride comparisons applicable to Australian context

⁵ As reported

SKELETAL FLUOROSIS

Skeletal fluorosis is a pathological condition that may arise following long-term exposure (either by inhalation or by ingestion) to elevated levels of fluoride (RSNZ 2014). It is prevalent in parts of India, China, South Africa, and Tanzania. Fluoride increases bone density and appears to exacerbate the growth of osteophytes, resulting in joint stiffness and pain. The condition is categorized into one of four stages: a preclinical stage and three clinical stages that increase in severity (National Research Council 2006). The most severe stage (grade III) historically has been referred to as the “crippling” stage and is characterised by osteomalacia, osteoporosis, and/or osteosclerosis. At stage II, mobility is not significantly affected, but it is characterized by sporadic pain, stiffness of joints, and osteosclerosis of the pelvis and spine (National Research Council 2006). It should be noted that there have been no reported cases of skeletal fluorosis in Australia.

The McDonagh et al (2000) review included one study that had skeletal fluorosis as an outcome which reported an increased prevalence of skeletal fluorosis at higher fluoride concentrations.

The NHMRC (2007a) review did not include any studies that investigated skeletal fluorosis.

Literature Search Results

The literature search identified two ecological studies that examined the relationship between water fluoride levels and skeletal fluorosis (Hussain et al 2010; Srikanth et al 2008). Both studies were of low quality. They included only fluoride comparisons of above 1.5 ppm and so were considered to have very limited applicability in the Australian context.

Comparisons with Limited Applicability

Hussain et al (2010) measured the prevalence of skeletal fluorosis in 1,998 individuals from 41 villages in central Rajasthan. These villages were a subset of 60 villages in one district who had a fluoride concentration of >5.0 ppm in at least one groundwater sample. This study was conducted in the context of water quality investigation. The diagnosis of skeletal fluorosis was based on symptoms, deformity, and range of movement. The overall prevalence of Grade II skeletal fluorosis was 16.8% in villages where the mean fluoride level was under 4 ppm, 20.1% where the mean fluoride level was between 4 and 6 ppm, and 17.4% (93/535) where fluoride was greater than 6 ppm. Grade III fluorosis was not identified in any villages with a mean fluoride of less than 4 ppm. There was a prevalence of 0.9% and 0.6% respectively in villages with groundwater fluoride levels of between 4 and 6 ppm, and over 6 ppm respectively. No statistical analysis was conducted. The results of these studies are presented in Table 109.

Srikanth et al (2008) measured the prevalence of skeletal fluorosis in 818 adults in five Indian villages in Palamau district. The mean fluoride concentration of drinking water sources in each village ranged between 1.51 to 3.71 ppm. The method of diagnosing skeletal fluorosis was not described. The overall prevalence of moderate skeletal fluorosis (grade II) was 7.6% (range: 4.7% to 14.8%) and severe (grade III) was 1.3% (range: 0.7% to 3.9%). Again, no statistical analysis was conducted. The results of these studies are presented in Table 110.

The GRADE assessment is reported in Table 111.

Table 109 Skeletal Fluorosis – Results for Comparison with Limited Applicability

Study Design Quality	Population	Outcome	Analysis	Results:		
				NOF <4.0 ppm	NOF 4.0–6.0 ppm	NOF >6.0 ppm
Hussain 2010 Ecological Low -	Households in India -	Grade II skeletal fluorosis ¹	None	81/482 (16.8%)	197/981 (20.1%)	93/535 (17.4%)
		Grade III skeletal fluorosis ¹	-	0/482 (0.0%)	9/981 (0.9%)	3/535 (0.6%)

Abbreviations: NOF = naturally occurring fluoride; ppm = parts per million

¹ Determined by house-to-house survey

Table 110 Skeletal Fluorosis – Results for Comparison with Limited Applicability

Study Design Quality	Population	Village	Fluoride level (ppm)	Skeletal fluorosis ¹ grade II	Skeletal fluorosis ¹ grade III
Srikanth 2008 Ecological Low - - - -	Adults in five villages in India - - - -	Ganke	1.51	4/85 (4.7%)	1/85 (1.2%)
		Mukhiya	2.54	17/115 (14.8%)	1/115 (0.9%)
		Chukru	2.91	14/277 (5.1%)	2/277 (0.7%)
		Satyari	2.97	7/103 (6.8%)	4/103 (3.9%)
		Bakhari	3.71	20/238 (8.4%)	3/238 (1.3%)

Abbreviations: ppm = parts per million

¹ Method of diagnosis not reported

Discussion

The two included studies are both from regions in India where skeletal fluorosis is endemic due to high levels of fluoride in drinking water sources. Interpretation of these two studies is difficult due to their significant methodological shortcomings and poor applicability due to the high levels of fluoride (especially Hussain 2010). The raw data does not appear to show any clear relationship between increasing water fluoride levels and an increase in the prevalence of skeletal fluorosis.

This review has not identified any evidence that water fluoride at levels used in Australia for CWF is associated with an increase in the rate of skeletal fluorosis. The total cumulative dose of fluoride ingested by an individual in these studies is likely to be greater than that from water alone: other sources of fluoride such as from food, tea, and coal fires were not measured. Other factors may also be important such as nutrition and climate, which influence fluid uptake.

Evidence statement

The evidence evaluation identified two ecological studies which provided insufficient evidence to draw a conclusion about any association between skeletal fluorosis and water fluoridation at current Australian levels.

Table 111 Skeletal Fluorosis – GRADE Report for Comparisons with Limited Applicability

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Serious ³	Very serious ⁴	Very serious ⁵	None	2816	Skeletal fluorosis prevalence (range): grade II: 4.7% to 20.1% grade III: 0% to 3.9%	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological studies

² Unclear recruitment methods; uncertainty around validity of diagnosis; no statistical analysis

³ Prevalence values inconsistent within studies

⁴ All fluoride comparisons higher than 1.5 ppm; socioeconomic conditions & healthcare systems likely different than Australian context

⁵ No variance data reported

HIP FRACTURE

A proportion of the fluoride consumed from fluoridated water is deposited in bone. This has led to concern that intentional water fluoridation could lead to an increase in bone fractures, particularly in the frail elderly. Hip fracture was included as an outcome in both the McDonagh et al (2000) review and the 2007 NHMRC systematic review of water fluoridation.

Evidence from prior reviews

The McDonagh et al (2000) systematic review identified 18 studies mostly of low quality that investigated hip fracture. Of the thirty analyses in these studies, 14 found that increasing water fluoride level was associated with fewer hip fractures, with 5 analyses being statistically significant; 13 analyses found that increasing water fluoride levels were associated with an increase in hip fractures, with 4 being statistically significant, and 3 analyses found no association between fluoride level and the risk of hip fracture. The 2007 NHMRC review included one additional study of fair quality that found no increased risk of hip fracture at water fluoride levels comparable to those used for CWF. Both the NHMRC (2007a) and McDonagh et al (2000) reviews concluded that water fluoridation at levels aimed at preventing dental caries has little effect on fracture risk.

Literature Search Results

The literature search identified two studies that captured hip fracture as an outcome. One was an acceptable quality ecological study (Public Health England 2014) (Level IV evidence) and the other was an acceptable quality retrospective cohort study (Nasman et al 2013) (Level III-2 evidence). Public Health England (2014) included comparisons between unfluoridated water and water fluoridated at Australian levels and therefore was deemed to be highly applicable to the Australian context. Nasman et al (2013) included two fluoride comparisons which were highly applicable and one which was partially applicable.

Highly Applicable Comparisons

The results of the highly applicable comparisons from these two studies are presented in Table 112.

In the Public Health England (2014) study, fracture occurrence was determined from a national hospital episode database. After the initial unadjusted analysis, the authors examined the following confounding variables in multivariate analyses: age (proportion of population above 65 years), gender (proportion of the population male), deprivation (measured by Index of Multiple Deprivation, 2010) and ethnicity (proportion of the population white). The crude rate of hip fracture from the unadjusted univariate model in Public Health England (2014) was 7.2% higher (95% CI: 4.9%, 9.6%; $p < 0.001$) in local super output areas receiving fluoridated water. These areas are standardised English small areas of 1000–3000 persons used for decennial census data. After adjusting for age, gender and deprivation, the difference in hip fracture rates fell to 0.9% (95% CI: –0.8%, 2.6%; $p = 0.29$), and further adjustment incorporating ethnicity reduced the incidence rate ratio to 0.7% (95% CI: –1.0%, 2.4%; $p = 0.42$). Therefore, after adjusting for relevant confounding factors the difference in hip fracture incidence was no longer statistically significant.

Nasman et al (2013) compared unfluoridated water with two naturally occurring water fluoride levels within the range seen in the Australian setting and one level above that used for CWF in Australia. The authors considered the relationship between fluoride exposure and both hip fracture and first low-trauma hip fracture. Fracture incidence was determined from appropriate national sources by ICD code and fluoride exposure linked to municipalities using data from the Swedish Water and Wastewater Association. Cohort members were grouped into one of four fluoride exposure categories: ≥ 1.5 ppm, 0.7–1.49 ppm, 0.3–0.69 ppm and < 0.3 ppm. All comparisons were made with the lowest fluoride group, < 0.3 ppm. The 95% confidence intervals for all hazard ratios derived from the adjusted cox proportional hazard models spanned unity. Therefore, the authors concluded there was no increased risk for either hip fracture or first low-trauma hip fracture due to fluoride exposure.

The GRADE assessment for these two highly applicable comparisons can be found in Table 113.

Partially Applicable Comparison

As described above, Nasman et al (2013) also included one comparison considered to be partially applicable (≥ 1.5 ppm vs. < 0.3 ppm). As for the highly applicable comparisons, the hazard ratio spanned unity.

The result of the partially applicable comparison from this study is presented with the highly applicable comparisons in Table 112. The GRADE assessment for this partially applicable comparison can be found in Table 114.

Table 112 Hip Fracture – Results for Highly and Partially Applicable Comparisons

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results -		Effect Estimate (95%CI)	Sig
Nasman 2013 Retrospective cohort Acceptable	Individuals in Sweden born between 1900 and 1919, alive and living in area of birth at start of follow-up ¹	NOF <0.3 ppm	NOF 0.3–0.69 ppm	Time to hip fracture ²	Adjusted Cox proportional hazards model ³	NR/250,222	NR/134,554	HR: 0.97 (0.94–0.99)	NR
			NOF 0.7 – 1.49 ppm	-		-	NR/54,312	HR: 0.97 (0.94–1.00)	NR
			NOF ≥.5 ppm	-		-	NR/13,736	HR: 0.98 (0.93–1.04)	NR
		NOF <0.3 ppm	NOF 0.3–0.69 ppm	Time to first low-trauma hip fracture ²	Adjusted Cox proportional hazards model ³	NR/250,222	NR/134,554	HR: 0.95 (0.93–0.98)	NR
			NOF 0.7 – 1.49 ppm	-		-	NR/54,312	HR: 0.97 (0.93–1.00)	NR
			NOF ≥1.5 ppm	-		-	NR/13,736	HR: 1.00 (0.94–1.06)	NR
Public Health England 2014 Ecological Acceptable	Residents in areas with and without CWF in England	CWF (0.8–1.0 ppm)	No CWF ⁴	Hip fracture incidence per 100,000 pyar ⁵	Unadjusted univariate model	119 (45,219/37,971,918 person-years at risk)	111 (303,848/274,884,530 person-years at risk)	Difference in incidence: 7.2% (4.9, 9.6)	p<0.001
						NR	NR	Difference in incidence: 0.9% (-0.8, 2.6)	p=0.29
						NR	NR	Difference in incidence: 0.7% (-1.0, 2.4)	p=0.42

Note: Effect estimate in Public Health England (2014) is expressed as percentage change in incidence, e.g. 8.2% (-9.3, 29) equates to an incidence rate ratio of 1.082 (0.907, 1.290)

Abbreviations: NOF = naturally occurring fluoride; CWF = community water fluoridation; HR = hazard ratio; pyar = person-years at risk; Public Health England 95%CI = 95% confidence interval; NR = not reported; ppm = parts per million

¹ The start of follow-up was when area of residence had full coverage in National In-Patient Register which started in 1964, covered 83% by 1971, and all inpatient care since 1987

² Determined from the Swedish National In-Patient Register and the Swedish Cause of Death Register by ICD code

³ Adjusted for gender, age group, county of residence, calendar group

⁴ Areas classified as naturally fluoridated to 1 ppm were excluded

⁵ All emergency consultant in-patient episodes with hip fractures registered in the Hospital Episode Statistics between 2007 and 2013

⁶ Adjusted for age, gender, deprivation

⁷ Adjusted for age, gender, deprivation, and ethnicity

Summary of the available evidence

The effect estimates from the McDonagh et al (2000), NHMRC (2007) reviews have been plotted with estimates from the current review to illustrate the body of evidence for hip fracture. Separate forest plots have been created for each type of effect estimate: relative risks (RR), odds ratios (OR) and incidence rate ratios (IRR). For studies with multiple fluoride level comparisons, the findings for the level closest to 1 ppm fluoride versus the lowest fluoride level were used. Note that some of the estimates that were previously classified as relative risks in McDonagh et al (2000) are in fact rate ratios. The results from Nasman et al (2013) were not plotted as it was the only study reporting hazard ratios. The results were not pooled due to high clinical and statistical heterogeneity.

Studies reporting relative risks

Five studies identified by McDonagh et al (2000) reported the risk of hip fracture using an RR. The results from these studies do not support any clear relationship between water fluoride levels and the risk of hip fracture.

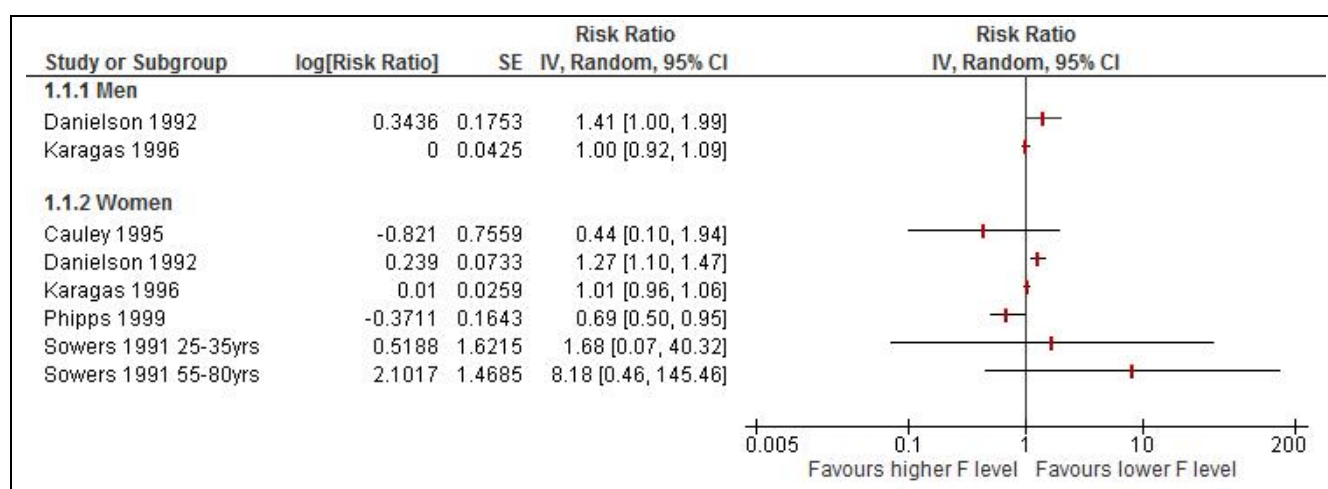


Figure 19 Hip fracture RR: Higher fluoride level vs. lower fluoride level

Abbreviations: CI = confidence interval; F = fluoride; SE = standard error; IV = inverse variance

Studies reporting odds ratios

Three studies identified by McDonagh et al (2000) and one study identified in the 2007 NHMRC review reported the risk of hip fracture using odds ratios. The two studies by Jacqmin-Gradda suggested that the risk of hip fracture may be reduced in areas with lower water fluoride. However, these results were not consistent with the results from the other two studies, which found no significant difference in the risk of hip fracture.

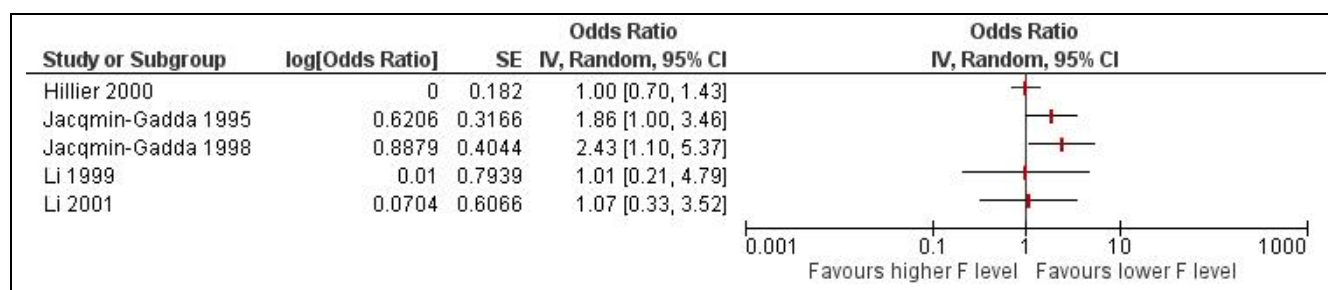


Figure 20 Hip fracture OR: Higher fluoride level vs. lower fluoride level

Abbreviations: CI = confidence interval; F = fluoride; SE = standard error; IV = inverse variance

Studies reporting incidence rate ratios

Eight studies identified by McDonagh et al (2000) reported the risk of hip fracture using incidence rate ratios. The current review identified one additional study that reported incidence rate ratios for

hip fracture (Public Health England 2014). Of the 18 analyses reported, 5 found a significantly lower risk of hip fracture with the higher fluoride level, 1 found a significantly lower risk of hip fracture with the lower fluoride level, and 12 found no significant difference in the risk of hip fracture.

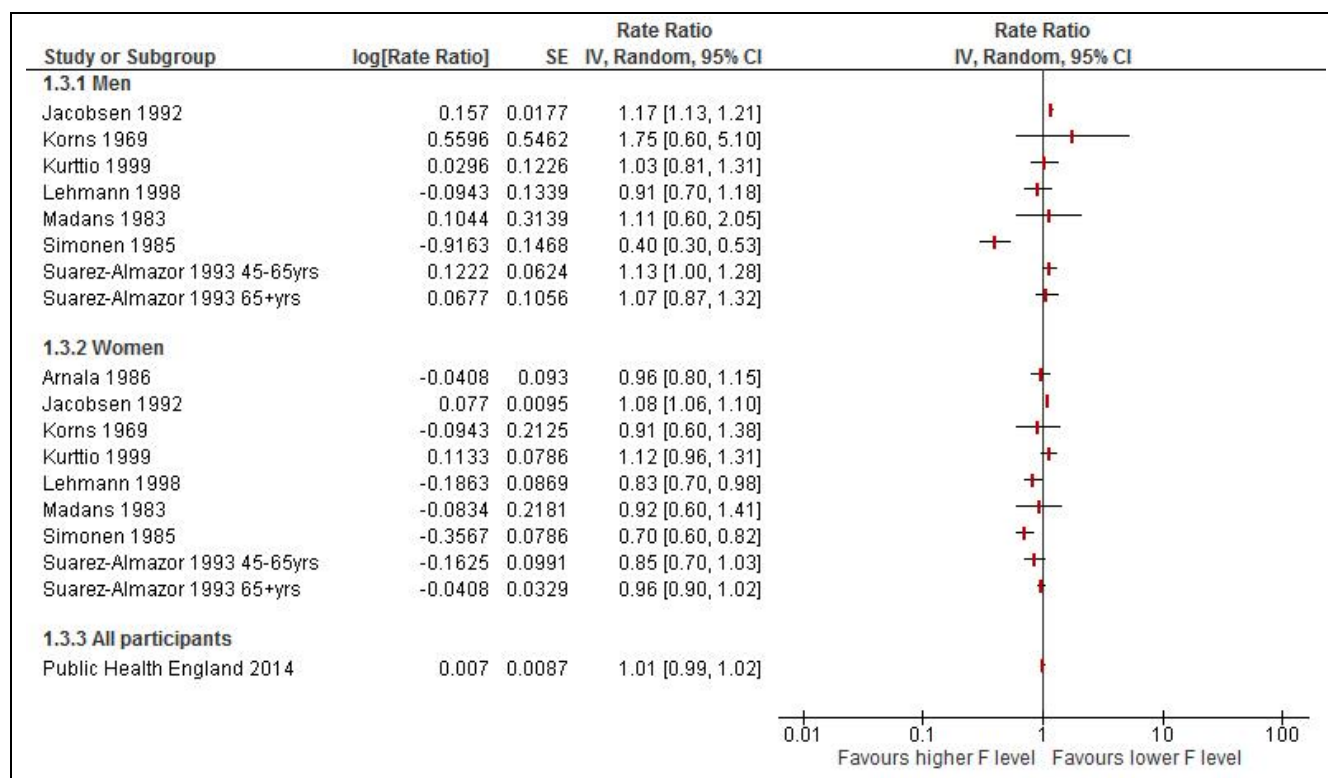


Figure 21 Hip fracture IRR: Higher fluoride level vs. lower fluoride level

NB: The results for Cooper et al (1990) were not included as they only reported a range of rates

Abbreviations: CI = confidence interval; F = fluoride; SE = standard error; IV = inverse variance

Discussion

Both of the studies identified in the current review were of acceptable quality, with large sample sizes and consideration of gender and age in their analyses. The Public Health England (2014) report is particularly relevant as it compares the incidence of hip fracture in areas with CWF with the incidence in areas without. They found no significant increase in the incidence in the CWF areas after adjusting for gender and age; both important independent risk factors for hip fracture. The Swedish study compares the risk at various levels of fluoride in water to a level (<0.3 ppm) equivalent to unfluoridated water in Australia. Again, they found no increase in hip fracture with increasing water fluoride levels. This adds to the body of evidence from prior reviews that indicates water fluoridation is unlikely to be associated with a large change in the incidence of hip fractures.

Evidence statement

The evidence evaluation identified two studies (one ecological and one retrospective cohort) which found no association between the incidence of hip fracture and water fluoridation at current Australian levels.

Table 113 Hip Fracture – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	313,045,314 person-years at risk	Effect estimates from both studies found no statistically significant difference in the incidence of hip fracture.	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ One ecological and one retrospective cohort study

² Good sample size and adjustment for confounders

³ Similar findings between the two studies

⁴ Highly applicable to the Australian context with similar community water fluoridation schemes and socioeconomic parameters

⁵ Narrow 95% CIs

Table 114 Hip Fracture – GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
1	Observational study ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	13,736 person-years at risk	HR = 0.98 (95%CI: 0.93–1.04)	⊕⊕⊕○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: HR = hazard ratio

¹ One retrospective cohort study

² Good sample size and adjustment for confounders

³ One study only

⁴ Partially applicable to the Australian context with similar community water fluoridation schemes and socioeconomic parameters

⁵ Narrow 95% CIs

OSTEOPOROSIS

The NHMRC (2007a) review included one systematic review that included bone mineral density (BMD) or osteoporosis as an outcome (Demos et al 2001). This review, Demos et al (2001), was a poor quality systematic review that included 27 human studies, 12 of which looked at the use of fluoride to treat osteoporosis. The authors concluded that the addition of fluoride to drinking water at level of approximately 1 ppm does not decrease BMD, when compared to drinking unfluoridated water. The McDonagh et al (2000) review did not include any studies that investigated osteoporosis as a negative effect of exposure to fluoridated water.

Literature Search Results

Only one low quality ecological study was located that included osteoporosis as an outcome (Huang 2013).

Partially applicable comparison

Huang (2013) investigated the relationship between water fluoride levels and osteoporosis in 675 people aged 16 to 60 years from 15 villages in China. Osteoporosis was determined by plain x-ray of the shin and forearm. No further information regarding diagnostic criteria was reported. Selection of participants was not specified. The prevalence of osteoporosis was not significantly different between the villages with fluoride levels of 0.5–1.0 ppm compared to fluoride levels of 1.5–7.0 ppm (6.8% vs. 6.2% respectively). The results of this study and the GRADE assessment are presented in Table 115 and Table 116, respectively.

Discussion

The results from this low quality partially applicable ecological study show no evidence of an association between fluoride water level and the prevalence of osteoporosis. It is generally not possible to make any certain conclusions from a single study unless there is a very large effect and the study is methodologically sound. This study has a high likelihood of bias, only partial applicability to the Australian setting and limited external validity. Therefore, there is insufficient evidence to determine a relationship between water fluoridation and osteoporosis.

Evidence statement

The evidence evaluation identified a single ecological study which provided insufficient evidence to draw a conclusion about any association between osteoporosis and water fluoridation at current Australian levels.

Table 115 Osteoporosis – Results for Partially Applicable Comparison

Study Design Quality	Population	Exposures		Outcome	Analysis	Results -		Sig
Huang 2013 Ecological Low	Adults (16–60 years) of 15 villages in China	NOF range 1.5–7.0 ppm	NOF range 0.5–1.0 ppm	Prevalence of osteoporosis ¹	Chi-squared test	30/485 (6.2%)	13/190 (6.8%)	p>0.05

Abbreviations: NOF = naturally occurring fluoride; ppm = parts per million

¹ Determined by x-ray of crus and forearm

Table 116 Osteoporosis - GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
1	Observational studies ¹	Very serious ²	Not serious ³	Serious ⁴	Very serious ⁵	None	675	Prevalence of osteoporosis: 6.2% with 1.5–7.0 ppm exposure 6.8% with 0.5–1.0 ppm exposure ⁶	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Ecological study

² Selection method not specified; no known confounding factors considered; accuracy of diagnosis uncertain

³ Single study

⁴ Upper fluoride comparator level above 0.4–1.5 ppm range; socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data reported

⁶ No statistical analysis

MUSCULOSKELETAL PAIN

Musculoskeletal pain can be a symptom of skeletal fluorosis and so is a relevant outcome to investigate (National Research Council 2006). Musculoskeletal pain was not included as an outcome in either the NHMRC (2007a) or the McDonagh et al (2000) systematic review of the efficacy and safety of water fluoridation.

Literature Search Results

The literature search identified one low quality ecological study by Ranjan and Yasmin (2012) and one low quality, cross-sectional study by Namkaew and Wiwatanadate (2012) (both Level IV evidence). Both studies investigated water fluoride levels that are partially applicable to the Australian context.

Partially Applicable comparison

The study by Namkaew and Wiwatanadate (2012) was conducted in Thailand and compared a high fluoride area where fluoride in drinking water exceeded 0.7 ppm with a low fluoride area where fluoride in drinking water was <0.7 ppm. Participants were recruited using quota sampling by keeping the number recruited from each village proportional to the village's total population. Samples were taken from all individual's sources of water for drinking and cooking and analysed for fluoride concentration.

Musculoskeletal pain was assessed using a questionnaire using the Thai version of the 11-point Likert scale. The pain was classified into four levels and then regrouped into two categories with 'pain' consisting of levels 1–3 and 'no pain' those who selected level 0 only. The authors calculated the average daily fluoride dose from drinking water from birth until the date of data collection using a mathematical expression modified from the US Environmental Protection Agency. The association between average daily fluoride dose and chronic pain was analysed using a binary logistic regression using a forward stepwise technique to identify the most appropriate model. Presumably because it was the only outcome for which a potentially meaningful difference in results was determined, regression results for lower back pain were reported only.

The prevalence of chronic knee and leg pain captured in the study were very similar in the two groups: 59.9% vs. 60.4% and 36.9% vs. 37.3% for the low vs. high fluoride groups respectively. The authors conducted a binary logistic regression of the presence of lower back pain against fluoride exposure category. The resulting odds ratio, adjusted for a history of lower body injury and family history of pain, was 1.58 (95% CI: 1.10, 2.28; $p=NR$) suggests that higher fluoride levels may be associated with increased lower back pain. The results of this study are presented in Table 117.

The study by Ranjan and Yasmin (2012) measured joint pain by health survey in 2,732 participants from 31 villages in 6 groups in Gaya district of Bihar state. Twenty samples of drinking water were collected from each group of villages and analysed for fluoride and other physiochemical parameters. Results were presented for each of the six groups of villages separately. To improve the relevance of the results to the Australian context, the groups of villages were re-categorised by the evidence reviewers based on mean water fluoride concentration into those with fluoride levels of <0.4 ppm, those between 0.4 ppm and 1.5 ppm and those >1.5 ppm.

The numbers of self-reported cases of joint pain were totalled for each of these fluoride categories. The overall prevalence of joint pain was 14.8% in villages with <0.4 ppm fluoride in their groundwater, 12.4% in villages with fluoride levels between 0.4 to 1.5 ppm, and 54.3% in villages with groundwater containing >1.5 ppm of fluoride. No tests of significance were conducted. The results of this study are presented in Table 118. The GRADE assessment for both studies is presented in Table 119.

Discussion

Namkaew & Wiwatanadate (2012) reported that they had found no difference in the prevalence of knee pain and leg pain between different fluoride exposures, however there was no statistical analysis for these outcomes. There was an association between fluoride levels and lower back pain, and although the authors adjusted for a history of injury to the lower body and a family history of pain, there are other potential confounding variables not measured. These include smoking, being overweight, and prolonged sitting or standing.

Ranjan and Yasmin (2012) reported crude prevalence data for self-reported joint pain according to the mean drinking water fluoride levels and there are significant concerns about this study's methodological quality. It is unlikely that a study from India which has high levels of naturally occurring fluoride, and different socioeconomic parameters would be generalisable to the Australian context. Musculoskeletal pain can be caused by many factors which were not considered in this study.

Taken together, the data presented in these two studies does not provide convincing evidence of any association between fluoride in drinking water and musculoskeletal pain.

Evidence statement

The evidence evaluation identified two studies (one ecological study and one cross-sectional) which provided insufficient evidence to draw a conclusion about any association between musculoskeletal pain and water fluoridation at current Australian levels.

Table 117 Musculoskeletal Pain – Results from Namkaew and Wiwatanadate 2012

Study Design Quality	Population	Exposures		Outcome ¹	Analysis	Results		Effect Estimate
		NOF ≥0.7 ppm	NOF <0.7 ppm			NOF ≥0.7 ppm	NOF <0.7 ppm	
Namkaew 2012 Cross-sectional Low	Adults (50–80 years) in Thailand	NOF ≥0.7 ppm	NOF <0.7 ppm	Prevalence of lower back pain	Binary logistic regression ²	191/274 (69.7%)	157/260 (60.4%)	OR: 1.58 (1.10–2.28)
-	-	-	-	Prevalence of knee pain	None	164/274 (59.9%)	157/260 (60.4%)	NR
-	-	-	-	Prevalence of leg pain	-	101/274 (36.9%)	97/260 (37.3%)	NR

Abbreviations: NOF = naturally occurring fluoride; OR = odds ratio; NR = not reported; ppm = parts per million

¹ Assessed using the Thai version of the 11-point Likert scale

² Adjusted for family history of pain and history of injury to lower body

Table 118 Musculoskeletal Pain – Results from Ranjan and Yasmin 2012

Study Design Quality	Population	Outcome	Results			
			NOF <0.4 ppm	NOF 0.4–1.5 ppm	NOF >1.5 ppm	
Ranjan 2012 Ecological Low	Residents in 31 villages in Bihar state, India	Prevalence of self-reported joint pain ¹	Adults males	18/174 (10.3%)	23/684 (3.4%)	141/272 (51.8%)
-	-	-	Adult females	44/165 (26.7%)	183/685 (26.7%)	151/264 (57.2%)
-	-	-	Children	0/79 (0.0%)	0/295 (0.0%)	61/114 (53.5%)
-	-	-	Total population	62/418 (14.8%)	206/1664 (12.4%)	353/650 (54.3%)

Abbreviations: NOF = naturally occurring fluoride; ppm = parts per million

¹ Determined by health survey

Table 119 Musculoskeletal Pain - GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Serious ³	Very serious ⁴	Serious ⁵	None	3,266	Odds of lower back pain significantly greater in the high fluoride area. Prevalence of joint pain higher in the high fluoride area.	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study and cross-sectional study

² Minimal consideration of confounding factors; no relevant participant information supplied; selection process unclear; no statistical analysis

³ Results internally inconsistent

⁴ Fluoride level range up to 6.2 ppm; socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data reported by ecological study

LOW BIRTH WEIGHT

Neither the NHMRC (2007a) report nor the McDonagh et al (2000) systematic review identified any studies assessing the relationship between fluoride exposure and low birth weight. There does not appear to be any plausible biological rationale for an association between fluoride exposure and low birth weight.

Literature Search Results

The literature search identified one low quality case-control study (Level III-3 evidence) that evaluated the relationship between dental fluorosis and low birth weight (Diouf et al 2012). The study also captured maternal fluoride exposure and as such was eligible for inclusion in this systematic review. Each mother's source of drinking water was categorised as either mineral, well or drill water with regional average fluoride concentrations (0.0 ppm, 0.009 ppm and 4.7 ppm respectively) applied to each category. As the two lower fluoride concentrations groups are equivalent to the unfluoridated category in this review the comparisons were classified as partially applicable to the Australian context.

Partially Applicable Comparisons

Successive mothers giving birth in a single Senegalese hospital were recruited into the study. Newborns weighing less than 2.5 kg were categorised as having low birth weight. A multivariate analysis using a backwards selection procedure was used to select the relevant confounding variables.

Two multivariate regression analyses were performed comparing mothers who drank well and drill water, with naturally occurring fluoride of 0.009 ppm and 4.7 ppm respectively, with mothers who drank mineral drinking water containing no fluoride. As well as drinking water source and Dean's index, the final model included variables for hypertension, anaemia, consanguinity and parity. No significant difference in the incidence of low birth weight was detected in the well (0.009 ppm) versus mineral (0.00 ppm) water analysis; however, a score ratio of 1.99 (95% CI: 1.3, 3.67; $p=0.04$) was generated from the drill (4.7 ppm) versus mineral (0.00 ppm) water analysis. The results and the GRADE assessment are presented in Table 120 and Table 121, respectively.

Discussion

The authors conclude that the results support the hypothesis that exposure to high water fluoride in pregnant women is associated with a risk of giving birth to a low weight infant. However, this study is of low methodological quality with serious concerns surrounding the methods used to capture fluoride exposure. Therefore, there is insufficient evidence to form a conclusion on the relationship between exposure to high water fluoride levels and low birth weight. As this is the only study identified that reported low birth weight as an outcome, this review provides insufficient evidence on the effect of water fluoridation at Australian levels on birth weight.

Evidence statement

The evidence evaluation identified a single ecological study which provided insufficient evidence to draw a conclusion about any association between low birth weight and water fluoridation at current Australian levels.

Table 120 Birth Weight – Results for Partially Applicable Comparison

Study Design Quality	Population	Cases	Controls	Exposure	Analysis	Results -		Effect estimate	Sig
						Cases	Controls		
Diouf 2012 Case-control Low	Mothers giving birth at a hospital in Senegal	Newborns of low birth weight ¹ (n=108)	Newborns not of low birth weight (n=216)	Mineral water (0.0 ppm)	Multivariate regression analysis ²	11/108	30/216	Reference group (OR = 1.00)	-
-	-	-	-	Well water (0.009 ppm)		30/108	92/216	OR = 0.88 (0.5–2.51)	NR
-	-	-	-	Drill water (4.7 ppm)		67/108	94/216	OR = 1.99 (1.3–3.67)	p=0.04

Abbreviations: NR = not reported; OR = odds ratio; ppm = parts per million

¹ <2.5 kg measured using a baby scale

² Adjusted for Dean's index, parity, consanguinity, anaemia, & hypertension

Table 121 Birth Weight – GRADE Report for Partially Applicable Comparisons

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Very serious ²	Not serious ³	Serious ⁴	Serious ⁵	None	108 cases 216 controls	Increased odds of low birth weight associated with exposure to high fluoride levels (4.7 ppm)	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Case-control study

² Exposure was not measured directly (average regional measurements used); adjustment for Dean's index is an adjustment for fluoride exposure and therefore introduces bias;

³ Not relevant - only one study

⁴ Poor applicability to the Australian context due to socioeconomic & healthcare system differences

⁵ Wide 95% CI around the odds ratios

DOWN SYNDROME

Down syndrome was included as an outcome of interest in both the NHMRC (2007a) and McDonagh et al (2000) systematic reviews. Both sets of authors identified the same six studies that considered the relationship between fluoride exposure and Down syndrome. In addition, NHMRC (2007a) included an extra study that found no association. The authors concluded that the evidence for an association between water fluoride level and the incidence of Down syndrome was limited, and that all the identified studies were rated as being of poor quality.

Literature Search Results

The literature review identified one acceptable quality ecological (Level IV evidence) study conducted in England that included an analysis of the relationship between fluoride exposure and Down syndrome (Public Health England 2014).

Highly Applicable Comparison

Data on the incidence of Down syndrome was obtained from The National Down Syndrome Cytogenetic Register that included all cases of Down syndrome in England between 2009 and 2012 inclusive.

As the risk of Down syndrome is highly associated with maternal age, the authors calculated the expected number of Down syndrome births for each local authority using published maternal-age specific risks for Down syndrome. A Poisson model was fitted with expected births as a measure of exposure. After adjusting the Poisson regression for maternal age the incidence rate was 0.9% greater in the fluoridated areas (95% CI: -0.8%, 2.6%; $p=0.68$). The results of this study and the GRADE assessment are presented in Table 122 and Table 123, respectively.

Discussion

This is a population-based ecological study of acceptable methodological quality that found that the incidence of Down syndrome births, adjusted for maternal age, were not significantly increased in areas with CWF in England.

Evidence statement

The evidence evaluation identified a single ecological study that found no association between Down syndrome and water fluoridation at current Australian levels.

Table 122 Down Syndrome – Results for Highly Applicable Comparison

Study Design Quality	Population	Exposures		Outcome	Analysis	Results		Effect Estimate (95%CI)	Sig
		-	-			-	-		
Public Health England 2014 Ecological Acceptable -	Residents in areas with and without CWF in England -	Areas with CWF (0.8–1.0 ppm) ¹ -	Areas without CWF ² -	Down syndrome age-standardised incidence per 10,000 live births (95%CI) ³ -	Unadjusted Poisson regression model	21.7 (20.0, 23.4) ⁴	24.6 (24.0, 25.2) ⁵	Difference in incidence: -12% (-19, -4)	<i>p</i> <0.01
					Adjusted Poisson regression model ⁶	NR	NR		

Note: Effect estimate in Public Health England (2014) is expressed as percentage difference in incidence, e.g. 8.2% (-9.3, 29) equates to an incidence rate ratio of 1.082 (0.907, 1.290)

Abbreviations: CWF = community water fluoridation; PHE = Public Health England; NR = not reported; 95%CI = 95% confidence interval; ppm = parts per million

¹ Areas where >50% of constituent subareas were located in a fluoridated water zone

² Areas where >50% of constituent subareas were classified as naturally fluoridated were excluded

³ All cases of Down syndrome registered with the National Down Syndrome Cytogenetic Register from 2009 to 2012

⁴ 658 cases per 303,818 live births

⁵ 5,961 cases per 2,423,482 live births

⁶ Adjusted for maternal age

Table 123 Down Syndrome – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational study ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious	None	2,727,300 person-years at risk	Incidence of Down syndrome births were 0.9% higher (95%CI: 0.8% lower to 2.6% higher) in areas with CWF	⊕⊕○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Good sample size, adjustment for confounders

³ Not applicable, single study

⁴ Community water fluoridation scheme applicable to Australian context

IQ AND COGNITIVE FUNCTION

There have concerns raised that fluoride may affect the intelligence (as measured by IQ) and cognitive development of children (RSNZ 2014). IQ is a component of overall cognitive function, and they are considered together in this section due to this overlap. However, it should be noted that age related decline in cognitive function is distinct from the development of cognitive function in children and is not considered here.

A recent systematic review by Choi et al (2012) reported the possibility of an adverse effect of high fluoride exposure on children's neurodevelopment with an estimated pooled standardised weighted mean difference (SMD) in IQ scores of -0.45 (95%CI: -0.56 to -0.34) when comparing high fluoride with lower fluoride exposure. The majority of the 27 included studies in the Choi review were from China and many did not measure potential confounders, such as exposure to lead or arsenic, iodine deficiency, socioeconomic status, parental education, or nutritional status. In addition, the meta-analyses were affected by high statistical heterogeneity ($I^2 = 80\%$) and were based on crude effect estimates only. Overall, this is not convincing or robust evidence of an association between fluoride in drinking water and a reduction in children's IQ. Most of the included studies have serious methodological flaws and have a high risk of bias, with a reasonable likelihood that their findings are a consequence of residual confounding by some other, unmeasured variable. Also, importantly, the comparator fluoride levels are generally much higher than those seen in Australia and, as such, are not directly applicable to the water fluoridation context in Australia.

McDonagh et al (2000) included two studies that examined the relationship between water fluoridation and IQ (Lin et al 1991; Zhao et al 1996) and one study (Jacqmin et al 1994) that captured cognitive function as an outcome. Both IQ studies were ecological studies of children aged 7–14 years in China and were assessed as having a high risk of bias. They provided insufficient evidence for McDonagh et al to make any confident conclusions. The single study investigating cognitive function was in adults 65 years and older and found that the risk of having cognitive problems was less with exposure to fluoride but no test of significance was conducted.

The NHMRC (2007a) systematic review included the evidence from McDonagh et al (2000) and did not identify any additional studies with IQ as an outcome. Overall, the studies located by both McDonagh et al (2000) and NHMRC (2007a) did not provide evidence of sufficient quality for them to make any conclusions.

Literature Search Results

The literature search identified 11 additional studies with IQ as an outcome: one prospective cohort study (Level II evidence) of high quality (Broadbent et al 2014); one cross-sectional (Level IV evidence) study of acceptable quality (Rocha-Amador et al 2007); two cross-sectional studies of low quality (Saxena et al 2012; Singh et al 2013); and seven ecological studies (Level IV evidence) of low quality (Eswar et al 2011; Fan et al 2007; Karimzade et al 2014; Seraj et al 2012; Trivedi et al 2007; Trivedi et al 2012; Wang et al 2007). In addition, one ecological study (Level IV evidence) of acceptable quality was identified that evaluated the relationship between water fluoride exposure and cognitive function (Choi et al 2015).

Highly Applicable Comparisons

One study (Broadbent et al 2014) included fluoride levels that were considered to be highly applicable to the Australian context as it compares areas with CWF with fluoride levels of 0.85 ppm to areas without CWF and naturally occurring fluoride levels of between 0.0 ppm and 0.3 ppm. In addition, the healthcare system and socioeconomic factors are very similar.

This study was a prospective cohort study of high quality with data retrieved from a longitudinal population-based study of a general population sample of 1037 people born in one city in New Zealand between 1972, and 1973. This consecutive birth cohort has been prospectively followed for

38 years with a 96% retention rate¹⁹. Residence in an area with CWF (CWF), use of fluoride toothpaste and intake of fluoride tablets prior to age 5 years was assessed. IQ had been measured for each study participant at ages 7, 9, 11, and 13 years using the Wechsler Intelligence Scale for Children-Revised (WISC-R). The IQ scores for these ages were averaged and standardised. The Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) was used to assess IQ at age 38 years. The authors found no significant differences in the unadjusted IQ scores between those exposed to CWF in early life compared to those with no early life CWF exposure both at 7–13 years and 38 years. The findings were the same when adjusted for gender, socioeconomic status, breastfeeding, childhood maltreatment, number of perinatal insults, and birth weight (as well as educational attainment for adult IQ outcomes). The authors concluded that these findings did not support the assertion that fluoride exposure in the context of CWF (i.e. fluoride concentration of 0.7 to 1.0 ppm) can affect neurological development or IQ. The results from this study and the GRADE assessment are presented in Table 124 and Table 131, respectively.

¹⁹ 30 have died and 96% of the remaining 1007 consented to be examined at age 38

Table 124 IQ – Results for Highly Applicable Comparisons

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results -		Effect Estimate	Sig
Broadbent 2014 Prospective cohort High -	Consecutive birth cohort in New Zealand (7 to 13 years)	CWF 0.85 ppm	NOF 0.0–0.3 ppm	Mean IQ score ± SD ¹	General linear models ²	100.0 ± 13.5	99.8 ± 13.0	b=0.15 (-2.83, 3.14)	p=0.92
	Consecutive birth cohort in New Zealand (38 years)	-	-	-		-	100.2 ± 14.2	98.1 ± 13.5	b=2.20 (-1.04, 5.44)

Abbreviations: CWF = community water fluoridation; NOF = naturally occurring fluoride; SD = standard deviation; ppm = parts per million

¹ Measured by Wechsler Intelligence Scale for Children - Revised at ages 7, 9, 11 and 13, and Wechsler Adult Intelligence Scale - Fourth Edition at age 38

² Adjusted for sex, socioeconomic status, low birth weight, and breastfeeding, with the addition of educational attainment for adult IQ outcomes

Partially Applicable Comparisons

Nine of the studies identified (Choi et al 2015; Eswar et al 2011; Karimzade et al 2014; Fan et al 2007; Seraj et al 2012; Trivedi et al 2012; Wang et al 2007; Saxena et al 2012; Rocha-Amador et al 2007; Singh et al 2013) included one fluoride level comparison above 1.5 ppm and so were considered to be only partially applicable to the Australian context.

Two low quality ecological studies (Eswar et al 2011; Karimzade et al 2014) compared IQ scores from subjects living in areas with water supplies containing naturally occurring fluoride levels higher than 1.5 ppm with IQ scores of residents in areas with naturally occurring fluoride levels below 0.4 ppm i.e. equivalent to unfluoridated water supplies in the Australian context.

Eswar et al (2011) compared the IQ scores in a total of 133 schoolchildren, aged 12 to 14 years from two villages, one in a high fluoride area (NOF 2.45 ppm) and the other in a low fluoride area (NOF 0.29 ppm). The participants were convenience samples of continuous residents from each village who had been drinking water from the same public water supply. The IQ scores were measured using Raven's Standard Progressive Matrices test and found no significant difference in the IQ scores between the two groups ($p=0.30$).

Karimzade et al (2014) evaluated the IQ scores of a random sample of 39 boys aged between 9 and 12 years from two villages in Iran. The mean fluoride level of drinking water from wells and springs was 3.94 ppm in one village and 0.25 ppm in the other. IQ was measured using the Iranian version of the Cattell IQ test. They found a statistically significant lower mean IQ score in the 19 boys from the village with high fluoride water levels compared to the mean IQ score of the 20 boys in a village with low fluoride water level ($p=0.0004$).

Four low quality ecological studies (Fan et al 2007; Seraj et al 2012; Trivedi et al 2012; Wang et al 2007) included comparisons from groups exposed to fluoride levels within the range of 0.4 ppm to 1.5 ppm with groups exposed to fluoride levels above 1.5 ppm.

A study from China of 79 schoolchildren aged 7 to 14 years old by Fan et al (2007) found no significant difference in IQ scores between children with water supplies with fluoride levels of 3.15 ppm compared with children exposed to drinking water supplies with 1.03 ppm fluoride levels. IQ was measured with the Chinese Combined Raven's Test. All participants came from one village where water improvement schemes (WIS) had been instituted in some of the water supplies to reduce the level of fluoride. Again, no potential confounding factors were measured and little information was given about recruitment methods.

Seraj et al (2012) measured the mean IQ of 239 schoolchildren aged 6 to 11 years from five villages in Iran and divided them into three groups depending on the mean fluoride level of their water supply: 'normal' 0.5–1.0 ppm; 'medium' 3.1 ppm; and 'high' 5.2 ppm. IQ was measured using Raven's Colour Progressive Matrices, and the authors found a significantly lower IQ score in both the 'high' and 'medium' fluoride groups compared to the 'normal' group ($p=0.001$). However, the method of identification and recruitment of the participants was not reported, and no demographic, health, socioeconomic, occupational, or nutritional status information was reported. The comparison of the 'medium' and 'high' groups is discussed under the section on comparisons of limited applicability.

Trivedi et al (2012), in another study from India, compared the IQ scores from 84 schoolchildren aged 12 to 13 years in three villages with naturally occurring mean fluoride levels of 2.3 ppm in their groundwater with children from three villages with 0.84 ppm mean fluoride levels. How the subjects were selected for the study was not described. IQ was measured using a locally created questionnaire which had been standardised on the Gujarati population with a 97% reliability rate in relation to the Stanford-Binet Intelligence Scale. The mean IQ scores were significantly lower in the children from the high fluoride groundwater villages compared to the other children.

Wang et al (2007) compared the IQ scores in a total of 376 school children from 6 villages, of which, three had high levels of naturally occurring fluoride in their groundwater (mean level was 8.3 ppm) and three had a mean fluoride level of 0.5 ppm. These participants were part of a larger study evaluating the health effects of arsenic levels in water supplies. How the participant children were selected was not reported. There were significant differences in the mean levels of arsenic in the groundwater, and the participants from the high fluoride village were shorter than those from the low fluoride (control) villages ($p < 0.05$). IQ was measured using the Rural Chinese version of the Combined Raven's Test. The authors reported that the mean IQ scores were 100.5 and 104.8 for the high fluoride and low fluoride (control) groups respectively. This difference was statistically significant.

The results from these six studies (Eswar et al 2011; Karimzade et al 2014; Fan et al 2007; Seraj et al 2012; Trivedi et al 2012; Wang et al 2007) are presented in Table 125.

Table 125 IQ – Results for Partially Applicable Comparisons

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results -		Sig
Eswar 2011 Ecological Low	Children (12–14 years) recruited from two high schools in India	NOF 2.45 ppm	NOF 0.29 ppm	Mean IQ score ± SD ¹	Z-test	88.8 ± 15.3	86.3 ± 12.8	p=0.30
Karimzade 2014 Ecological Low	Male children (9–12 years) in villages in Iran	NOF 3.94 ppm	NOF 0.25 ppm	Mean IQ score ± SD ²	Unpaired t-test	81.21 ± 16.17	104.25 ± 20.73	p<0.001
Fan 2007 Ecological Low	Children (7–14 years) recruited from primary schools in one village in China	NOF 3.15 ppm	WIS 1.03 ppm	Mean IQ score ± SD ³	Student's t-test	96.11 ± 12.00	98.41 ± 14.75	p>0.05
Seraj 2012 Ecological Low -	Children (6–11 years) residing in villages in Iran -	NOF 3.1 ± 0.9 ppm	NOF 0.5–1.0 ppm	Mean IQ score ± SD ⁴	ANOVA	89.03 ± 12.99	97.77 ± 18.97	p=0.001
		NOF 5.2 ± 1.1 ppm	NOF 0.5–1.0 ppm	-	-	88.58 ± 16.01	97.77 ± 18.97	p=0.001
Trivedi 2012 Ecological Low - -	Children (12–13 years) from schools in six villages in India (all participants)	NOF 2.3 ppm	NOF 0.84 ppm	Mean IQ score ± SE ⁵	Student's t-test	92.53 ± 3.13	97.79 ± 2.54	p<0.05
	Children (12–13 years) from schools in six villages in India (females)	-	-	-	-	90.18 ± 3.32	94.37 ± 2.98	p<0.05
	Children (12–13 years) from schools in six villages in India (males)	-	-	-	-	94.88 ± 2.96	99.97 ± 2.10	p<0.05
Wang 2007 Ecological Low	Children (8–12 years) in three villages in China	NOF 8.3 ± 1.9 ppm	NOF 0.5 ± 0.2 ppm	Mean IQ score ± SD ⁶	Student's t-test	100.5 ± 15.8	104.8 ± 14.7	p<0.05

Abbreviations: CWF = community water fluoridation; IQ = intelligence quotient; NOF = naturally occurring fluoride; WIS = water improvement schemes; ANOVA = analysis of variance; SD = standard deviation; SE = standard error; ppm = parts per million

¹ Measured by Raven's Progressive Matrices Intelligence Test

² Measured by Iranian version of the Cattell IQ test

³ Measured by Chinese Combined Raven's Test image book

⁴ Measured by Raven's Colour Progressive Matrices

⁵ Measured using a locally created questionnaire

⁶ Measured by Rural Chinese version of the Combined Raven's Test

The following three studies (Saxena et al 2012; Rocha-Amador et al 2007; Singh et al 2013) were cross-sectional studies that all had at least one comparator within the 0.4–1.5 ppm range.

Saxena et al (2012) is a cross-sectional study (Level IV evidence) of low quality measured IQ score in a total of 170 schoolchildren aged 12 years and allocated them into four groups according to the level of fluoride present in each child's drinking water (>4.5 ppm; 1.5–3.0 ppm; 3.1–4.5 ppm; and <1.5 ppm). Subjects were selected by a stratified cluster sampling of areas. Children who were not lifelong residents, had changed water source since birth, or had a history of neurological disease and/or head injury, were excluded from the study. The IQ scores were measured using Raven's Standard Progressive Matrices and then converted into an 'intelligence grade' consisting of 4 categories based on a range of IQ scores (lower score = higher intelligence). There was a statistically significant difference between the mean 'intelligence grade' of all groups. The results from this study are presented in Table 126.

Table 126 IQ – Results for Partially Applicable Comparison (Saxena 2012)

Study Design Quality	Population	Exposures	Outcome	Analysis	Effect Estimate	Sig	
Saxena 2012 Cross-sectional Low	Children (12 years) from villages in India	NOF >4.5 ppm	Mean 'intelligence grade' ¹	ANOVA	4.45	$p < 0.001$	
-		-	NOF 3.1–4.5 ppm	-	4.23	-	
-		-	NOF 1.5–3.0 ppm	-	-	3.85	-
-		-	NOF <1.5 ppm	-	-	3.16	-

Abbreviations NOF = naturally occurring fluoride; ANOVA = analysis of variance; ppm = parts per million

¹ Measured by Raven's Standard Progressive Matrices, then converted into 'intelligence grade' (1–5)

Rocha-Amador et al (2007) examined the relationship between exposure to fluoride and arsenic in drinking water and intelligence in a random sample of 132 children aged 6 to 10 years attending public schools in three rural areas in Mexico. The mean levels of fluoride in the drinking water for each area were 0.8, 5.3, and 9.3 ppm. The mean arsenic levels were 5.8, 169, and 194 µg/L, respectively. IQ was assessed using the revised Mexican version of the Wechsler Intelligence Scale for children. The results from multivariable regression which were adjusted for the children's blood lead level, mothers' education, socioeconomic status, height-for-age, and serum transferrin saturation demonstrated a significant negative correlation between drinking water fluoride and IQ. Of note, the authors state that it was not possible to statistically test the interaction between fluoride and arsenic. The results from this study are presented in Table 127.

Table 127 IQ – Results for Partially Applicable Comparison (Rocha-Amador 2007)

Study Design Quality	Population	Exposures	Outcome	Analysis	Effect Estimate	Sig
Rocha-Amador 2007 Cross-sectional Acceptable	Children (6–10 years) from public schools in three rural areas, Mexico	NOF 9.4 ± 0.9 vs. 5.3 ± 0.9 vs. 0.8 ± 1.4 ppm	Performance IQ	Multivariable regression ¹	Log coefficient = -6.7	p<0.001
-	-	-	Verbal IQ	-	Log coefficient = -11.2	p<0.001
-	-	-	Full IQ	-	Log coefficient = -10.2	p<0.001

Abbreviations: IQ = intelligence quotient; NOF = naturally occurring fluoride; ppm = parts per million

¹ Adjusted for blood lead level, mother's education, socioeconomic status, height-for-age z-score and transferrin saturation

Singh et al (2013) was a cross-sectional study (Level IV evidence) of low quality which investigated IQ in male schoolchildren aged between 9 and 14 years old in India. Recruitment procedures were not reported. The compared the IQ of seventy boys from a region where fluoride content in the water is greater than 2.0 ppm (actual mean level was 6.8 ppm) with seventy-two boys from a region with water fluoride level of less than 1.5 ppm (actual mean level was 1.0 ppm). No known confounders were measured and no statistical analysis was undertaken. The results from this study are presented in Table 128.

Table 128 IQ – Results for Partially Applicable Comparison (Singh 2013)

Study Design Quality	Population	Outcome	Results	
			NOF 6.8 ppm	NOF 1.5 ppm
Singh 2013 Cross-sectional Low	Male children (9–14 years) in two regions in India	IQ >130	0%	0%
-	-	IQ 120–129	1.4%	2.8%
-	-	IQ 110–119	2.8%	6.9%
-	-	IQ 90–109	29.2%	47.2%
-	-	IQ 80–89	34.7%	30.6%
-	-	IQ 70–79	22.2%	9.7%
-	-	IQ <69	6.9%	2.8%

Abbreviations: IQ = intelligence quotient; NOF = naturally occurring fluoride; ppm = parts per million

The final ecological study of acceptable quality by Choi et al (2015) assessed lifetime exposure to fluoride in drinking water and cognitive function in children in China. The publication details a pilot study in 51 children aged 6 to 8 years in south Sichuan. Fluoride concentration from the well-water of the mother's residence during pregnancy and onwards was used to characterise each child's lifetime exposure. The children were exposed to naturally occurring fluoride ranging from 1.0 to 4.07 ppm (mean: 2.20 ppm). The multivariable regression analysis adjusted for the following confounding factors: gender, age, parity, illness <3yrs old, household income, carer's age and

education. In order to capture a wide range of functional domains, a battery of cognitive grading tests were performed on each child. The results of the regression analyses are presented in Table 129. None of these adjusted effect estimates for fluoride in drinking water were statistically significant at the 5% level.

Table 129 Cognitive Function – Results for Partially Applicable Regression Analysis from Choi et al (2015)

Test	Subtest	Adjusted ¹ effect (β) of fluoride in drinking water	95% CI
Wide Range Assessment of Memory and Learning	Finger Windows	1.46	-3.81, 6.74
	Visual Learning total	0.92	-9.30, 11.1
	Visual Learning delay	0.53	-4.30, 5.35
	Visual Learning difference	-0.44	-3.52, 2.65
	Design Memory	4.81	-5.90, 15.5
Wechsler Intelligence Scale for Children-Revised	Squareroot block design	1.10	-0.94, 3.14
	Digit span – Forward	-0.95	-4.44, 2.53
	Digit span – Backward	-0.44	-3.37, 2.50
	Digit span – Total	-1.39	-6.76, 3.98
Wide Range Assessment of Visual Motor Ability	Drawing subset	1.02	-3.19, 5.24
Finger tapping task	Preferred hand	1.23	-7.01, 9.46
	Non-preferred hand	5.03	-2.17, 12.2
Grooved pegboard test	Log10 dominant hand	0.07	-0.11, 0.25
	Log10 non-dominant	-0.02	-0.18, 0.14

¹ Adjusted for child's sex, age, parity, illness before 3 years old, household income last year, and caretaker's age and education and presented on the log (10) scale

The GRADE assessment for all the eleven studies with partially applicable comparisons can be found in Table 132.

Comparison with Limited Applicability

Two of the studies investigating IQ as an outcome (Seraj et al 2012; Trivedi et al 2007) included comparisons of limited applicability to the Australian context as the comparators are above 1.5 ppm.

Seraj et al (2012) measured the mean IQ of 239 schoolchildren aged 6 to 11 years from five villages in Iran and divided them into three groups depending on the mean fluoride level of their water supply: 'normal' 0.5–1.0 ppm; 'medium' 3.1 ppm; and 'high' 5.2 ppm. IQ was measured using Raven's Colour Progressive Matrices. The difference in mean IQ score between the 'high' and 'medium' groups was not significant ($p=0.995$). Of note, the method of identification and recruitment of the participants was not reported, and no demographic, health, socioeconomic, occupational, or nutritional status information was reported.

The final study by Trivedi et al (2007) has limited applicability to the Australian context as the comparators are above 1.5 ppm. This low quality ecological study (Level IV evidence) included groups of schoolchildren exposed to groundwater with naturally occurring mean fluoride levels of 5.55 ppm and 2.01 ppm. The mean IQ score for the group of 89 children exposed to the higher level of fluoride in their drinking water was significantly lower than the mean IQ of the 101 children exposed to the lower level of fluoride. The results from this study and the GRADE assessment are presented in Table 130 and Table 133, respectively.

Table 130 IQ – Results for Comparison with Limited Applicability

Study Design Quality	Population	Outcome	Analysis	Results		Sig
Seraj 2012 Ecological Low	Children (6–11 years) residing in villages in Iran	Mean IQ score \pm SD ¹	ANOVA	NOF 5.2 \pm 1.1 ppm: 88.58 \pm 16.01	NOF 3.1 \pm 0.9 ppm: 89.03 \pm 12.99	$p=0.995$
Trivedi 2007 Ecological Low	Children (12–13 years) recruited from two schools in India (all participants)	Mean IQ score \pm SE ²	Student's t-test	NOF 5.55 ppm: 91.72 \pm 1.13	NOF 2.01 ppm: 104.44 \pm 1.23	$p<0.001$
-	Children (12–13 years) recruited from two schools in India (females)	-	-	94.15 \pm 1.35	103.87 \pm 2.21	$p<0.01$
-	Children (12–13 years) recruited from two schools in India (males)	-	-	90.24 \pm 1.58	108.80 \pm 1.47	$p<0.001$

Abbreviations: IQ = intelligence quotient; NOF = naturally occurring fluoride; ANOVA = analysis of variance; SE = standard error; ppm = parts per million

¹ Measured by Raven's Colour Progressive Matrices

² Measured using a locally created questionnaire

Discussion

The single study with highly applicable comparisons (Broadbent et al 2014) found no evidence of a detrimental effect of fluoride exposure at 0.85 ppm on IQ. Broadbent et al (2014) is of higher methodological quality than the other included studies due to its prospective cohort design, and adjustment for known confounders (gender, low birth weight, breastfeeding, and socioeconomic status in childhood). It also is set in the context of a country with CWF with very similar socioeconomic conditions and healthcare provision.

Eight (Eswar et al 2011; Fan et al 2007; Karimzade et al 2014; Saxena et al 2012; Seraj et al 2012; Singh et al 2013; Trivedi et al 2012; Wang et al 2007) of the nine studies with partially applicable comparators have similar shortcomings: all were assessed as having a high risk of bias with unclear participant selection, no measurement or adjustment for confounding factors, and no reporting of blinding to exposure status. All of these studies were conducted in Iran, China or India which limits their applicability to the Australian context, because of differences in healthcare system services and socioeconomic conditions. The tenth study (Rocha-Amador et al 2007) with partially applicable comparators was of acceptable quality, however it, too, is unlikely to be applicable to the Australian context for the same reasons. It also has smaller participant numbers and confounding by exposure to arsenic cannot be excluded. The final study (Trivedi et al 2007) has similar shortcomings to those already mentioned as well as being much less applicable due to all the fluoride level comparators being >1.5 ppm.

The study looking at cognitive function (Choi et al 2015) found no significant association between fluoride levels in drinking water and any of the measures of cognitive performance however; the authors concluded that their research supported the notion that fluoride in drinking water may produce development neurotoxicity. This was based on the finding that participants with moderate to severe dental fluorosis had a significantly decreased mean total and backward digit span score compared to participants with normal to questionable dental fluorosis (data not presented). Of note,

there were no other differences in any of the other measures of cognitive performance at the 0.05 significance level between participants with varying severity of dental fluorosis. Taken in its entirety, this study provides insufficient evidence to establish any negative effect of water fluoridation on cognitive function.

Overall, the body of evidence for an adverse effect of fluoride on IQ and cognitive function is largely of very limited quality and is not particularly relevant to the Australian context. The best and most relevant evidence is from the only high quality study (Broadbent et al 2014) which found no evidence for an adverse effect of fluoridated water at levels comparable to that seen in Australia on intelligence in children (as measured by IQ).

Evidence statement

The evidence evaluation identified 11 studies (nine ecological and two cross-sectional) which provided insufficient evidence to draw a conclusion about any association between water fluoridation and IQ or cognitive function. This was due to lack of adjustment for confounding, poor measurement of fluoride exposure and poor measurement of IQ and cognitive function. In addition, the exposure to fluoride in these studies was much higher than water fluoridation levels within the Australian context. One further prospective cohort study of sufficient quality was identified that found no association between the IQ of children and adults and water fluoridation at current Australian levels.

Table 131 IQ - GRADE Report for Highly Applicable Comparison (IQ assessed with: Wechsler Intelligence Scale for Children & Revised Wechsler Adult Intelligence Scale)

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
1	Observational studies ¹	Not serious ²	Not serious ³	Not serious ⁴	Not serious	None	1,037	No significant difference in IQ scores	⊕⊕⊕○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Prospective cohort study

² Longitudinal population-based study; all major fluoride intake considered; confounders adjusted for

³ Findings consistent for subgroups

⁴ Populations and fluoride comparisons applicable to Australian context

Table 132 IQ - GRADE Report for Partially Applicable Comparisons

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
11	Observational studies ¹	Very serious ²	Not serious	Serious ³	Not serious	None	1,565	11 of 14 analyses reported a significantly lower IQ score in the high fluoride exposure group.	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Two cross-sectional and six ecological studies

² Poor recruitment reporting; no confounding factors considered; no blinding to exposure status reported

³ One comparator within 0.4–1.5 ppm range but applicability to Australian context unlikely due to socioeconomic & healthcare system differences

Table 133 IQ - GRADE Report for Comparison with Limited Applicability

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
1	Observational studies ¹	Very serious ²	Serious ³	Very serious ⁴	Not serious	None	392	One of two studies reported statistically significant lower IQ score in the high fluoride exposure group.	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ One cross-sectional study and one ecological study

² Poor recruitment reporting; no confounding factors considered; no blinding to exposure status reported

³ Inconsistent findings across studies

⁴ Both comparators >1.5 ppm and applicability to Australian context unlikely due to socioeconomic & healthcare system differences

THYROID FUNCTION

Some human studies have suggested a potential for thyroid effects following fluoride exposure, mostly at high levels (SCHER 2011). The potential effect of fluoride on thyroid function has been raised due to fluoride uptake by the thyroid (McDonagh et al 2000). The McDonagh et al (2000) and NHMRC (2007a) systematic reviews did not include any studies that reported on thyroid function as an outcome.

Literature Search Results

The literature search identified two low quality studies—one cross-sectional study (Xiang et al 2009) and one ecological study (Singh et al 2014)—with thyroid function as an outcome. One additional low quality ecological study (Kutlucan et al 2013) measured thyroid volume as an outcome. All of the studies were conducted in countries which have areas with naturally-occurring fluoride levels much higher than that used in Australia water fluoridation and two of the studies (Xiang et al 2009; Kutlucan et al 2013) used a comparator level of fluoride below the lower level for CWF. The three studies (Xiang et al 2009; Kutlucan et al 2013; Singh et al 2014) had one comparator greater than 1.5 ppm and the other below 1.5 ppm and so were considered to be partially applicable comparisons.

Partially Applicable Comparisons

The single cross-sectional study by Xiang et al (2009) compared thyroid function in 170 children aged 8 to 13 years old from two villages, one in a severe endemic fluorosis area and the other in a non-endemic area. The mean water fluoride levels were 2.36 ppm and 0.36 ppm respectively. There was no statistically significant difference in the serum total triiodothyronine (TT3) and total thyroxine (TT4) levels between the two groups; however, there was a significant difference in serum thyroid-stimulating hormone (TSH) ($p < 0.001$). The authors concluded that high fluoride exposure can cause functional abnormalities of the thyroid.

Singh et al (2014) compared the thyroid function of 10 school children aged 8 to 15 years from one village with a drinking water fluoride level of 1.0 ppm with 60 children from five other villages with higher water fluoride levels (mean 2.7 ppm). Of the 60 children in the high fluoride group, half were specifically selected with dental fluorosis and the other half without. There were no statistically significant differences in any of the thyroid function tests between each group and the test results were all within the reference range. The authors did however report the difference in TSH to be significant even with a borderline p -value ($p = 0.057$).

Kutlucan et al (2013) measured the thyroid gland volume in 559 school children aged between 10 and 15 years old from three areas in Isparta, Turkey. Two areas had naturally occurring water fluoride levels of 4.6 ppm and 2.8 ppm respectively compared to 0.19 ppm in the third. Thyroid volume was measured by ultrasound. The authors found no significant difference between the combined mean thyroid volume from the two 'high' fluoride areas compared to the mean thyroid volume in the 'low' fluoride area ($p = 0.624$). There was a significant difference in the 'Echobody index', a measure of thyroid volume adjusted for body surface area; however, the clinical significance of this is unclear and this result may be a result of the significant differences in weight and height between the two groups. Stratification by age showed that a significant difference in the Echobody Index only in 13 to 14-year-olds.

The results from all studies are presented in Table 134. The GRADE assessments for thyroid function and thyroid volume are presented in Table 136 and Table 137, respectively.

Table 134 Thyroid Function – Results for Partially Applicable Comparisons

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results -		Sig	
Xiang 2009 Cross-sectional Low	Children (8–13 years) recruited from two villages in China	NOF mean 2.36 ± 0.70 ppm (0.62–4.00)	NOF mean 0.36 ± 0.10 ppm (0.23–0.77)	TT3 (ng/mL) ¹	Student's t-test	1.47 ± 0.28	1.47 ± 0.33	p=0.394	
				TT4 (µg/dL) ¹		-	9.67 ± 1.76	9.22 ± 2.54	p=0.269
				TSH (µIU/mL) ¹		-	3.88 ± 2.15	2.54 ± 2.07	p<0.001
Singh 2014 Ecological Low	Children (8–15 years) recruited from schools in India	NOF mean 2.7 ppm (1.6–5.5)	NOF mean 1.0 ppm (0.98–1.0)	FT3 (pg/mL) ²	Student's t-test	3.06 ± 1.10	2.50 ± 0.71	p=0.117	
				FT4 (ng/dL) ²		-	1.20 ± 0.22	1.18 ± 0.22	p=0.796
				TSH (µIU/mL) ²		-	3.71 ± 1.94	2.50 ± 0.75	p=0.057
Kutlucan 2013 Ecological Low	Children (10–15 years) recruited from schools in Turkey	NOF 4.6 ppm and 2.8 ppm ³	NOF 0.19 ppm	Total thyroid volume (ml) ⁴	Student's t-test	8.60 ± 3.11	8.73 ± 2.75	p=0.624	
				Echobody Index (ml/m ²)		-	6.94 ± 2.14	6.48 ± 1.53	p=0.003

Abbreviations: NOF = naturally occurring fluoride; TT3 = total triiodothyronine; TT4 = total thyroxine; FT3 = free total triiodothyronine; FT4 = free thyroxine; TSH = thyroid-stimulating hormone; ppm = parts per million

¹ Measured with the BioCheck Test Kit from Hainan Huamei Medicine Co. Ltd

² Measured by Immuno Chemiluminiscence Microparticle Assay with the Bayer Centaur Autoanalyzer

³ Two areas in one city

⁴ Measured by ultrasound

Table 135 Reference Ranges for Thyroid Function Tests (The Royal College of Pathologists of Australasia)

Test	Range
TSH	0.4–4.0 mU/L
FT4	10–25 pmol/L
FT3	4.0–8.0 pmol/L

Discussion

All three studies have significant methodological shortcomings and were assessed as being of low quality. Recruitment of participants was poorly reported, if at all, and two studies (Xiang et al 2009; Singh et al 2014) did not report participant characteristics, so it is not possible to ascertain how comparable the groups were within the studies. In addition, Singh et al (2014) selected half of the 60 children in the high fluoride group were specifically selected because they had dental fluorosis therefore conflating fluoride exposure with fluorosis—it's results should be treated with extreme caution. The two groups in Kutlucan et al (2003) had significant differences in body weight and height which likely introduced bias. None of the studies measured known confounders for thyroid function. Even when statistically significant differences were found in TSH levels, all the TSH levels in all the studies were within the reference ranges (see Table 135) for the specific age groups, so there appears to be no clinical relevance to these findings. When looking at the body of evidence from these three studies, the evidence for water fluoridation being associated with thyroid dysfunction is insufficient.

Evidence statement

The evidence evaluation identified two studies (one ecological study and one cross-sectional) which provided insufficient evidence to draw a conclusion about any association between thyroid function and water fluoridation at current Australian levels.

Table 136 Thyroid Function - GRADE Report for Partially Applicable Comparisons

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (N)	Comparator (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Not serious ³	Serious ⁴	Not serious	None	142	98	All thyroid function tests within reference range	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ One ecological and one cross-sectional study

² Subject recruitment methods poorly reported, no confounding factors measured, participant characteristics very poorly reported

³ All thyroid function results within reference range

⁴ Both studies have one fluoride comparator >1.5 ppm, and differences in socioeconomic & healthcare system factors likely to be very different to Australian context

Table 137 Thyroid Volume - GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (N)	Comparator (N)	Effect	Quality	Importance
1	Observational studies ¹	Very serious ²	Serious ³	Serious ⁴	Not serious	None	261	298	Thyroid volumes are inconsistent using two measures of thyroid volume	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Subject recruitment methods poorly reported, no confounding factors measured, participant characteristics very poorly reported

³ Different results using two measures

⁴ Upper fluoride comparator level >1.5 ppm; socioeconomic & healthcare system factors likely to be very different to Australian context

KIDNEY STONES

Kidney stones are an important outcome to explore because fluoride is mainly excreted via the kidney, which is consequently exposed to relatively high concentrations of fluoride.

The McDonagh et al (2000) systematic review of the efficacy and safety of water fluoridation did not include any studies with that had the occurrence of kidney stones as an outcome.

The NHMRC (2007a) systematic review included one cross-sectional study (Level IV evidence) from India of poor quality that had kidney stone prevalence as an outcome (Singh et al 2001). The authors compared the prevalence of kidney stones in an area with endemic skeletal fluorosis (water fluoride level between 3.5 and 4.9 ppm) to a non-endemic area (water fluoride level of 0.5 ppm) and found an increased prevalence of kidney stones in the endemic area: OR = 4.63 (95%CI: 2.07–7.92). It is important to note that this study involved fluoride levels that would not be observed in Australia, the increased risk was for people with clear signs and symptoms of skeletal fluorosis, and that the odds ratio is not adjusted for any confounding factors. The review concluded that insufficient evidence to reach a conclusion on kidney stones.

Literature Search Results

The present literature search identified one ecological study (Level IV evidence) of acceptable quality with kidney stone incidence as an outcome (Public Health England 2014).

Highly Applicable Comparison

This was a report from Public Health England (2014) which sought to monitor any effect of water fluoridation schemes on the health of the people living in the areas covered by these schemes. Data for emergency admissions for kidney stones between April 2007 and March 2013 was extracted from Hospital Episode Statistics and matched to both demographic and water fluoridation scheme location data (sourced from various national databases). The adjusted incidence rate was –7.9% lower (95%CI: –9.6, –6.2) in areas with water fluoridation schemes compared to areas without. The authors commented that there were limitations to any conclusion that could be made from these results due to the possibility of residual confounding such as water hardness, misclassification and migration bias. Overall, they concluded that this finding was of interest but did not prove a causal relationship; it simply raised the possibility of a relationship.

The results of the study and the GRADE assessment are summarised in Table 138 and Table 139, respectively.

Discussion

This single study is highly applicable to the Australian situation as the fluoride levels are comparable. It was assessed as being of acceptable quality and provides limited evidence that CWF is not associated with an increase in the incidence of kidney stones as measured by acute admissions to hospital.

Evidence statement

The evidence evaluation identified a single ecological study which provided insufficient evidence to draw a conclusion about any association between kidney stones and water fluoridation at current Australian levels.

Table 138 Kidney Stones – Results for Highly Applicable Comparison

Study Design Quality	Population	Exposures -		Outcome	Analysis	Results -		Effect Estimate (95%CI)	Sig
Public Health England 2014 Ecological Acceptable	Residents in areas with and without CWF in England	Areas with CWF (0.8–1.0 ppm)	Areas without CWF ¹	Incidence of emergency admissions for kidney stones per 100,000 pyar ²	Unadjusted univariate model	48.9 (18,579 / 37,971,918 person-years at risk)	51.6 (141,963 / 274,884,530 person-years at risk)	Difference in incidence: -5.3% (-7.1, -3.5)	p<0.001
					Adjusted multivariate model ³	NR	NR	Difference in incidence: -8.4% (-10.0, -6.7)	p<0.001
					Adjusted multivariate model ⁴	NR	NR	Difference in incidence: -7.9% (-9.6, -6.2)	p<0.001

Note: Effect estimate in Public Health England (2014) is expressed as percentage difference in incidence, e.g. 8.2% (-9.3, 29) equates to an incidence rate ratio of 1.082 (0.907, 1.290)

Abbreviations: CWF = community water fluoridation; pyar = person-years at risk; 95%CI = 95% confidence interval; NR = not reported

Abbreviations: ppm = parts per million

¹ Areas classified as naturally fluoridated to 1 ppm were excluded

² All emergency admissions for kidney stones in England from 2007 to 2013 registered in Hospital Episode Statistics

³ Adjusted for age, gender, & deprivation

⁴ Adjusted for age, gender, deprivation, & ethnicity

Table 139 Kidney Stones - GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients	Impact	Quality	Importance
1	Observational studies ¹	Serious ²	Not serious ³	Not serious ⁴	Not serious ⁵	None	312,856,448 person-years at risk	Incidence of emergency admissions for kidney stones was 7.9% lower (95%CI: 9.6% lower to 6.2% lower) in the areas with CWF	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: IRR = incidence rate ratio

¹ Ecological study

² Acceptable quality; population-based; several known confounders not considered

³ Not applicable; one study

⁴ Population, and comparisons applicable to Australian water fluoridation

⁵ Confidence intervals within an effect size of ±0.5

CHRONIC KIDNEY DISEASE

Chronic Kidney Disease (CKD) is an important outcome to explore as most ingested fluoride is excreted via the kidney, which is consequently exposed to relatively high concentrations of fluoride. With the high prevalence of CKD in Australia, it is important to consider any potential effects of water fluoridation on kidney function. Moreover CKD is frequently asymptomatic, and many individuals will have significant reduction of kidney function but no overt signs or symptoms, and hence will be unaware they have the condition (Ludlow et al 2007). CKD was not included as an outcome in either the NHMRC (2007a) or the McDonagh et al (2000) systematic review of the efficacy and safety of water fluoridation.

Of relevance to the Australian context is a literature review by Ludlow et al (2007) that summarised the literature pertaining to the health effects of CWF on people with CKD. There was no evidence found that drinking water fluoridated at the level used in Australia increases the risk of CKD, or that drinking water fluoridated at the level used in Australia poses any health risks to people with CKD. There was limited evidence that people with stage 4 or 5 CKD who ingest substances with high concentrations of fluoride may be at risk of fluorosis, and therefore that the avoidance of fluoride-rich substances and monitoring of fluoride intake in people with stage 4 or 5 CKD would be prudent, as well as regular investigations for possible signs of fluorosis. Moreover, fluoride levels in the final feed water to dialysis machines must comply with established water quality guidelines.

Literature Search Results

The literature search identified one ecological study of low quality that evaluated the relationship between naturally occurring fluoride in drinking water and the prevalence of CKD of unknown aetiology in 5,685 adults from three villages in northern Sri Lanka (Chandrajith et al 2011).

Highly Applicable Comparison

The mean fluoride levels in the drinking water from the three villages were 0.74 ppm, 1.02 ppm, and 1.03 ppm respectively (ranges are presented in Table 140). These comparisons are all within the 0.4 ppm to 1.5 ppm range and are therefore considered to be highly applicable. The prevalence of CKD of unknown aetiology was based on population studies (citations not provided) that used proteinuria as an indicator.

The results of the study are presented in Table 140. The results were reported as crude proportions: 84% of those with CKD in the village with 1.02 ppm fluoride level had CKD of no known aetiology; none of the residents with CKD in the 1.03 ppm village had CKD of unknown aetiology; whereas, 96% of the villagers in the 0.74 ppm village with CKD had CKD of unknown aetiology. This was a poorly reported and conducted study. The authors concluded that the results demonstrated that fluoride levels in the drinking water could not be clearly and directly related to the aetiology of CKD. The GRADE assessment is presented in Table 141.

Discussion

No conclusions can be clearly drawn from this study due to its significant limitations. There is no way of evaluating the validity of the prevalence of chronic kidney disease as no information was given to how this was estimated. Moreover, there is no information about the populations with respect to demographics, no confounding factors were considered, and there was no statistical analysis.

Evidence statement

The evidence evaluation identified a single ecological study which provided insufficient evidence to draw a conclusion about any association between chronic kidney disease and water fluoridation at current Australian levels.

Table 140 CKD – Results for Highly Applicable Comparisons

Study Design Quality	Population	Sample size	Exposures mean (range)	Results	
				Crude CKD prevalence ¹	% of CKDua
Chandrajith 2011 Ecological Low	Adults (>18 years) in 3 north central Sri Lankan villages	4,107	NOF 1.02 ppm (0.52–4.90)	3.7%	84%
-	-	233	NOF 1.03 ppm (NR–1.68)	3.2%	0%
-	-	1,345	NOF 0.74 ppm (NR– 2.14)	3.9%	96%

Abbreviations: NOF = naturally occurring fluoride; CKD = chronic kidney disease; CKDua = chronic kidney disease of unknown aetiology; NR = not reported; ppm = parts per million

¹Prevalence was based on other population studies (citations NR)

Table 141 CKD – GRADE Report for Highly Applicable Comparisons

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality	Importance
1	Observational studies ¹	Very serious ²	Not serious ³	Serious ⁴	Very serious ⁵	None	5,685	Proportion of participants with CKD that was of unknown aetiology in the three villages was 96%, 0%, and 84%	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

¹ Ecological study

² Characteristics of populations not reported; measurement of outcome not reported; no confounding factors considered; no statistical analysis

³ Not applicable; one study

⁴ Fluoride comparisons applicable to Australian context; socioeconomic and healthcare system variables likely to be very different to the Australian context

⁵ No variance data reported

GASTRIC DISCOMFORT

Gastric discomfort was not included as an outcome in either the NHMRC (2007a) or McDonagh et al (2000) systematic reviews. There does not appear to be any plausible biological rationale for an association between fluoride exposure and gastric discomfort.

Literature Search Results

The literature search identified two low quality ecological (Level IV evidence) studies conducted in India that examined the relationship between reported rates of gastric discomfort and exposure to fluoride (Ranjan & Yasmin 2012; Sharma et al 2009a). Both studies included comparisons that were both partially and highly applicable to the Australian context. Results for these studies are reported in Table 142 and Table 143, respectively.

Highly Applicable Comparisons

Ranjan & Yasmin (2012) used a health survey to determine the prevalence of a variety of self-reported outcomes including gastro-intestinal problems, headache and insomnia. Thirty-one villages in 6 blocks in Gaya district of Bihar were included in the study. Twenty samples of drinking water were collected from each block and analysed for fluoride and other physiochemical parameters.

Results were presented for each of the six blocks of villages separately. To improve the relevance of the results to the Australian context, the groups of villages were re-categorised by the evidence reviewers into those with mean fluoride levels of <0.4 ppm, those between 0.4 ppm and 1.5 ppm and those >1.5 ppm. The numbers of self-reported cases of gastric discomfort were totalled for each of these fluoride categories.

For all participants, there was a similar prevalence of self-reported gastric discomfort in areas with a fluoride level of <0.4 ppm (23.4%) and 0.4–1.5 ppm (23.3%). However when considering adult men and women separately, the prevalence of gastric discomfort was higher in the 0.4–1.5 ppm areas. This contrasts with children, where a high prevalence of gastric discomfort (48.1%) was reported in the <0.4 ppm fluoride villages.

Sharma et al (2009a) used a health survey to determine whether participants were experiencing stomach ache, nausea, diarrhoea, constipation or feeling bloated in at least ten villages from each of the three fluoride exposure groups (<1.0 ppm, 1.0–1.5 ppm, >1.5 ppm). There was a higher prevalence of gastric discomfort reported by adults in the 1.0–1.5 ppm villages compared to the <1.0 ppm villages. No children reported gastric discomfort in either the 1.0–1.5 ppm or the <1.0 ppm villages.

The GRADE assessment is presented in Table 144.

Partially Applicable Comparisons

Ranjan & Yasmin (2012) reported that the prevalence of gastric discomfort increased to around 40% in the villages with >1.5 ppm fluoride levels in adult men and women. The prevalence was similar between the >1.5 ppm and <0.4 ppm areas in children (51% and 48% respectively).

In Sharma et al (2009a) both adults and children reported higher levels of gastric discomfort (88.8% and 17.0%, respectively) in villages with fluoride levels >1.5 ppm.

The GRADE assessment is presented in Table 145.

Table 142 Gastric Discomfort – Results for Highly and Partially Applicable Comparisons

Study Design Quality	Population	Outcome	Results			
			NOF <0.4 ppm	NOF 0.4–1.5 ppm	NOF >1.5 ppm	
Ranjan 2012 Ecological Low	Residents in 31 villages in Bihar state, India	Prevalence of gastric discomfort ¹	All participants	98/418 (23.4%)	387/1664 (23.3%)	278/650 (42.8%)
-	-	-	Male adults	32/174 (18.4%)	165/684 (24.1%)	110/272 (40.4%)
-	-	-	Female adults	28/165 (17.0%)	165/685 (24.1%)	110/264 (41.7%)
-	-	-	Children	38/79 (48.1%)	57/295 (19.3%)	58/114 (50.9%)

Abbreviations: NOF = naturally occurring fluoride; ppm = parts per million

¹ Determined using a health survey

Table 143 Gastric Discomfort – Results for Highly and Partially Applicable Comparisons

Study Design Quality	Population	Outcome	Results			
			NOF <1.0 ppm	NOF 1.0–1.5 ppm	NOF >1.5 ppm	
Sharma 2009a Ecological Low	Adults and children in 29 villages in India	Prevalence of gastric discomfort ¹	Adults	110/458 (24.0%)	155/489 (31.7%)	469/528 (88.8%)
-	-	-	Children	0/360 (0.0%)	0/375 (0.0%)	68/400 (17.0%)

NOF = naturally occurring fluoride; ppm = parts per million

¹ Determined using a health survey

Discussion

Ranjan & Yasmin (2012) lacked any form of statistical analysis assessing differences in the distribution of self-reported gastric discomfort between villages. There is a trend towards a greater frequency of self-reported gastric discomfort in the higher fluoride group; however, there may be important confounding variables that have not been adjusted for in this raw data.

In a similar manner, the results in Sharma et al (2009a) show a trend towards a higher frequency of reported gastric discomfort in the villages with higher naturally occurring fluoride. However, with no statistical analyses or adjustment for confounding factors, the statistical significance of this trend is unclear.

Given the concerns about the accuracy of the outcome data capture methods and lack of statistical analyses in both of these studies there is little that can be concluded in terms of the relationship between exposure to fluoride and gastric discomfort.

Evidence statement

The evidence evaluation identified two ecological studies which provided insufficient evidence to draw a conclusion about any association between gastric discomfort and water fluoridation at current Australian levels.

Table 144 Gastric Discomfort – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Very serious ³	Serious ⁴	Very serious ⁵	None	3,764 (in the villages with <1.5 ppm fluoride levels)	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Two ecological studies

² Poor outcome capture methods; no statistical analysis; no confounding factors measured

³ Inconsistent results within studies between adults and children and between studies for children

⁴ Socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data reported

Table 145 Gastric Discomfort – GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Very serious ³	Serious ⁴	Very serious ⁵	None	2,814 (in the villages with >1.5 ppm and lowest fluoride levels)	Higher prevalence of complaints of gastric discomfort in >1.5 ppm fluoride exposed group	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Two ecological studies

² Poor outcome capture methods; no statistical analysis; no confounding factors measured

³ Inconsistent results within studies between adults and children and between studies for children

⁴ Fluoride levels and socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data reported

HEADACHE

Headache was not included as an outcome in either the NHMRC (2007a) or McDonagh et al (2000) systematic reviews of water fluoridation. There does not appear to be any plausible biological rationale for an association between fluoride exposure and headache.

Literature Search Results

The literature search identified two low quality ecological (Level IV evidence) studies that included headache in their assessment of the effects of fluoride exposure (Ranjan & Yasmin 2012; Sharma et al 2009b). Both studies included highly and partially applicable comparisons.

Highly and Partially Applicable Comparisons

As previously reported, Ranjan & Yasmin (2012) used a health survey to determine the incidence of a variety of self-reported outcomes including joint pain, gastro-intestinal problems, headache and insomnia. 31 villages in 6 blocks in Gaya district of Bihar were included in the study. Twenty samples of drinking water were collected from each block and analysed for fluoride and other physiochemical parameters.

Results were presented for each of the six blocks of villages separately. To improve the relevance of the results to the Australian context, the groups of villages were re-categorised by the evidence reviewers based on mean water fluoride concentration into those with fluoride levels of <0.4 ppm, those between 0.4 ppm and 1.5 ppm and those >1.5 ppm. The numbers of self-reported cases of headache were totalled for each of these fluoride categories. The results from this study are presented in Table 146.

Sharma et al (2009b) conducted a health survey of 20 villages in Sanganer Tehsil, India. The survey reported the prevalence of headache categorised by water fluoride level (<1 ppm, 1.0–1.5 ppm and >1.5 ppm). Results were stratified by gender and age, but no statistical analysis comparing the distribution of neurological manifestations was performed. The results from this study are presented in Table 146

Both studies reported a higher prevalence of headache in all population groups for villages with water fluoride levels >1.5 ppm.

The GRADE assessment for the highly applicable comparisons is presented in Table 147 and for the partially applicable comparisons in Table 148.

Discussion

No statistical analysis of the distribution of reported headaches was performed in either study; however, there is a consistent trend towards fewer headaches among participants in villages with lower fluoride exposure, comparable to Australian levels. However, due to the low quality of the studies, there is insufficient evidence to make any conclusions.

Evidence statement

The evidence evaluation identified two ecological studies which provided insufficient evidence to draw a conclusion about any association between headache and water fluoridation at current Australian levels.

Table 146 Headache – Results for Highly and Partially Applicable Comparison

Study Design Quality	Population	Outcome	Analysis	Results			
				NOF <0.4 ppm	NOF 0.4–1.5 ppm	NOF >1.5 ppm	
Ranjan 2012 Ecological	Adults and children in 31 villages in India	Prevalence of headache ¹	None	Male adults	10/174 (5.7%)	71/684 (10.4%)	72/272 (26.5%)
Low	-	-	-	Female adults	21/165 (12.7%)	99/685 (14.5%)	72/264 (27.3%)
-	-	-	-	Children	7/79 (8.9%)	7/295 (2.4%)	18/114 (15.8%)
Sharma 2009b Ecological	Adults and children in 20 villages in India	Prevalence of headache ¹	None	Adults	8/513 (1.6%)	12/477 (2.5%)	179/566 (31.6%)
Low	-	-	-	Children	0/372 (0.0%)	0/355 (0.0%)	47/418 (11.2%)

Abbreviations: NOF = naturally occurring fluoride; ppm = parts per million

¹ Determined using a health survey

Table 147 Headache – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Very serious ³	Serious ⁴	Very serious ⁵	None	3,283 (in the villages with <1.5 ppm fluoride levels)	Prevalence was higher in the 0.4–1.5 ppm area for adults but not for children	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Two ecological studies

² Poor outcome capture methods; no statistical analysis; no confounding factors measured

³ Inconsistent results within studies between adults and children and between studies

⁴ Socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data

Table 148 Headache – GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Very serious ³	Serious ⁴	Very serious ⁵	None	2,937 (in the villages with >1.5 ppm and lowest fluoride levels)	Higher prevalence in >1.5 ppm fluoride group	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Two ecological studies

² Poor outcome capture methods; no statistical analysis; no confounding factors measured

³ Inconsistent results within studies between adults and children and between studies for children

⁴ Socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data

INSOMNIA

Insomnia was not included as an outcome in either the NHMRC (2007a) or McDonagh et al (2000) systematic reviews on water fluoridation. There does not appear to be any plausible biological rationale for an association between fluoride exposure and insomnia.

Literature Search Results

The literature review identified two low quality, ecological (Level IV evidence) studies conducted in India that captured self-reported insomnia using a health survey (Ranjan & Yasmin 2012 and Sharma et al 2009b). Both studies included highly and partially applicable comparisons.

Highly and Partially Applicable Comparisons

As previously reported, Ranjan & Yasmin (2012) used a health survey to determine the incidence of a variety of self-reported outcomes including gastro-intestinal problems, headache and insomnia. 31 villages in 6 blocks in Gaya district of Bihar were included in the study. Twenty samples of drinking water were collected from each block and analysed for fluoride and other physiochemical parameters.

Results were presented for each of the six blocks of villages separately. To improve the relevance of the results to the Australian context, the groups of villages were re-categorised by the evidence reviewers based on mean water fluoride concentration into those with fluoride levels of <0.4 ppm, those between 0.4 ppm and 1.5 ppm and those >1.5 ppm. The numbers of self-reported cases of headache were totalled for each of these fluoride categories.

Sharma et al (2009b) conducted a health survey of 20 villages in Sanganer Tehsil, India. The survey reported the prevalence of insomnia categorised by water fluoride level (<1 ppm, 1.0–1.5 ppm and >1.5 ppm). Results were stratified by gender and age, but no statistical analysis comparing the distribution of neurological manifestations was performed.

The results of these studies and the GRADE assessment are presented in Table 149. Both studies reported a higher prevalence of insomnia in all population groups for villages with water fluoride levels >1.5 ppm, although in Ranjan & Yasmin (2012) this effect was only observed in adults.

The GRADE assessment for the highly applicable comparisons is presented in Table 150 and for the partially applicable comparisons in Table 151.

Discussion

No statistical analyses were performed; however, there is a trend towards fewer cases of insomnia in villages with lower exposures to fluoride, comparable to Australian levels. The low methodological quality of the two included studies provides insufficient evidence to form a robust conclusion on the relationship between insomnia and exposure to water fluoride.

Evidence statement

The evidence evaluation identified two ecological studies which provided insufficient evidence to draw a conclusion about any association between self-reported insomnia and water fluoridation at current Australian levels.

Table 149 Insomnia – Results for Highly and Partially Applicable Comparisons

Study Design Quality	Population	Exposures			Outcome	Subpopulation	Results		
Ranjan 2012 Ecological Low	Adults and children in 31 villages in India	NOF <0.4 ppm	NOF 0.4–1.5 ppm	NOF >1.5 ppm	Prevalence of insomnia ¹	Adult males	0/174 (0.0%)	28/684 (4.1%)	38/272 (14.0%)
		-	-	-		Adult females	8/165 (4.8%)	59/169 (8.6%)	36/264 (13.6%)
		-	-	-		Children	0/79 (0.0%)	0/295 (0.0%)	0/114 (0.0%)
Sharma 2009b Ecological Low	Adults and children in 20 villages in India	NOF <1.0 ppm	NOF 1.0–1.5 ppm	NOF >1.5 ppm	Prevalence of insomnia ¹	Adults	6/513 (1.2%)	7/477 (1.5%)	151/566 (26.7%)
		-	-	-		Children	0/372 (0.0%)	0/355 (0.0%)	47/418 (11.2%)

Abbreviations: NOF = naturally occurring fluoride; ppm = parts per million

¹ Determined using a health survey

Table 150 Insomnia – GRADE Report for Highly Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Very serious ³	Serious ⁴	Very serious ⁵	None	3,283 (in the villages with <1.5 ppm fluoride levels)	Prevalence was higher in the 0.4–1.5 ppm area for adults but not for children	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Two ecological studies

² Poor outcome capture methods; no statistical analysis; no confounding factors measured

³ Inconsistent results within studies between adults and children and between studies

⁴ Socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data

Table 151 Insomnia – GRADE Report for Partially Applicable Comparison

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients (N)	Effect	Quality	Importance
2	Observational studies ¹	Very serious ²	Very serious ³	Serious ⁴	Very serious ⁵	None	2,937 (in the villages with >1.5 ppm and lowest fluoride levels)	Higher prevalence in >1.5 ppm fluoride group	⊕○○○	IMPORTANT

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

¹ Ecological studies

² Poor outcome capture methods; no statistical analysis; no confounding factors measured

³ Inconsistent results within studies between adults and children and between studies

⁴ Socioeconomic & healthcare system factors likely to be very different to Australian context

⁵ No variance data

OUTCOMES IDENTIFIED IN PREVIOUS REVIEW FOR WHICH NO ADDITIONAL STUDIES WERE IDENTIFIED

There were a number of outcomes included in both the McDonagh et al (2000) and NHMRC (2007a) reviews for which no additional evidence was identified in the current review. There were 14 outcomes in McDonagh et al (2000) and they are summarised in Table 152.

Table 152 Outcomes from McDonagh et al (2000) for which there are no additional studies

Outcome	Summary of evidence
Goitre	McDonagh et al (2000) included four studies that had goitre as an outcome. One study (Lin et al 1991) found an association between the combination of low iodine and high fluoride and combined goitre and intellectual disability, but could not separate individual effects. The other studies found no association between fluoride and goitre. All of the studies had methodological limitations and the authors concluded there was insufficient evidence to support an association between fluoride and goitre.
Fractures other than hip ²⁰	There was no definite pattern of association for any of the fractures. A total of 30 analyses were conducted in 12 studies. Overall, 14 analyses found a positive association (more fractures with water fluoridation), with one being statistically significant. Thirteen analyses found a negative association (fewer fractures with water fluoridation), with one being statistically significant, and two not reporting variance data. Three analyses found no association.
Otosclerosis	Two studies found a beneficial effect of fluoridation although no statistical test of significance was conducted.
Slipped epiphysis	One study reported conflicting findings for men (increased risk) and women (decreased risk) but neither was statistically significant at the 5% level.
Thyroid cancer	Two studies found no association between water fluoridation and the incidence thyroid cancer
Alzheimer's disease/Impaired mental functioning	One study found a statistically significant increased incidence of Alzheimer's disease with water fluoridation and a statistically significant decreased incidence of impaired mental functioning.
Primary degenerative dementia	One study found a decreased risk of primary degenerative dementia associated with water fluoridation but did not report any variance data.
Cognitive impairment	One study found that exposure to water fluoridation was associated with a decreased risk of cognitive impairment but did not report any variance data.
Anaemia during pregnancy	A single study found a non-significant increase in the rate of anaemia during pregnancy associated with water fluoridation
Congenital malformations	One study found a statistically significant reduced risk of congenital malformations in one set of data and a non-statistically significant increase in another. Another study found no association between water fluoridation and the risk of congenital malformations.
Infant mortality	Three studies found an increased risk of infant mortality associated with water fluoridation but no measure of the statistical significance of these findings were reported, "so it is difficult to draw conclusions from these results."
Sudden Infant Death Syndrome (SIDS)	One study found a non-significant increase in the odds of SIDS associated with water fluoridation.
Age at menarche	A single study found no difference in the mean ages of menarche in young women exposed to water fluoridation and those not exposed.
Other	Three other outcomes were identified in the McDonagh (2000) review but were not included in the main analysis. The outcomes were birth rates, childhood behaviour problems, and fetal and perinatal mortality.

The authors of McDonagh et al (2000) noted that interpreting the results for many outcomes was very difficult because of the small number of studies, the study designs, and the low study quality. A major weakness was the lack of control for possible confounding factors. Their overall conclusion was that these studies provided insufficient evidence on any particular outcome to reach any conclusions.

²⁰ Includes wrist, vertebral, osteoporotic, humerus, distal forearm, ankle, 'all', non-hip, non-spine, and 'other'

There were five outcomes in the NHMRC (2007a) review for which no additional studies were identified in the current review. These outcomes and the findings are summarised in Table 153. Three systematic reviews (Jones et al, 1999; McDonagh et al, 2000; Demos et al, 2001) were included that looked at the effect of water fluoridation on fracture risk. As noted before, the McDonagh (2000) review concluded that there was no consistent indication of either a harmful or protective effect of water fluoridation on fracture risk. The authors of Jones et al (1999) concluded that water fluoridation at the levels aimed at preventing dental caries, and possibly at somewhat higher naturally occurring levels, appeared to have little effect on fracture risk, either protective or deleterious. Demos et al (2001) concluded that the body of epidemiological evidence suggests either no association or a slight beneficial effect of water fluoridation on bone strength, bone density, and fracture risk. Results of subsequent original studies identified in the NHMRC 2007 review supported these conclusions, and also suggested that optimal fluoridation levels of 1 ppm may result in a lower risk of fracture vs excessively high levels (well beyond those experienced in Australia). One study also indicated optimal fluoridation levels may lower overall fracture risk vs no fluoridation (the latter was not the case when hip fractures were considered in isolation).

Table 153 Outcomes from NHMRC (2007a) for which there are no additional studies

Outcome	Summary of evidence
'Unexpected fractures'	One study found a greater risk of "unexpected" fracture in participants exposed to levels of fluoride between 1.5 and 8.5 ppm compared to participants exposed to <1.5 ppm fluoride. They also found no significant difference in fracture risk for those exposed to 8.50–11.99 ppm and 12.00–16.00 ppm fluoride in water compared to <1.5 ppm.
Osteoporotic or non-osteoporotic fractures	One study found no difference in the risk of osteoporotic or non-osteoporotic fractures between participants exposed to 4 ppm fluoride in drinking water and 1 ppm fluoride.
Overall fractures	One study found an increased odds of fracture in those exposed to 4.32–7.97 ppm and 0.25–0.34 ppm fluoride in water compared to those exposed to 1.00–1.06 ppm. All other exposures (0.58–0.73 ppm, 1.45–2.19 ppm, and 2.62–3.56 ppm) were not associated with a statistically significant difference in odds of any fracture when compared to 1.00–1.06 ppm fluoride. The authors commented that these results should be interpreted cautiously due to many potential confounding factors.
Still birth and congenital abnormalities	One study found no significant difference in the odds of still births, all trisomies, Down syndrome, or neural tube defects between participants residing in areas with water fluoridation and without. They did find that the odds of clefts were significantly less in areas with water fluoridation.
Coronary heart disease mortality	One study found that the risk coronary heart disease mortality was statistically significantly reduced in areas with water fluoride levels of 0.00–0.064 ppm compared to areas with 0.064–2.15 ppm.

Abbreviations: ppm = parts per million

DISCUSSION

SUMMARY OF THE REVIEW FINDINGS

Findings from systematic review of caries and other dental outcomes

An independent review was undertaken to identify evidence of the effect of water fluoridation on dental caries and other dental effects. The review aimed to update the evidence presented in the earlier NHMRC review (NHMRC 2007a). It consisted of two parts: an overview of existing reviews published after the NHMRC review and a systematic review of primary studies about the effect of water on dental caries not identified in the overview. The systematic review identified 3 relevant systematic reviews and 30 primary studies that reported on dental outcomes. The results for dental caries and dental fluorosis are reported separately from other outcomes.

Dental caries in deciduous teeth

Studies reporting on dental caries have measured caries by using the number of decayed, missing and filled deciduous or permanent teeth.

Studies reporting on dental caries in deciduous teeth measured caries by using the number of decayed, missing and filled deciduous teeth per individual (dmft) or the number of decayed, missing and filled tooth surfaces (dmfs). The results are reported as mean dmft/s, proportion individuals caries-free (%dmft/s=0) or prevalence of caries experience (%dmft/s>0).

The quality of the included reviews was mixed with one review scoring high on the AMSTAR tool and the other scoring low. The primary studies included in one review were all of low quality—the other review did not undertake an assessment of methodological quality.

Most of the primary studies identified in the systematic review of recent primary studies were assessed as being of acceptable quality with moderate risk of bias, representative included populations, and measurement of known confounding factors. Those studies assessed as low quality generally had high risk of bias due to poor or unclear selection methods.

The review identified consistent evidence that water fluoridation was associated with a reduced mean dmft/s and prevalence of caries in deciduous teeth and also an increase in the proportion of individuals caries-free.

Table 154 Summary of findings for dental caries in deciduous teeth

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in deciduous teeth assessed using dmft	The pooled effect estimate was a reduction of 1.81 (95%CI: 1.31 to 2.31) in dmft for children aged 3–12 years. This indicates a reduction in dmft of 35% in the water fluoridation groups over and above that for the control groups.	44,268 (9 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
-	Median caries reduction of 44% (range 29% to 68%) in children aged 3–12 years	NR (21 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
-	Significant reduction in mean dmft in children (5–10 years) with exposure to community water fluoridation. Mean dmft decreased by 0.37 (95%CI: 0.48, 0.2) in one study.	>40,000 (3 observational studies)	⊕⊕○○	Includes one large study from England using national data and a single study set in Australia with good sample size. Both were of acceptable quality, with adjustment for confounders in a setting of CWF.
Caries in deciduous teeth assessed using dmfs	Median caries reduction of 33% (range: 14%–66%) in 5 to 11-year-olds	NR (21 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
-	Significant reduction in mean dmfs in children (5–11 years) with exposure to community water fluoridation in two studies Significant inverse association between mean dmfs and increasing fluoride levels in two studies	5,546 (4 observational studies)	⊕⊕○○	Two acceptable quality studies set in Australia using national survey data with good sample size and adjustment for confounders in the setting of CWF. Two studies (one low quality and one acceptable quality) in the US and Vietnam of limited applicability to the Australian context.
Proportion of caries-free deciduous teeth assessed using %dmft/s=0	The pooled effect estimate was an increase of 15% (95%CI: 11% to 19%) in the proportion of caries-free infants and children (3–12 years) in areas with water fluoridation. ⁶	39,966 (9 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
-	The proportion of caries-free Indigenous children (5–10 years) was greater with exposure to community water fluoridation (OR=1.27; 95%CI: 0.98–1.63).	NR (1 observational study)	⊕⊕○○	A single acceptable quality study from Australia in the setting of CWF.
Caries prevalence in deciduous teeth assessed using %dmft/s>0	Significant reduction in the prevalence of caries in children (4–11 years) with exposure to community water fluoridation	>4,323 (6 observational studies)	⊕⊕○○	Includes one large study from England using national data and four studies set in Australia with good sample size. All were of acceptable quality, with adjustment for confounders in a setting of CWF.
Prevalence of early childhood caries	Water fluoridation was significantly associated with a reduction in the prevalence of early childhood caries in infants and children aged 36–71 months (OR=0.40; 95%CI: 0.25–0.63)	5,822 (1 observational study)	⊕○○○	A single study of acceptable quality set in South Africa using survey data. Downgraded for indirectness.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; NR = not reported

¹For details of the assessment, please see the individual outcome in the Results section of this report.

Dental caries in permanent teeth

Studies reporting on dental caries in permanent teeth also measured caries by using the number of decayed, missing and filled permanent teeth per individual (DMFT) or the number of decayed, missing and filled tooth surfaces (DMFS). The results are reported as mean DMFT/S, proportion individuals caries-free (%DMFT/S=0) or prevalence of caries experience (%DMFT/S>0).

The quality of the included reviews was mixed with one review scoring high on the AMSTAR tool, one scoring in the middle range and the last scoring low. The primary studies included in one review were all of low quality—the other two reviews did not undertake an assessment of methodological quality.

Most of the primary studies identified in the systematic review of recent primary studies were assessed as being of acceptable quality with moderate risk of bias, representative included populations, and measurement of known confounding factors. Those studies assessed as low quality generally had high risk of bias due to poor or unclear selection methods.

The review identified consistent evidence that water fluoridation was associated with a reduced mean DMFT/S and prevalence of caries in deciduous teeth and also an increase in the proportion of individuals caries-free.

Table 155 Summary of findings for dental caries in permanent teeth

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in permanent teeth assessed using DMFT	The pooled effect estimate was a reduction of 1.16 (95%CI: 0.72 lower to 1.61 lower) in mean DMFT in the areas with water fluoridation for children aged 8–11 years. This indicates a reduction in DMFT of 26% in the water fluoridation groups over and above that for the control groups ⁶ .	78,764 (10 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
-	The median percentage reduction of caries in permanent teeth was 37% (range: 5%–85%) in participants aged 8–51 years.	NR (37 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
-	Significant reduction in mean DMFT in adults (18–65+years) with exposure to fluoridated water	3,080 (4 observational studies)	⊕○○○	One systematic review of reasonable methodological quality downgraded because of no clear reporting of assessment of risk of bias, and serious indirectness and imprecision

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
-	Significant reduction in mean DMFT in adolescents and adults (≥ 11 years) with exposure to community water fluoridation (reduced by 0.19; 95%CI: 0.27 reduction, 0.11 reduction in one study)	>12,700 (7 observational studies)	⊕⊕○○	Five acceptable quality studies set in Australia in the context of CWF. Single large study of acceptable quality from England using a national database with adjustment for confounders in a setting of CWF.
Caries in permanent teeth assessed using DMFS	The median percentage reduction of caries in permanent teeth was 29% (range: 0%–50%) in participants aged 5–35 years.	NR (16 observational studies)	⊕○○○	A single systematic review of very limited methodological quality. Downgraded for unclear risk of bias, indirectness and imprecision.
-	Significant reduction in mean DMFS in children and adolescents (8–14 years) with exposure to community water fluoridation in two studies Significant inverse association between $\geq 75\%$ lifetime exposure to water fluoridation and mean DFS (participants 15+ years) in one study. Non-significant inverse relationship between naturally occurring fluoride levels and mean DMFS (participants 6–17 years) in one study.	12,344 (4 observational studies)	⊕⊕○○	Two studies of acceptable quality set in Australia in the context of CWF. One study set in Vietnam of limited applicability. One regression analysis from Australia.
Caries prevalence (permanent teeth) assessed with %DMFT/S>0	Significant reduction in the prevalence of caries in children, adolescents and adults (6–21 years) with exposure to community water fluoridation	>39,750 (9 observational studies)	⊕⊕○○	Includes a large study of acceptable quality from England using a national database with adjustment for confounders in a setting of CWF. Also six acceptable quality studies from Australia.
Proportion of caries-free children (permanent teeth) assessed with %DMFT/S =0	The pooled effect estimate was an increase of 14% (95%CI: 5% to 23%) in the proportion of caries-free children (8–12 years) in areas with water fluoridation.	53,538 (8 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded twice for high risk of bias and indirectness (due to lack of contemporary evidence). The authors also upgraded twice for a very large effect size, however GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
-	Significant increase in proportion of caries-free Indigenous children and adolescents (6–15 years) for permanent teeth with exposure to water fluoridation in one study (OR=1.30; 95%CI: 1.01–1.68). Non-significant positive association between water fluoridation and proportion of caries-free 12-year-olds in one study.	>97,809 (2 observational studies)	⊕○○○	One acceptable quality study from Australia of Indigenous children set in context of CWF. One acceptable study from Brazil using national data. Downgraded for imprecision.
Incidence of first molar occlusal caries in permanent teeth	Non-significant decrease in the incidence of first molar occlusal caries at age 13 with exposure to water fluoridation (OR=0.32; 95%CI: 0.10–1.02)	93,622 (1 observational study)	⊕○○○	A single study from US of acceptable quality. Downgraded for imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States; NR = not reported

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Dental caries in mixed dentition

There were no reviews that reported on dental caries of mixed dentition. The studies identified in the systematic review of recent primary studies used the number of decayed, missing and filled teeth of both deciduous and permanent teeth as a measure of caries (dmft + DMFT). They were all assessed a being of acceptable quality. Combined measures of caries (dmft + DMFT) in mixed dentition is problematic due to the changing numbers of deciduous and permanent teeth over this stage of life (from 5 years to about 12 years) such that the combined measure does not necessarily reflect true caries experience during this period.

The review identified insufficient evidence to reach a conclusion about any association between water fluoridation and caries in mixed dentition.

Table 156 Summary of findings for dental caries in mixed dentition

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Caries in mixed dentition	Non-significant reduction in caries in one study in infants and children aged 3–12 years Non-significant inverse association between dmft/DMFT and water fluoridation in children aged 6–11 years	4,784 (2 observational studies)	⊕○○○	One study from Australia and another from Canada in the context of CWF. Downgraded for imprecision.
Caries incidence in mixed dentition	Non-significant inverse association between incidence of cavitated and non-cavitated caries in mixed dentition and water fluoridation (aged 3–13 years).	154 (1 observational study)	⊕○○○	A single study from the US using Iowa Fluoride Study data. Downgraded for indirectness and imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Disparities in dental outcomes

These studies used the difference in a caries measure between levels of socioeconomic status and deprivation or Indigenous status to estimate disparities in dental outcomes.

One review was identified that investigated the effect of water fluoridation on disparities in caries levels. This review scored high on the AMSTAR tool. The studies identified in the systematic review of recent primary studies were of mixed quality: two of acceptable quality and two of low quality.

The review identified evidence with mixed results: insufficient evidence that water fluoridation results in a change in disparities in caries levels in deciduous teeth across socioeconomic status; insufficient evidence that water fluoridation reduces disparities in caries levels in deciduous and permanent teeth by Indigenous status; and limited evidence that water fluoridation reduces the disparities in caries levels in deciduous and permanent teeth and hospital admissions for caries by levels of deprivation.

Table 157 Summary of findings for disparities in dental outcomes

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Disparities in caries by SES status	There is insufficient information to determine whether initiation of a water fluoridation programme results in a change in disparities in caries levels (deciduous teeth) across SES	>35,399 (3 observational studies)	⊕○○○	A single well-conducted systematic review. The GRADE assessment was downgraded once for high risk of bias. The authors reported the quality of evidence as being ⊕⊕○○ and provided no reason why they upgraded. GRADE does not allow upgrading if the evidence has already been downgraded. Therefore the quality has been revised.
Disparities in caries by Indigenous status	Water fluoridation increased the gap in proportion caries-free children in deciduous and permanent teeth between Indigenous and non-Indigenous Australians aged 5–15 years	97,809 (1 observational study)	⊕○○○	A single Australian study of low quality in the context of CWF. Downgraded for risk of bias and imprecision.
Disparities in caries by deprivation	Water fluoridation had a greater effect in the most deprived subgroup of participants with respect to mean d ₃ mft and caries prevalence in 5-year-olds, mean D ₃ MFT and caries prevalence in 12-year-olds, and hospital admissions for caries of 1 to 4-year-olds compared to the four least deprived subgroups in one study. Difference in D ₄₋₆ MFT between most and least deprived groups was reduced in areas with fluoridated water for 11 to 13-year-olds in one study.	>1,783 (2 observational studies)	⊕○○○	A single large study of acceptable quality from England using a national database setting of CWF. Exploratory analysis of subgroups. No adjustment for confounding. Downgraded for risk of bias and imprecision. Another single large study from the UK downgraded for risk of bias.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; SES = socioeconomic status; CI = confidence interval; US = United States

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Other dental effects

Other dental effects included tooth loss, delayed eruption of permanent teeth, tooth wear and hospital admissions for caries in children aged 1–4 years. All included studies, except one, were of acceptable quality.

The review identified insufficient evidence that water fluoridation reduces tooth loss or hospital admission for caries. In addition, the review identified limited evidence of no association between water fluoridation and reduced tooth wear and delayed eruption of permanent teeth.

Table 158 Summary of findings for other dental effects

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Number of missing permanent teeth	Four of five studies show lower prevalence of tooth loss with fluoridation of water	>120,625 (5 observational studies)	⊕○○○	Downgraded for inconsistency and indirectness.
Erupted permanent teeth assessed by clinical examination	No significant difference in mean number of permanent teeth erupted	13,348 (1 observational study)	⊕⊕○○	A single study of acceptable quality from the US with representative sample and adjustment for confounding factors.
Delayed eruption of permanent teeth (assessment method NR)	Prevalence of delayed eruption was 53% in 2.7 ppm fluoride area and 0% in 1.0 ppm area	70 (1 observational study)	⊕○○○	A single small, low quality study from India in school children aged 8–15 years with poor reporting of recruitment method and outcome ascertainment, no adjustment for confounding, and no statistical analysis. Set in the context of naturally occurring fluoride in water of up to 2.7 ppm
Tooth Wear assessed with modified version of the Smith and Knight index	No consistent association with water fluoridation	2,456 (1 observational study)	⊕○○○	A single study of acceptable quality from the Republic of Ireland. Downgraded in the GRADE assessment for imprecision and inconsistency.
Hospital admissions	The rate of hospital admissions for 1 to 4-year-olds was 55% lower in fluoridated areas (95%CI: 73% lower, 27% lower)	NR (1 observational study)	⊕○○○	A single population-based study using national admission data from England of acceptable quality in a setting of CWF. Downgraded for imprecision.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: dmft/s = number of decayed, missing and filled deciduous teeth/surfaces; dft = number of decayed and filled deciduous teeth; DMFT/S = number of decayed, missing and filled permanent teeth/surfaces; CWF = community water fluoridation; CI = confidence interval; US = United States; ppm = parts per million

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

Findings of the review of dental fluorosis

The evidence evaluation identified one review which provided consistent evidence that an increase in the fluoride concentration in water supplies is associated with an increase in the prevalence of dental fluorosis. However, the majority of the evidence is derived from countries where naturally occurring fluoride levels are up to five times greater than the levels of fluoride in artificially fluoridated water in Australia. This evidence has limited applicability in the Australian context and is of insufficient quality to predict the prevalence of any dental fluorosis or dental fluorosis of aesthetic concern associated with the current levels of water fluoridation in Australia. This is due to a lack of control for other fluoride sources and marked between-study variation across non-comparable populations. There is also some uncertainty as to what level of dental fluorosis is perceived to be of aesthetic concern.

Table 159 Summary of findings for dental fluorosis

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Dental fluorosis of aesthetic concern (measured by Dean's Index, TFI, TSIF)	For a fluoride level of 0.7 ppm the percentage of participants with dental fluorosis of aesthetic concern was estimated to be 12% (95% CI 8% to 17%).	59,630 (40 observational studies)	⊕○○○ ²	The estimate for any level of dental fluorosis at 0.7 ppm was 40% (95% CI 35% to 44%; 90 studies). This includes dental fluorosis that can only be detected under clinical conditions and other enamel defects. The GRADE assessment has been revised and downgraded for high risk of bias, indirectness and inconsistency.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: ppm = parts per million

Abbreviations: CI = confidence interval; TFI = Thylstrup-Fejerskov Index; TSIF = Tooth Surface Index of Fluorosis

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

² The quality assessment has been revised—the Iheozor-Ejiofor et al (2015) review reported the quality as ⊕⊕○○ but this should have been downgraded for high risk of bias and inconsistency

Findings of the systematic review on other health effects

An independent systematic review was undertaken to identify evidence for any additional health effects of water fluoridation. The review aimed to update the evidence presented in the earlier NHMRC review (NHMRC 2007a). The systematic review included 41 relevant primary studies that reported on 23 separate health outcomes. As the studies reported on a wide range of different water fluoride levels, the results for each study were categorised based on the applicability of their comparison to the Australian setting.

Evidence from highly applicable comparisons

The highly applicable comparisons were those that compared unfluoridated water (<0.4 ppm) with water fluoride of between 0.4 ppm and 1.5 ppm. The summary of findings for these comparisons is presented in Table 160. The individual studies that provided highly applicable comparisons were generally of low methodological quality and many had a high risk of bias. This has affected the ability to draw conclusions from the available information.

The review identified evidence that there is no association between water fluoridation at Australian levels and the IQ of both adults and children, compared to unfluoridated water. We have moderate confidence in this assessment because of the high methodological quality of the prospective cohort study and the high similarity between the Australian setting and New Zealand, where the study was conducted.

The review identified evidence that there may be no association between water fluoridation at Australian levels and the outcomes of delayed tooth eruption, tooth wear, osteosarcoma, Ewing sarcoma, total cancer incidence, hip fracture and Down syndrome. However, our confidence in these assessments is limited due to the methodological shortcomings of the individual studies. The review also identified evidence that water fluoridation at Australian levels may be associated with a small reduction in all-cause mortality; however, our confidence in this association is limited, and the size of the effect was small.

The review included five outcomes where the available evidence was considered insufficient to draw any conclusions. Those outcomes were kidney stones, chronic kidney disease, gastric discomfort, headache, and insomnia.

Table 160 Summary of findings for other health outcomes with highly applicable fluoride level comparisons

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
All-cause mortality assessed using official mortality statistics	Adjusted incidence was 1.3% lower in areas with CWF (95%CI: 2.5% lower to 0.1% lower)	208,570,962 person-years at risk (1 observational study)	⊕⊕○○	A single large study of acceptable quality from England using a national database with adjustment for confounders in a setting of CWF.
Osteosarcoma assessed using official mortality statistics	No statistically significant difference in incidence of osteosarcoma between areas with water fluoridation and those without	519,128,941 person-years at risk (5 observational studies)	⊕⊕○○	Four of these studies were large population-based studies from countries with CWF all assessed as being of acceptable methodological quality. The fifth study was a population-based study of national statistics that reported only crude incidence rates.
Osteosarcoma (assessment method NR)	Participants with osteosarcoma lived in areas with higher fluoride water levels than people without osteosarcoma (1.30 ppm vs. 0.48 ppm)	20 (1 observational study)	⊕○○○	A single very small case-control study from India of low methodological quality (high risk of bias) with no information about participant demographics, recruitment, assessment of disease status, or the presence of potential confounding factors.
Ewing sarcoma assessed using national cancer registries	No significant increase in the risk of Ewing sarcoma with increasing fluoride level	992,213 person-years at risk (1 observational study)	⊕⊕○○	A single population-based study using national cancer registries from England of acceptable quality in a setting of CWF
All cancer incidence assessed using a national cancer register	Adjusted incidence of all cancer was 0.4% lower in areas with CWF (95%CI: 1.2% lower to 0.4% higher)	208,570,962 person-years at risk (1 observational study)	⊕⊕○○	A single population-based study using national cancer register from England of acceptable quality in a setting of CWF
Bladder Cancer assessed using a national cancer register	Adjusted bladder cancer incidence was 8.0% lower in areas with CWF (95%CI: 9.9% lower to 6.0% lower)	555,127,448 person-years at risk (1 observational study)	⊕⊕○○	A single population-based study using national cancer register data from England of acceptable quality in a setting of CWF.
Eye Cancer assessed using a national cancer register	Negative correlation between incidence of eye cancer and water fluoride level	NR (1 observational study)	⊕⊕○○	A single acceptable quality study of the correlation between the proportion of the population each US state exposed to CWF with eye cancer incidence
Hip Fracture assessed by national hospital statistics	Effect estimates from both studies found no statistically significant difference in the incidence of hip fracture.	313,045,314 person-years at risk (2 observational studies)	⊕⊕○○	Two population-based studies from Sweden and England of methodologically acceptable quality.
Down Syndrome assessed using a national register	Incidence of Down syndrome births were 0.9% higher (95%CI: 0.8% lower to 2.6% higher) in areas with CWF	2,727,330 person-years at risk (1 observational study)	⊕⊕○○	One population-based study of methodologically acceptable quality from England in the setting of CWF

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
IQ assessed using Wechsler Intelligence Scales	No significant difference in IQ scores between people exposed to CWF compared to those not exposed	1,037 (1 observational study)	⊕⊕⊕○	A longitudinal population-based study of high methodological quality from New Zealand with all major fluoride intakes considered and confounders adjusted for in a setting of CWF.
Kidney Stones assessed with national hospital statistics	Incidence of emergency admissions for kidney stones was 7.9% lower (95%CI: 9.6% lower to 6.2% lower) in the areas with CWF	312,856,448 person-years at risk (1 observational study)	⊕○○○	A population-based study of methodologically acceptable quality from England in a setting of CWF. Possibility of residual confounding.
Chronic kidney disease assessed using existing prevalence studies	Prevalence of chronic kidney disease of unknown aetiology in the three villages was 96%, 0%, and 84%	5,685 (1 observational study)	⊕○○○	A single study from Sri Lanka of low methodological quality (high risk of bias) in three villages with mean water fluoride levels of 0.74, 1.03, and 1.02 ppm, respectively. No trend was observed.
Gastric Discomfort assessed with self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	3,764 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.
Headache assessed by self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	3,283 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.
Insomnia assessed by self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	3,283 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: CI = confidence interval; CWF = community water fluoridation; IQ = intelligence quotient; ppm = parts per million; US = United States

¹ For details of the assessment please see the individual outcome in the Results section of this report.

Evidence from partially applicable comparisons

Studies categorised as highly applicable included those that compared unfluoridated water to water containing >1.5 ppm fluoride; and those that compared water with 0.4–1.5 ppm fluoride to water with >1.5 ppm fluoride. The summary of findings from these comparisons is presented in Table 161.

The review found evidence that there may be no association between higher levels of fluoride (>1.5 ppm) and the risk of hip fracture. Our confidence in this assessment is moderate, due to the acceptable methodological quality of the study and the low risk of bias in the study estimates. For all other outcomes, the quantity and quality of the evidence was insufficient to allow any conclusions to be drawn.

Table 161 Summary of findings for other health outcomes with partially applicable fluoride level comparisons

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Atherosclerosis assessed by carotid ultrasound	Higher prevalence in areas with fluoride levels >1.20 ppm	585 (1 observational study)	⊕○○○	A single study in adults >40 years from China of acceptable quality in the context of high naturally occurring water fluoride levels. Important known confounders not included in analysis e.g. smoking, exercise, diabetes
Hypertension assessed by sphygmomanometer	Conflicting results from the two continuous analyses Significantly higher odds of hypertension for ≥3.01 ppm fluoride compared to ≤1.20 ppm fluoride exposure only (all other comparisons between intermediate levels and lowest level not significant)	NR (2 observational studies) 487 (1 observational study)	⊕○○○	Two studies of low methodological quality from Iran using regression analysis to investigate a correlation between prevalence of hypertension and water fluoride levels (range 0.02–2.2 ppm). Single small study of adults 40–75 years from China of acceptable methodological quality found only significant raised odds with ≥3.01 ppm fluoride compared to lowest comparator (≤1.20 ppm)
Hip Fracture assessed by national hospital statistics	Hazard ratio = 0.98 (95%CI: 0.93–1.04)	13,736 person-years at risk (1 observational study)	⊕⊕⊕○	One population-based study from Sweden of methodologically acceptable quality.
Osteoporosis assessed by x-ray	Prevalence of osteoporosis: 6.2% with 1.5–7.0 ppm exposure 6.8% with 0.5–1.0 ppm exposure ⁶	675 (1 observational study)	⊕○○○	A single study in adults from China of low methodological quality with poor reporting of selection method, no consideration of known confounding factors, uncertain accuracy of diagnosis, and no statistical analysis.
Musculoskeletal pain assessed with self-report health survey	Odds of lower back pain significantly greater in the high fluoride area. Prevalence of joint pain higher in the high fluoride area.	3,266 (2 observational studies)	⊕○○○	One small study of low quality (high risk of bias) from India and a single study from Thailand of low methodological quality in adults 50–90 years.
Birth weight assessed with baby scale	Increased odds of low birth weight associated with exposure to high fluoride levels (4.7 ppm)	324 (1 observational study)	⊕○○○	A single study from Africa of low methodological quality in a setting of high naturally occurring fluoride levels (4.7 ppm).
IQ and cognitive function assessed with various instruments	11 of 13 analyses reported a significantly lower IQ score with high fluoride levels (range 2.3–9.2 ppm) No association between fluoride water levels and cognitive performance in one analysis	1,565 (11 observational studies)	⊕○○○	Nine studies from China, Iran, and India were of low methodological quality (high risk of bias) due to poor recruitment reporting, no consideration of confounding factors, and no blinding of outcome assessors. One study from Mexico and another from China were of acceptable quality.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Thyroid function assessed with thyroid function tests	All thyroid function tests within reference range	240 (2 observational studies)	⊕○○○	Two studies of low methodological quality from India and China of school children in areas with high naturally-occurring levels of fluoride in water.
Thyroid volume assessed with ultrasound	Thyroid volumes were inconsistent using two measures of thyroid volume	559 (1 observational study)	⊕○○○	A single study from Iran in schoolchildren of low quality found no difference in thyroid volume but a significant difference in Echobody index. The clinical validity of this measure and its implications are unclear.
Gastric Discomfort assessed with self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	2,814 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.
Headache assessed by self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	2,937 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.
Insomnia assessed by self-report health survey	Prevalence was higher in the 0.4–1.5 ppm area adults but not for children	2,937 (2 observational studies)	⊕○○○	Two studies from India of low methodological quality (high risk of bias) in setting of naturally occurring fluoride. No statistical analysis.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: CI = confidence interval; IQ = intelligence quotient; NR = not reported; ppm = parts per million

¹ For details of the assessment please see the individual outcome in the Results section of this report.

Evidence from low applicability comparisons

Low applicability comparisons compared groups that all had water fluoride levels >1.5 ppm. The summary of findings from these comparisons is presented in Table 162. The evidence for all outcomes was insufficient to draw any conclusions about the differential effect of multiple high water fluoride levels.

Table 162 Summary of findings for other health outcomes with limited applicability in fluoride level comparisons

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
Atherosclerosis assessed by carotid ultrasound	No significant difference in prevalence	399 (1 observational study)	⊕○○○	A single acceptable quality study from China in adults >40 years in the context of high naturally occurring fluoride levels. All comparisons were >1.21 ppm.
Skeletal fluorosis (assessment NR)	Skeletal fluorosis prevalence (range): grade II: 4.7% to 20.1%; grade III: 0% to 3.9%	2816 (2 observational studies)	⊕○○○	Two low quality prevalence studies from India in the setting of naturally occurring fluoride levels from 1.5 ppm to >6.0 ppm. The diagnostic method was not reported, and no statistical analysis was done.

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
IQ assessed with various IQ instruments	One of two studies reported statistically significant lower IQ score in high fluoride group	392 (2 observational studies)	⊕○○○	Two low quality studies from India and Iran of schoolchildren 6–13 years old from villages with drinking water fluoride levels of 2–3 ppm and >5 ppm, respectively.

Note: Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations.

Abbreviations: CI = confidence interval; IQ = intelligence quotient; NR = not reported; ppm = parts per million

¹ For details of the assessment, please see the individual outcome in the Results section of this report.

QUALITY OF THE EVIDENCE

The majority of the studies included in this review were of low methodological quality, and only one study was judged to be of high methodological quality. This increases the risk that the results of the studies may be biased and reduces our ability to draw conclusions from the identified evidence.

There were a number of methodological failings that have affected the quality of these studies. Firstly, in many studies the quality of the reporting of both study methods and results was very poor. The lack of basic information, such as details of how exposures and outcomes were measured and basic participant demographics, makes the interpretation of the study results very difficult. Many studies also have small numbers of participants, which undermines the ability of the study to detect meaningful differences in health outcomes.

The majority of the included studies made only a rudimentary assessment of the fluoride exposures experienced by their participants. This involved the measurement of water fluoride, at the individual or community level, but no attempt to control for other potential sources of fluoride. In developed countries, people may be exposed to fluoride in tablets, in fluoridated toothpastes, and in fluoride varnishes and gels. In children, the consumption of fluoridated toothpaste may contribute significantly to their total fluoride exposure. In developing countries, people may be exposed to additional fluoride through tablets and toothpastes, but also through coal burning. Additionally, in some cultures, the consumption of specific teas, such as brick-type tea, can add significantly to total fluoride consumption. Without consideration of these other fluoride sources, it can be challenging to determine whether any effects observed are due to water fluoride alone.

The types of analyses used in the included studies were often insufficient to address their research question. In many cases, the studies did not include any adjustment in their analyses for the effects of potential confounding variables. For all of the outcomes considered in this review, there are key confounding factors, such as age, gender, socioeconomic factors, lifestyle factors and medical history that must be adjusted for in the analysis. Without these adjustments it is impossible to tell if the effect is due to the water fluoride, or to the presence of these confounding factors. This is particularly important for outcomes such as IQ, which are heavily influenced by environmental and economic factors. The lack of adjustment for confounding variables has seriously limited the ability of this review to draw conclusions from the majority of the results identified.

LIMITATIONS OF THE GRADE ASSESSMENT

The GRADE assessment system has been used in this review to summarise the strength of the evidence collected for each outcome. GRADE is increasingly being named internationally as the preferred system for summarising the strength and quality of evidence in systematic reviews and clinical practice guidelines. However, there are a number of issues with GRADE that reduce its utility in assessing the effectiveness of public health interventions. For many public health

interventions, and particularly in the case of water fluoridation, carrying out randomised controlled trials of the intervention is not feasible. In these cases, evidence from randomised trials will never be available and the only available evidence will come from observational studies. For interventions like water fluoridation, the evidence will often come from ecological studies, simply because of the scale of the intervention and the complexity of monitoring individual study participants.

Under the GRADE system, evidence from all observational studies is automatically rated as “low”. The evidence can be downgraded if there are concerns related to imprecision, indirectness, inconsistency and study quality. Evidence from the lower level observational studies, such as ecological studies, often ends up being downgraded to “very low” due to the inherent problems in the study design that result in bias or other issues. For the current review we have implemented the suggestion of Harder et al (2015) that observational study designs with a lower risk of bias should be rated as “moderate” initially.

Evidence from observational studies can be upgraded to “moderate” or “high”, based on the existence of very strong effects, evidence of a dose-response gradient, or where all confounding factors should bias the effect in the opposite direction. These criteria for upgrading evidence assume that what is being evaluated is an actual difference or clear health effect. This can be problematic where what is found is actually no difference between groups or no effect. In such cases there is no real opportunity to upgrade observational evidence. For the current review, we allowed the possibility for upgrading the evidence if the effects observed were consistent across study designs, as suggested by Harder et al (2015), but we did not identify any outcomes for which the evidence met this standard.

The authors of the Cochrane review of dental caries and dental fluorosis also noted the inherent limitations in the GRADE system. They discuss a number of suggested modifications for the use of GRADE with public health interventions, but note that these are still controversial. We agree with Iheozor-Ejiofor et al (2015) that under the GRADE system, the evidence for most public health interventions will always be rated as “low” or “very low” and that “high” quality evidence will never exist.

As a large-scale population level intervention, which has effects over lifetime exposure, CWF is best studied using observational studies, and arguably, effects need to be assessed at the level of the population and not the individual. There is a large and consistent body of observational evidence demonstrating a positive impact of CWF on the prevention of caries combined with physiological evidence which does not form part of this assessment and is not considered under the GRADE approach. Nevertheless, for the GRADE assessments, in the majority of dental outcomes the GRADE rating is that “our confidence in the reported associations is limited.”

This poses a challenge for decision-makers who must recognise the limitations of both the available evidence and the tools used to assess and rate them. High-quality observational research can be the appropriate approach to assess the value of a public-health intervention enabling long-term, population level effects to be assessed. Consequently, decision-makers must recognise this limitation and weigh the balance of benefits and harms based on the best available evidence, placing this assessment into a broader consideration of issues such as cost-effectiveness, equity, ethics, acceptability and prioritisation.

POTENTIAL BIASES IN THE REVIEW PROCESS

The evaluation of the evidence for the effect of water fluoridation on dental caries was planned as a critical review of the Cochrane review by Iheozor-Ejiofor et al (2015). However, the inclusion criteria for studies reporting on the caries outcome were stringent, requiring studies to have a concurrent control group and observations at multiple time points. It was therefore felt that the Cochrane review may have missed some useful evidence, in particular evidence from interrupted time series studies that investigate the effect of the initiation of water fluoridation schemes, and more contemporary

evidence from Australia. Therefore, two further systematic reviews were undertaken to address this limitation.

An overview of systematic reviews was undertaken due to limited time-frames and the need to capture a large body of evidence. The rationale was to provide a comprehensive overview of water fluoridation and dental caries, including studies not included in the systematic reviews which were captured in the search for primary studies. However, this approach is at risk of bias as the ability to report on the existing reviews is dependent on their quality and reporting of the included primary studies. Where key data is absent from the review, we were unable to report it and we were unable to undertake further analysis of the studies included in the reviews as they were excluded from the systematic search for primary studies.

In the search for primary studies, the decision was made to only include studies in which a multivariate analysis had been undertaken. This is also a potential source of bias as it restricted the type of analysis able to be undertaken in the review. Multivariate analysis is not able to be pooled and is more difficult to assess for the veracity of the statistical calculations so while this inclusion criteria ensured that only studies which considered confounders were included, it also restricted the data we were able to extract and utilise in the review.

The evaluation of the evidence for the effect of water fluoridation on dental fluorosis was based entirely on the Cochrane review by Iheozor-Ejiofor et al (2015). The Cochrane review was developed at the same time as this review and represents the most up-to-date assessment of this outcome. The review was of a high methodological quality, however, the analysis for dental fluorosis was a dose-response analysis and included levels of fluoride much higher than that used for water fluoridation in Australia. Of note, the review did not undertake an analysis which compared water fluoridated at comparable levels to Australia to un-fluoridated water, which would be the most applicable analysis for this review. There was no consideration of fluoride ingestion from other sources (for example, fluoridated toothpaste, food sources, tea and coal smoke) which impact on the prevalence of dental fluorosis. In addition, the definitions of 'fluorosis of aesthetic concern' used in the Cochrane review did not reflect contemporary thresholds. Therefore, more recent thresholds for 'fluorosis of aesthetic concern', data from Australia on the prevalence of dental fluorosis and its impact on quality of life were considered by the Fluoride Reference Group when weighing up the potential harm of dental fluorosis from water fluoridation.

The aim of the current second part of the review was to update the evidence on the health effects of fluoride presented in the 2007 NHMRC review. Because of this, the evidence for all outcomes other than dental caries and dental fluorosis was drawn solely from studies published after the 2007 NHMRC review. Of the 25 health outcomes presented, 9 were included in the earlier review: all-cause mortality, osteosarcoma, other cancers, skeletal fluorosis, hip fracture, Down syndrome, cognitive function, IQ and kidney stones. For the other health outcomes, there may be additional evidence published prior to 1st October, 2006 that was not identified in the NHMRC review or the earlier review by McDonagh et al (2000). Given the methodologies used in those two reviews, it seems unlikely that any high quality, high-level evidence for these additional outcomes would have missed.

The literature search undertaken for this review specifically excluded studies that were published in a language other than English. This was the final selection criterion to be applied and resulted in the exclusion of 69 potentially eligible studies. Of these, 68 were published in Chinese and one was published in Korean. A number of studies conducted in China and published in English have been included in the review. The studies conducted in China often investigated very high levels of naturally occurring fluoride that are not applicable to the fluoride levels found or maintained in Australia. In addition, the socioeconomic conditions and the healthcare provision systems in China have significant differences to those in Australia, further limiting the applicability of these studies. In fact, all of these studies met at least one other exclusion criteria. Based on the information presented in the study abstracts, 32 were not comparative studies; 11 did not report moderate and

severe skeletal fluorosis separately; nine did not supply sufficient data for any appraisal or conclusion to be made; seven did not report the level of fluoride in the water supply; two each were conflated by iodine, the wrong intervention, wrong outcome or wrong publication type; one was conflated by high fluoride levels in the air and food; and one was a duplicate publication.

During the review of articles in full text, a total of 12 studies were excluded because the selection methods used in these studies confounded the assessment of the study outcomes. These studies purported to compare subjects from areas with differing water fluoride levels, but actually compared people with fluorosis in one region to those without fluorosis in another region. It was the opinion of both the reviewers and the NHMRC that the results reported in these studies were irretrievably confounded and that it was impossible to assess the true effect of water fluoride on the reported outcomes. As such, the inclusion of these studies would likely have introduced additional bias and reduced confidence in the results of the review.

AGREEMENT AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

The evidence for the effect of water fluoridation on dental caries comes from three systematic reviews and 325 primary studies. The authors of the Cochrane review note that the effects they report on caries levels in children are comparable to the effects found for caries levels in adults in the recent publications by Griffin et al (2007) and Slade et al (2013). Furthermore, the effects identified in the Cochrane review on caries levels in children were consistent with the evidence identified in the primary studies which included more studies published post-1975 when access to fluoridated toothpaste was more widespread, suggesting a continued effect of CWF in more contemporary settings.

The evidence for the effect of water fluoridation on dental fluorosis comes from the Cochrane review by Iheozor-Ejiofor et al (2015). This review considered all evidence published up to February 2015. Consequently, the review includes much of the evidence considered in the McDonagh et al (2000) review. The effect estimates reported in the Cochrane review for dental fluorosis are highly similar to those reported by McDonagh et al (2000), and consistent with NHMRC 2007 review.

The current independent systematic review updates the evidence for the health effects of fluoride presented in the 2007 NHMRC review. Our review covers 24 outcomes, 9 of which were included in the 2007 NHMRC review. For the outcomes of total cancer incidence, osteosarcoma, Ewing sarcoma and hip fracture risk, the new evidence presented in this review is consistent with the existing evidence summarised in the earlier NHMRC review. For all of these outcomes, the available evidence suggests that there may be no association between water fluoridation, as practised in Australia, and the incidence of these outcomes. These findings are also consistent with those reported in the Royal Society of New Zealand report on fluoridation (RSNZ 2014).

The current systematic review adds to the body of evidence on the association between fluoride and Down syndrome that was presented in the 2007 NHMRC review. We identified one highly relevant, very large ecological study that investigated the incidence of Down syndrome in the UK (PHE 2014). The study found no significant association between the use of water fluoridation and the incidence of Down syndrome. The earlier review had categorised the evidence as uncertain, but the addition of this study may allow this to be revised to reflect the likely lack of any relationship between water fluoridation at Australian levels and the incidence of Down syndrome.

The literature search for this review identified four relevant systematic reviews that were not eligible for inclusion. The review by Choi et al (2014) investigated the association between environmental fluoride levels and children's IQ. The review included 27 studies, mostly from China, and reported the possibility of an adverse effect of high fluoride exposure on children's neurodevelopment, with an estimated pooled standardised weighted mean difference in IQ scores of -0.45 (95%CI: -0.56 to -0.34) when comparing "high" fluoride with "lower" fluoride exposure. The actual fluoride levels compared in the included studies varied widely, so that the comparison between "low" and "high" is

very difficult to interpret. In many cases the “low” levels were the same as those maintained in Australia. In addition, most of the included studies have serious methodological flaws, with a high risk of bias, and the pooled analysis did not include any adjustment for potential confounding variables. Our review adds 13 additional studies to the evidence base identified in the Choi review. The majority of these studies are also of poor methodological quality and report only crude effect estimates without considering confounding variables. However, we did identify one high quality prospective cohort study that provides highly relevant evidence. The study by Broadbent et al (2014) was conducted in New Zealand and followed 1,037 people from birth to age 38. The study has collected extensive information about fluoride exposures and known social and environmental confounding variables. The authors report that there was no association between water fluoridation and the IQ of both children and adults compared with unfluoridated water. The addition of this study to the evidence base may change the interpretation of the relationship between fluoride and IQ, and provides directly applicable evidence to guide decision-making in the Australian setting.

The review by Ludlow et al (2007) investigated the health effects of CWF on people with CKD. The review found no evidence water fluoridation at the level used in Australia increases the risk of CKD or that drinking water fluoridated at the level used in Australia poses any health risks to people with CKD. Our review found only one additional study investigating CKD. The study by Chandrajith et al (2011) was of low quality and only presented the prevalence of CKD of unknown aetiology in three villages in northern Sri Lanka. Consequently, our review has not added any substantial evidence that would warrant a reconsideration of the findings of the Ludlow review.

CONCLUSION

IMPLICATIONS FOR PRACTICE

The evidence collected in this review supports the findings of the previous NHMRC review (2007a), that water fluoridation at levels comparable to those used in Australia reduces the incidence of caries in the deciduous and permanent teeth of children by approximately 35%, compared to unfluoridated water. Water fluoridation also increases the proportion of children who have no dental caries by approximately 15%. Fluoridation of water increases the prevalence of dental fluorosis, and the prevalence of dental fluorosis of aesthetic concern was estimated to be 12% for 0.7 ppm fluoride.

There is limited evidence that there is no association between water fluoridation at Australian levels and the IQ of children and adults. There is also limited evidence that there may be no association between water fluoridation at Australian levels and the outcomes of delayed tooth eruption, tooth wear, osteosarcoma, Ewing sarcoma, total cancer incidence, hip fracture and Down syndrome. The review also identified evidence that water fluoridation at Australian levels may be associated with a small reduction in all-cause mortality; however, our confidence in this association is limited and the size of the effect was small and may be due to chance. For all other outcomes canvassed in this review, the evidence was of insufficient quality to draw any conclusions.

Taken together, the evidence in this review indicates that water fluoridation, as practised in Australia, may improve the dental health of children and adults. Water fluoridation may increase the number of people who experience dental fluorosis of aesthetic concern, but does not appear to be associated with any other significant harm. The evidence available to assess the effects of water fluoridation will likely always come from observational studies, many of which will be of low methodological quality. Decision-makers must recognise these limitations and be prepared to make pragmatic decisions based on the best available evidence about the implementation and maintenance of water fluoridation programs in Australia.

IMPLICATIONS FOR RESEARCH

The key limitations of this review were the paucity of evidence about the effect of fluoridation on disparities in caries outcomes and the poor quality of the included primary studies. It is

acknowledged that for public health interventions such as water fluoridation, it may be impossible to conduct randomised trials and observational study designs must be used. Observational study designs are highly susceptible to bias from confounding variables and this problem is widespread in the literature on water fluoridation. Consequently, it is imperative that any researchers undertaking new observational studies on water fluoridation must collect as much information as possible on any relevant confounding variables and ensure that this information is included in their analyses.

CONTRIBUTIONS OF AUTHORS

The following staff of the NHMRC Clinical Trials Centre were involved in planning and conducting the overview, and contributed to the preparation of this report:

Dr Briony Jack	NHMRC Clinical Trials Centre	Project manager, scoping and overall design of the research project, development of the research protocol, performed literature searches, review of citations, checking of data, collation of summary data and writing of reports.
Dr Samara Lewis	NHMRC Clinical Trials Centre	Scoping and overall design of the research project, development of the research protocol and writing of reports.
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Mr Adam Irving	NHMRC Clinical Trials Centre	Data extraction and quality assessment, collation of summary data and writing of reports.
Mr Blaise Agresta	NHMRC Clinical Trials Centre	Development of the research protocol, performed literature searches, review of citations, data extraction and quality assessment.

DECLARATIONS OF INTEREST

All authors from the NHMRC Clinical Trials Centre declare that they have no financial, personal or professional interests that could be construed to have influenced the conduct or results of this review.

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CHANGES FROM PROTOCOL TO FINAL REPORT

The research protocol for the review of evidence on the health effects of water fluoridation (October 2014) did not specify a quality assessment instrument for cross-sectional studies and ecological studies. The protocol had specified that the quality of ecological studies would be described only, and cross-sectional studies had been unintentionally omitted from this section of the protocol. In order to standardise the consideration of these study types, and in the absence of validated specific instruments, the NHMRC approved the use of a generic instrument produced by NICE for the assessment of quantitative studies reporting correlations and associations.

To aid in the interpretation of the results, the evidence for each outcome was presented based on the applicability of the included studies, as described in the methodology section (see page 36).

On the advice of the NHMRC, and with the approval of the Fluoride Reference Group, this review has adopted some modifications of the GRADE assessment process for the assessment of a public health intervention (Harder et al 2015). For this review, all Level II, Level III-1 and Level III-2 studies were initially categorised as moderate quality and all Level III-3 and Level IV studies were initially graded as low quality. The review also allowed the possibility for upgrading the evidence if the effects observed were consistent across study designs, as suggested by Harder et al (2015). For this review, this was applied if consistent results were observed across different levels of evidence.

The structure of the GRADE summary of findings tables was adapted to give a single cell for the illustrative comparative risks. This was done to simplify the presentation of the available evidence.

Twelve studies were identified that conflated the effects of water fluoridation with the effects of dental and skeletal fluorosis. It was the opinion of both the reviewers and the NHMRC that the results reported in these studies were irretrievably confounded, and that it was impossible to assess the true effect of water fluoride on the reported outcomes. The NHMRC and FRG agreed that these studies should be excluded.

3. As noted under 'a systematic review of the dental effects of water fluoridation, which consisted of:
 - a. an overview of reviews on the effects of water fluoridation on dental caries,
 - b. a systematic review of recent primary studies on the effects of water fluoridation on dental caries not identified in the reviews included in the overview,
 - c. a critical appraisal of the evidence on dental fluorosis included in the existing Cochrane review (Iheozor-Ejiofor et al 2015); and
4. a systematic review of the other health effects of water fluoridation.

History of the reviews' on page 33, the review was initially commissioned as a systematic review of the health effects of water fluoridation excluding dental effects, paired with a critical appraisal of the Cochrane Review (Iheozor-Ejiofor et al 2015) on the dental effects of fluoride. After publication of the Cochrane Review, further work was commissioned in September 2015. Two separate research protocols were developed for this additional work (Part A: overview of reviews and Part B: Systematic review of recent primary studies).

Due to the large volume of primary studies retrieved in the systematic review of primary studies on the effect of water fluoridation on dental caries, two additional inclusion criteria were agreed to by the Fluoride Reference Group. These were that only studies which included a multivariate analysis were included and that where studies reported results from routine data collections, only the most recent study was included.

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