NHS CENTRE FOR
REVIEWS AND
DISSEMINATION

A Systematic Review Of Water Fluoridation

THE UNIVERSITY *of York*

REPORT 18

A Systematic Review of Public Water Fluoridation

Marian McDonagh[1]
Penny Whiting[1]
Matthew Bradley[1]
Janet Cooper[2]
Alex Sutton[3]
Ivor Chestnutt[2]
Kate Misso[1]
Paul Wilson[1]
Elizabeth Treasure[2]
Jos Kleijnen[1]

[1]NHS Centre for Reviews and Dissemination, University of York
[2]Dental Public Health Unit, The Dental School, University of Wales, Cardiff
[3]University of Leicester, Department of Epidemiology and Public Health

September 2000

© 2000 NHS Centre for Reviews and Dissemination, University of York

ISBN 1 900640 16 3

This report can be ordered from: Publications Office, NHS Centre for Reviews and Dissemination, University of York, York YO10 5DD. Telephone 01904 433648; Facsimile: 01904 433661: email: crdpub@york.ac.uk
Price £20

The NHS Centre for Reviews and Dissemination is funded by the NHS Executive and the Health Departments of Wales and Northern Ireland. The views expressed in this publication are those of the authors and not necessarily those of the NHS Executive or the Health Departments of Wales or Northern Ireland.

Printed by York Publishing Services Ltd.

NHS CENTRE FOR REVIEWS AND DISSEMINATION

The NHS Centre for Reviews and Dissemination (CRD) is a facility commissioned by the NHS Research and Development Division. Its aim is to identify and review the results of good quality health research and to disseminate actively the findings to key decision makers in the NHS and to consumers of health care services. In this way health care professionals and managers can ensure their practice reflects the best available research evidence. The reviews will cover: the effectiveness of care for particular conditions; the effectiveness of health technologies; and evidence on efficient methods of organising and delivering particular types of health care.

Further Information

General Enquiries:	01904 433634
Information Service	01904 433707
Publications:	01904 433648
Fax:	01904 433661
Email:	revdis@york.ac.uk

CRD Reports

1.	Which Way Forward for the Care of Critically Ill Children? (1995)	£7.50
4.	Undertaking Systematic Reviews of Research on Effectiveness. CRD Guidelines for those Carrying Out or Commissioning Reviews (1996)	£7.50
5.	Ethnicity and Health: Reviews of literature and guidance for purchasers in the Areas of cardiovascular disease, mental health and haemoglobinopathies (1996)	£12.50
6.	Making Cost-Effectiveness Information Accessible: The NHS Economic Evaluation Database Project. CRD Guidance for Reporting Critical Summaries of Economic Evaluations (1996)	£7.50
7.	A Pilot Study of 'Informed Choice' Leaflets on Positions in Labour and Routine Ultrasound (1996)	£7.50
8.	Concentration and Choice in the Provision of Hospital Services (1997)	
	Summary Report	£6.00
	Part I - Hospital Volume and Quality of Health Outcomes	£12.50
	Part II - Volume and the scope of activity and hospital costs	£9.50
	Part III - Concentration, patient accessibility and utilisation of services	£7.50
	Complete set of reports	£30.00
9.	Preschool Vision Screening: Results of a Systematic Review (1997)	£9.50
	Systematic Review of Interventions in the Treatment and Prevention of Obesity (1997)	£12.50
10.	A Systematic Review of the Effectiveness of Interventions for Managing Childhood Nocturnal Enuresis (1997)	£12.50
13.	Screening for Ovarian Cancer: A Systematic Review (1998)	£12.50
14.	Women and Secure Psychiatric Services: A Literature Review (1999)	£12.50
15.	Systematic Review of the International Literature on the Epidemiology of Mentally Disordered Offenders (1999)	£12.50
16.	Scoping Review of Literature on the Health and Care of Mentally Disordered Offenders (1999)	£12.50
17.	Therapeutic Commuity Effectiveness. Community Treatment for People with Personality Disorders and Mentally Disordered Offenders (1999)	£12.50

TABLE OF CONTENTS

TABLES AND FIGURES

ACKNOWLEDGEMENTS

The review team gratefully acknowledges the invaluable contributions of the members of the Advisory Board: The Earl Baldwin of Bewdley, House of Lords; Sir Iain Chalmers, UK Cochrane Centre; Dr. Sheila Gibson, Glasgow Homeopathic Hospital; Ms. Sarah Gorin, Help for Health Trust; Professor MA Lennon, Department of Clinical Dental Sciences, University of Liverpool School of Dentistry, Chairman of the British Fluoridation Society; Dr. Peter Mansfield, Director of Templegarth Trust; Professor JJ Murray, Dean of Dentistry, University of Newcastle; Mr. Jerry Read, Department of Health; Dr. Derek Richards, Centre for Evidence-Based Dentistry; Professor George Davey Smith, Department of Social Medicine, University of Bristol; Ms. Pamela Taylor, Water UK.

Special thanks to Professor Trevor Sheldon, Department of Health Studies, University of York, who chaired the Advisory Board.

The team also acknowledges Dr. Keith Abrams, University of Leicester for commentary on the analysis, Marijke Van Gestel for assistance in the early stages of the review, and Vanda Castle for secretarial support.

Thanks to Dr. Alan Glanz from the Department of Health for efficient collaboration on the organisational aspects of the project.

We also greatly appreciate the contributions of many scientists and members of the public who submitted papers for inclusion and made valuable comments about the protocol, data extraction tables and results of the review.

EXECUTIVE SUMMARY

This systematic review has been commissioned by the Chief Medical Officer of the Department of Health to 'carry out an up to date expert scientific review of fluoride and health' (Paragraph 9.20, Our Healthier Nation).

Overall, the aim has been to assess the evidence on the positive and negative effects of population wide drinking water fluoridation strategies to prevent caries. To achieve this aim five objectives were identified:

Objective 1: What are the effects of fluoridation of drinking water supplies on the incidence of caries?

Objective 2: If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

Objective 3: Does water fluoridation result in a reduction of caries across social groups and between geographical locations, bringing equity?

Objective 4: Does water fluoridation have negative effects?

Objective 5: Are there differences in the effects of natural and artificial water fluoridation?

Methods

A search of 25 electronic databases (with no language restrictions) and the world-wide-web was undertaken. Relevant journals and indices were hand searched and attempts were made to contact authors for further information.

Quality inclusion criteria were based on a pre-defined hierarchy of evidence (A, B, and C). Studies of efficacy were included if they were of evidence level A or B. In order to allow the broadest search for evidence on potential adverse effects, studies of all levels of evidence were included. Objective specific inclusion criteria, based on selection of participants, intervention, outcomes assessed, and study design appropriate for a given objective were then applied. Study validity was formally assessed using a published checklist modified for this review (CRD Report 4, 1996).

Inclusion criteria were assessed independently by at least two reviewers. Extraction of data from, and validity assessment of, included studies was independently performed by two reviewers, and checked by a third reviewer. Disagreements were resolved through consensus.

Where the data were in a suitable format, measures of effect and 95% confidence intervals (CI) were plotted. Heterogeneity was investigated by visual examination and statistically using the Q-statistic. Where no evidence of heterogeneity was found a meta-analysis was conducted to produce a pooled estimate of the measure of effect. Statistically significant heterogeneity was investigated using meta-regression. Multiple regression analysis was used to explore the relationship between fluoridation and fluorosis.

Results

214 studies met full inclusion criteria for one or more of the objectives. No randomised controlled trials of the effects of water fluoridation were found. The study designs used included 45 'before and after' studies, 102 cross-sectional studies, 47 ecological studies, 13 cohort (prospective or retrospective) studies and 7 case-control studies. Several studies were reported in multiple papers over a number of years.

Results by Objective

Objective 1

A total of 26 studies of the effect of water fluoridation on dental caries were found. For this objective, the quality of studies found was moderate (no level A studies). A large number of studies were excluded because they were cross-sectional studies and therefore did not meet the inclusion criteria of being evidence level B or above. All but three of the studies included were before-after studies, two included studies used prospective cohort designs, and one used a retrospective cohort design. All before-after studies located by the search were included. The most serious defect of these studies was the lack of appropriate analysis. Many studies did not present an analysis at all, while others only did simple analyses without attempting to control for potentially confounding factors. While some of these studies were conducted in the 1940's and 50's, prior to the common use of such analyses, studies conducted much later also failed to use methods that were commonplace at the time of the study.

Another defect of many studies was the lack of any measure of variance for the estimates of decay presented. While most studies that presented the proportion of caries-free children contained sufficient data to calculate standard errors, this was not possible for the studies that presented dmft/DMFT scores. Only four of the eight studies using these data provided estimates of variance.

The best available evidence suggests that fluoridation of drinking water supplies does reduce caries prevalence, both as measured by the proportion of children who are caries free and by the mean change in dmft/DMFT score. The studies were of moderate quality (level B), but of limited quantity. The degree to which caries is reduced, however, is not clear from the data available. The range of the mean difference in the proportion (%) of caries-free children is -5.0 to 64%, with a median of 14.6% (interquartile range 5.05, 22.1%). The range of mean change in dmft/DMFT score was from 0.5 to 4.4, median 2.25 teeth (interquartile range 1.28, 3.63 teeth). It is estimtaed that a median of six people need to receive fluoridated water for one extra person to be caries-free (interquartile range of study NNTs 4, 9). The best available evidence from studies following withdrawal of water fluoridation indicates that caries prevalence increases, approaching the level of the low fluoride group. Again, however, the studies were of moderate quality (level B), and limited quantity. The estimates of effect could be biased due to poor adjustment for the effects of potential confounding factors.

Objective 2

To address this objective, studies conducted after 1974 were examined. While only nine studies were included for Objective 2, these would have been enough to provide a confident answer to the objective's question if the studies had been of sufficient quality. Since these studies were completed after 1974, one might expect that the validity assessments would be higher than the earlier studies following the introduction of more rigorous study methodology and analytic techniques. However, the average validity checklist score and level of evidence was essentially the same for studies after 1974 as those conducted prior to 1974. Hence, the ability to answer this objective is similar to that in Objective 1.

In those studies completed after 1974, a beneficial effect of water fluoridation was still evident in spite of the assumed exposure to non-water fluoride in the populations studied. The meta-regression conducted for Objective 1 confirmed this finding.

Objective 3

No level A or B studies examining the effect of water fluoridation on the inequalities of dental health between social classes were identified. However, because of the importance of this objective, level C studies conducted in England were included. A total of 15 studies investigating the association of water fluoridation, dental caries and social class in England were identified. The quality of the evidence of the studies was low, and the measures of social class that were used varied. Variance data were not reported in most of these studies, so a statistical analysis was not undertaken.

There appears to be some evidence that water fluoridation reduces the inequalities in dental health across social classes in 5 and 12 year-olds, using the dmft/DMFT measure. This effect was not seen in the proportion of caries-free children among 5 year-olds. The data for the effects in children of other ages did not show an effect. The small quantity of studies, differences between these studies, and their low quality rating, suggest *caution* in interpreting these results.

Objective 4

DENTAL FLUOROSIS

Dental fluorosis was the most widely and frequently studied of all negative effects. The fluorosis studies were largely cross-sectional designs, with only four before-after designs. Although 88 studies of fluorosis were included, they were of low quality. The mean validity score for fluorosis was only 2.8 out of 8. All, but one, of the studies were of evidence level C. Observer bias may be of particular importance in studies assessing fluorosis. Efforts to control for the effects of potential confounding factors, or reducing potential observer bias were uncommon.

As there may be some debate about the significance of a fluorosis score at the lowest level of each index being used to define a person as 'fluorosed', a second method of determining the proportion 'fluorosed' was selected. This method describes the number of children having dental fluorosis that may cause 'aesthetic concern'.

With both methods of identifying the prevalence of fluorosis, a significant dose-response relationship was identified through a regression analysis. The prevalence of fluorosis at a water fluoride level of 1.0 ppm was estimated to be 48% (95% CI 40 to 57) and for fluorosis of aesthetic concern it was predicted to be 12.5% (95% CI 7.0 to 21.5). A very rough estimate of the number of people who would have to be exposed to water fluoride levels of 1.0 ppm for one additional person to develop fluorosis of any level is 6 (95% CI 4 to 21), when compared with a theoretical low fluoride level of 0.4 ppm. Of these approximately one quarter will have fluorosis of aesthetic concern, but the precision of these rough estimates is low. These estimates only apply to the comparison of 1.0 ppm to 0.4 ppm, and would be different if other levels were compared.

BONE FRACTURE AND BONE DEVELOPMENT PROBLEMS

There were 29 studies included on the association between bone fracture and bone development problems and water fluoridation. Other than fluorosis, bone effects (not including bone cancers) were the most studied potential adverse effect. These studies had a mean validity score of 3.4 out of 8. All but one study were of evidence level C. These studies included both cohort and ecological designs, some of which included analyses controlling for potential confounding factors. Observer bias could potentially play a role in bone fracture studies, depending on how the study is conducted.

The evidence on bone fracture can be classified into hip fracture and other sites because there are more studies on hip fracture than any other site. Using a qualitative method of analysis (Figure 8.1), there is no clear association of hip fracture with water fluoridation. The evidence on other fractures is similar. Overall, the findings of studies of bone fracture effects showed small variations around the 'no effect' mark. A meta-regression of bone fracture studies also found no association with water fluoridation.

CANCER STUDIES

There were 26 studies of the association of water fluoridation and cancer included. Eighteen of these studies are from the lowest level of evidence (level C) with the highest risk of bias.

There is no clear association between water fluoridation and overall cancer incidence and mortality. This was also true for osteosarcoma and bone/joint cancers. Only two studies considered thyroid cancer and neither found a statistically significant association with water fluoridation.

Overall, no clear association between water fluoridation and incidence or mortality of bone cancers, thyroid cancer or all cancers was found.

OTHER POSSIBLE NEGATIVE EFFECTS

A total of 33 studies of the association of water fluoridation with other possible negative effects were included in the review. Interpreting the results of studies of other possible negative effects is very difficult because of the small numbers of studies that met inclusion criteria on each specific outcome, and poor study quality. A major weakness of these studies generally was failure to control for any confounding factors.

Overall, the studies examining other possible negative effects provide insufficient evidence on any particular outcome to permit confident conclusions. Further research in these areas needs to be of a much higher quality and should address and use appropriate methods to control for confounding factors.

Objective 5:

The assessment of natural versus artificial water fluoridation effects is greatly limited due to the lack of studies making this comparison. Very few studies included both natural and artificially fluoridated areas, and direct comparisons were not possible for most outcomes. No major differences were apparent in this review, however, the evidence is not adequate to make a conclusion regarding this objective.

Conclusions

This review presents a summary of the best available and most reliable evidence on the safety and efficacy of water fluoridation.

Given the level of interest surrounding the issue of public water fluoridation, it is surprising to find that little high quality research has been undertaken. As such, this review should provide both researchers and commissioners of research with an overview of the methodological limitations of previous research conducted in this area.

The evidence of a benefit of a reduction in caries should be considered together with the increased prevalence of dental fluorosis. The research evidence is of insufficient quality to allow confident statements about other potential harms or whether there is an impact on social inequalities. This evidence on benefits and harms needs to be considered along with the ethical, environmental, ecological, costs and legal issues that surround any decisions about water fluoridation. All of these issues fell outside the scope of this review.

Any future research into the safety and efficacy of water fluoridation should be carried out with appropriate methodology to improve the quality of the existing evidence base.

1. BACKGROUND

This review has been commissioned by the Chief Medical Officer of the Department of Health to 'carry out an up to date expert scientific review of fluoride and health' (Paragraph 9.20, Our Healthier Nation). The original objective given to the review team by the Department of Health was to conduct a systematic review of the efficacy and safety of water fluoridation. The protocol, including specific objectives, was then written by the review team, with the consultation and agreement of the advisory panel and in discussion with the Department of Health. The review agreed upon was a review of human epidemiological studies of water fluoridation.

The impact of fluoridation of drinking water supplies depends on a number of major issues: the potential benefits (including improved dental health and reductions in dental health inequalities); the potential benefits over and above that offered by the use of alternative interventions and strategies (e.g. fluoridated toothpaste); and the potential harms (including dental fluorosis, bone fractures and bone development problems, genetic mutations, birth defects, cancer and hypersensitivity).

This study aims to provide a systematic review of the best available evidence on potential positive and negative effects in order to assess the effects of water fluoridation. Decisions on artificial water fluoridation of course need to examine ethical issues, environmental and ecological impacts, cost and legal issues. These considerations are outside the scope of this review.

Systematic reviews locate, appraise and synthesise evidence from scientific studies in order to provide informative empirical answers to scientific research questions. They are therefore valuable sources of information for decision-makers. Systematic reviews differ from other types of review in that they adhere to a strict scientific design with the aims of making them more comprehensive, minimising the chance of bias and improving reliability. The intention is that a systematic review, rather than reflecting the views of authors or being based on only (a possibly biased) selection of the published literature, will contain a comprehensive assessment and summary of the available evidence. (For further information on systematic review methodology, see NHS Centre for Reviews and Dissemination Report 4 1996 and Sutton 1998.)

The history of health technology development shows that there have been numerous new interventions that were promising (or harmful) in animal and laboratory studies that turned out to be ineffective (or safe) when tested in humans. One example would be the drug omeprazole (Losec®) which caused gastric tumours in pre-clinical animal studies. However, such tumours have not been documented in humans, even in patients with conditions that require continuous treatment for many years. In general, when human data are available, animal or laboratory data provide far less reliable estimates of effect and, as such, do not bear significant weight on decisions about interventions. Such data will not be considered in this review.

A variety of study designs can be used to assess the effectiveness of a population-based intervention such as water fluoridation. These range from simple descriptive studies (e.g. cross-sectional), to studies of correlation at the population level (e.g. ecological studies), to studies of individual-based associations (e.g. case-control, before-after, and cohort studies) to formal experiments (e.g. randomised controlled trials).

The randomised controlled trial randomising individuals to fluoridated or non-fluoridated water would be the gold standard. However, studying the effects of water fluoridation poses problems for the use of the randomised controlled trial design. Water fluoridation affects population groups and it is thus difficult to randomly assign individuals to receive either fluoridated or non-fluoridated water. An alternative would be to randomise communities to fluoridated or non-fluoridated water. The fact that whole populations are either exposed or not exposed also poses a problem for cohort and case-control studies. Comparing exposures and outcomes between different population groups may cause problems as the two populations may differ with respect to other exposures or characteristics and so a causal relationship between the observed exposure and outcomes cannot be assumed. In observational studies (e.g. other than a randomised controlled trial) many people know whether or not a water supply is fluoridated and so blinding would not be possible, thus risking bias in observations.

Some possible adverse effects of water fluoridation may take many years to develop and so unless a study is specifically designed to investigate the relationship of these outcomes to fluoridation the relationship may go undetected. An assessment of the effectiveness of fluoridation on the incidence of caries is difficult because there are a number of factors that may influence caries prevalence other than fluoride in water, and these have changed over time. These factors include the introduction of fluoridated toothpaste, mouth rinses and improved dental hygiene in general. Traditional reviews of the literature tend to ignore the variable quality of studies and are therefore unlikely to present a reliable summary. Ideally, systematic reviews concentrate on studies that provide the strongest evidence, but where only a few good studies are available weaker designs may have to be considered.

Existing reviews do not address the major issues of benefit and harm in conjunction and in a systematic manner, as this review aims to do. The explicit methods used in this systematic review will limit bias through the use of specific inclusion criteria, and a formal assessment of the quality and reliability of the studies reviewed. The use of meta-analysis will increase statistical power and thus the precision of estimates of treatment effects and exposure risks. Finally, this review attempts to generate new questions and identify gaps in the research evidence.

1.1 Purpose

The aim of this systematic review is to assess the evidence on the positive and negative effects of population-wide drinking water fluoridation strategies to prevent caries. To achieve this aim five objectives have been identified:

Objective 1: What are the effects of fluoridation of drinking water supplies on the incidence of caries?

Objective 2: If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

Objective 3: Does water fluoridation result in a reduction of caries across social groups and between geographical locations, bringing equity?

Objective 4: Does water fluoridation have negative effects?

Objective 5: Are there differences in the effects of natural and artificial water fluoridation?

2. METHODS

A diagram illustrating the stages of this systematic review's methods is presented in Figure 2.1.

2.1 Search strategy

2.1.1 Preliminary search

A preliminary search was undertaken to provide information on available reviews of fluoridation and to estimate the potential size of the research evidence on the effects of fluoride supplementation of drinking water. The preliminary search was carried out in several stages:

- Identification and collection of reviews of fluoridation.
- Medline search using a methodology filter strategy to identify the scope of the systematic reviews and meta-analyses literature (date range 1966 - 03/1999).
- Medline and Embase searches using a methodology filter strategy to identify primary studies including any randomised trials. (Medline date range 1966 - 05/1999; Embase date range 1980 – 05/1999).

The Medline and Embase databases were both searched using WinSpirs/SilverPlatter software. Further details about the preliminary search process are given in Appendix B, Section 1. The preliminary search strategy to retrieve systematic review and meta-analyses literature is included in Appendix B, Section 3.

2.1.2 Electronic database search

The full search built on the preliminary search strategies and involved searching a wide range of medical, political and environmental/scientific databases to identify primary studies. Each database was searched from its starting date to June/October 1999 (due to the number of databases, searches were carried out over a four month period). A list of the databases searched at each stage of the review and the dates searched are given in Appendix B, Section 2. Full details of all the strategies used in this review are given in Appendix B, Section 4. The databases searched were as follows:

- Medline
- Embase
- NTIS (National Technical Information Service)
- Biosis
- Current Contents Search (Science Citation Index and Social Science Citation Index)
- Healthstar (Health Service Technology, Administration and Research)
- HSRProj
- TOXLINE
- Chemical Abstracts
- OldMedline
- CAB Health
- FSTA (Food Science and Technology Abstracts)
- JICST- E Plus (Japanese Science and Technology)
- Pascal
- EI Compendex (Engineering Index)
- Enviroline
- PAIS (Public Affairs Information Services)
- SIGLE (System for Information on Grey Literature in Europe)
- Conference Papers Index
- Water Resources Abstracts
- Agricola (Agricultural Online Access)
- Waternet
- AMED (Allied and Complementary Medicine Database)
- Psyclit
- LILACS (Latin American and Caribbean Health Sciences Literature)

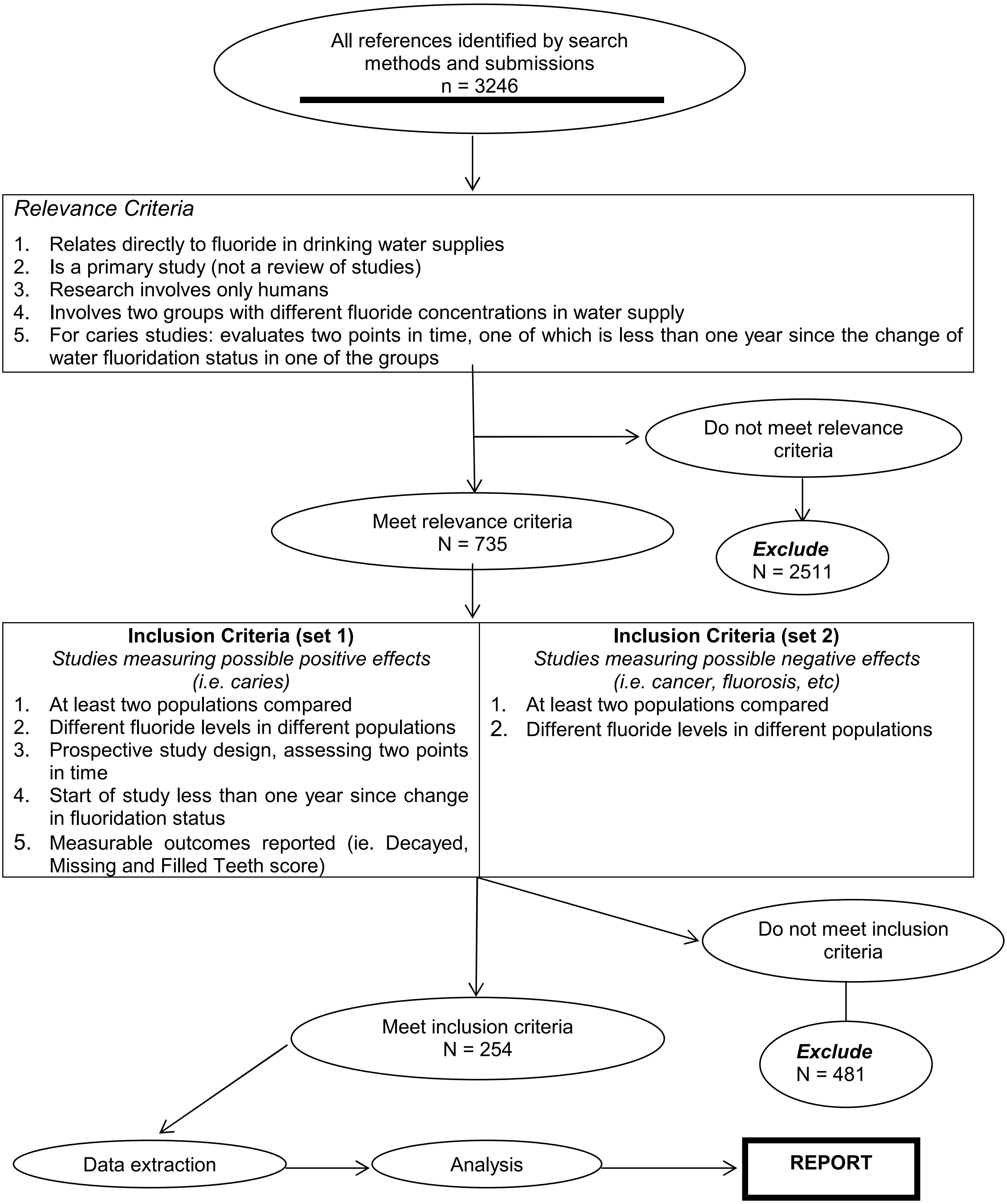


Figure 2.1 Review methods

2.1.3 Other searching

The World Wide Web was searched for web pages maintained by others interested in the issue of water fluoridation. A web page was designed and maintained by the NHS Centre for Reviews and Dissemination, University of York to inform the public on the purpose, methods and progress of the review. The web site included an e-mail response to enable members of the public and other organisations to submit articles for consideration. In addition to numerous individuals, examples of organisations that submitted lists of references are the National Pure Water Association and the British Fluoridation Society. Furthermore, advisory board members were asked to submit references or reports.

2.1.4 Hand searches

Hand searching of Index Medicus and Excerpta Medica was undertaken. Index Medicus was searched from 1959 back to 1945; Excerpta Medica was searched from 1973 back to 1955. A further sample of studies published before 1945 was retrieved from Index Medicus and Excerpta Medica and established that further searching was not required. Appendix B, Section 3 provides a list of search terms used in this hand searching process. The bibliographies of the eligible papers were also hand searched. Attempts were made to contact authors for further information if necessary. Further information about studies done in the UK was sought and obtained through the Public Records Office.

2.1.5 Updating the search

Update searches were undertaken at the beginning of February 2000. In order to identify the most useful databases, the included studies were examined to determine which of the above resources yielded the most studies included. Medline, Embase, Toxline and the Current Contents (Science Citation Index) were identified in this manner and included in the update search process.

2.1.6 Management of references

As such a wide range of databases had been searched, some degree of duplication of references resulted. In order to manage this issue, the titles and abstracts of the bibliographic records retrieved were downloaded and imported into Endnote (ISI ReSearch Soft, USA) reference management software to remove duplicate records.

2.2 Inclusion criteria

2.2.1 Methodological and quality criteria

Groups exposed or not exposed to fluoride may differ in respect to factors other than fluoride exposure itself. Some of these differences may be related to the outcomes under investigation (level of tooth decay, dental fluorosis, fractures etc) and so will confound any observed relationship and thus should be controlled for in the analysis. Confounding factors are factors that can cause or prevent the outcome of interest. In the case of water fluoridation these are likely to include age, gender, ethnicity, other sources of fluoridation and social class. Factors likely to modify the effect of fluoride on the outcomes under investigation, such as the level of tooth decay or delayed tooth eruption in the population before the introduction of fluoridation should also be considered.

Another important factor to be taken into account in assessing the effects of water fluoridation is blinding of outcome assessment. Blinding should be used to protect against the possibility that knowledge of participant's exposure to water fluoridation may affect the ways in which the investigators assess outcomes. Knowledge of outcomes may also affect assessment of fluoridation status and other factors in retrospective studies.

The following methodological issues were considered when assessing studies for inclusion: selection, confounding, and measurement. Study designs are often graded hierarchically according to their quality, or degree to which they are susceptible to bias. The hierarchy indicates which studies should be given most weight in a synthesis. In this review, the degree to which each study dealt with the methodological issues was graded into three levels of evidence:

LEVEL A (HIGHEST QUALITY OF EVIDENCE, MINIMAL RISK OF BIAS)

- Prospective studies that started within one year of either initiation or discontinuation of water fluoridation and have a follow up of at least two years for positive effects and at least five years for negative effects.
- Studies either randomised or address at least three possible confounding factors and adjust for these in the analysis where appropriate.
- Studies where fluoridation status of participants is unknown to those assessing outcomes.

LEVEL B (EVIDENCE OF MODERATE QUALITY, MODERATE RISK OF BIAS)

- Studies that started within three years of the initiation or discontinuation of water fluoridation, with a prospective follow up for outcomes.
- Studies that measured and adjusted for less than three but at least one confounding factor.
- Studies in which fluoridation status of participants was known to those assessing primary outcomes, but other provisions were made to prevent measurement bias.

LEVEL C (LOWEST QUALITY OF EVIDENCE, HIGH RISK OF BIAS)

- Studies of other designs (e.g. cross-sectional), prospective or retrospective, using concurrent or historical controls, that meet other inclusion criteria.
- Studies that failed to adjust for confounding factors.
- Studies that did not prevent measurement bias.

Studies meeting two of the three criteria for a given evidence level were assigned the next level down. For example, if a study met the criteria for prospective design and blinding for level A, but was neither randomised nor controlled for three or more potential confounding factors, it was assigned level B. Evidence rated below level B was not considered in our assessment of positive effects. However, this restricted assessment of the evidence for Objective 3, so the best level of evidence relevant to this objective (from any study design) was included. In our assessment of possible negative effects, all levels of evidence were considered. Adjustment for confounding factors required analysis of data, simply stating that two study groups were similar on noted confounding factors was not considered adequate.

2.2.2 Objective specific criteria

Specific inclusion criteria for each objective were based on the participants, intervention, outcomes measured and overall design of the study. All criteria were defined before the studies were assessed and were based on criteria commonly applied when critically appraising community based interventions (Elwood 1998). This review is limited to studies investigating the effects of water fluoridation on human populations. The objective-specific criteria for inclusion based on study design were:

OBJECTIVE 1. DOES FLUORIDATION OF DRINKING WATER SUPPLIES PREVENT CARIES?

Participants:

- Populations receiving fluoridated water (naturally or artificially)
- Populations receiving non-fluoridated water

Intervention:

- A change in the level of fluoride in the water supply of at least one of the study areas, within three years of the baseline survey.

Outcomes:

- Any measure of dental decay

Study designs:

- Prospective studies comparing at least two populations, one receiving fluoridated the other non-fluoridated water, with at least two points in time evaluated.

OBJECTIVE 2. IF FLUORIDATION IS SHOWN TO HAVE BENEFICIAL EFFECTS, WHAT IS THE EFFECT OVER AND ABOVE THAT OFFERED BY THE USE OF ALTERNATIVE INTERVENTIONS AND STRATEGIES?

Participants:

- Populations receiving fluoridated water (naturally or artificially) in addition to other interventions.
- Populations receiving non-fluoridated water in addition to other interventions.

Intervention:

- A change in the level of fluoride in the water supply of at least one of the study areas, within three years of the baseline survey.

Outcomes:

- Any measure of dental decay.

Study designs:

- Prospective studies comparing at least two populations, to investigate the differences in levels of tooth decay between the populations in the presence of other sources of fluoride, e.g. fluoridated toothpaste. Where specific information on the use of other sources of fluoride is not supplied, populations in studies conducted after 1975 in industrialised countries were assumed to have been exposed to fluoridated toothpaste.

OBJECTIVE 3. DOES FLUORIDATION RESULT IN A REDUCTION OF CARIES ACROSS SOCIAL GROUPS AND BETWEEN GEOGRAPHICAL LOCATIONS?

Participants:

- Populations from different social groups and geographic locations receiving fluoridated water (naturally or artificially).
- Populations from different social groups and geographic locations receiving non-fluoridated water.

Intervention:

- Fluoride at any concentration present in drinking water, either controlled or naturally occurring

Outcomes:

- Any measure of dental decay.

Study designs:

- Any study design comparing two populations, one receiving fluoridated the other non-fluoridated water, across different social groups and geographic locations.

OBJECTIVE 4. DOES FLUORIDATION HAVE NEGATIVE EFFECTS?

Participants:

- Populations receiving fluoridated water (either naturally or artificially).
- Populations receiving non-fluoridated water .

Intervention:

- Fluoride at any concentration present in the water supply, either naturally occurring or artificially added.

Outcomes:

- Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other possible negative effects reported in the literature.

Study designs:

- Any study design comparing the incidence of any possible adverse effect between two populations, one with fluoridated water and the other with non-fluoridated water.

OBJECTIVE 5. ARE THERE DIFFERENTIAL EFFECTS OF NATURAL AND ARTIFICIAL FLUORIDATION ?

Participants:

- Populations receiving artificially fluoridated water.
- Populations receiving naturally fluoridated water.

- Populations receiving non-fluoridated water.

Intervention:

- Fluoride at any concentration from a naturally or an artificially fluoridated water source.

Outcomes:

- Possible positive effects: Any measure of dental decay.
- Possible negative effects: Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other possible negative effects reported in the literature.

Study designs:

- Any study design comparing populations exposed to different water fluoride concentrations, results obtained from areas using artificially and naturally fluoridated water supplies were compared to investigate any differences in effect.

Studies meeting the above objective specific criteria for inclusion were also assigned a level of evidence, as described above.

2.3 Assessment of papers for inclusion

2.3.1 Relevance assessment

Three reviewers independently assessed each title and abstract located through the searches for relevance to the review. Decisions about the inclusion of studies were made according to the following pre-determined criteria:

- Relates directly to fluoride in drinking water supplies.
- Is a primary study (not a review of studies).
- Research involves humans.
- Involves two groups with different fluoride concentrations in water supply.
- For caries studies: evaluates two points in time, one of which is less than three years since the change of water fluoridation status in one of the two groups.

Full articles of titles and abstracts found to be relevant to the review were obtained for full assessment of inclusion criteria.

2.3.2 Assessment of papers for inclusion criteria

Three reviewers independently assessed each paper for the pre-determined inclusion criteria, as stated above. Inclusion criteria were assessed for each of the objectives separately. Disagreements were resolved through consensus.

2.4 Data extraction

Extraction of data from individual included studies was independently performed by two reviewers, and checked by a third reviewer. Disagreements were resolved through consensus. Papers in languages other than English were assessed for inclusion criteria and data extracted using appropriate translators. Languages translated were Bulgarian, Chinese, Czech, Dutch, French, German, Greek, Hungarian, Italian, Portuguese, Russian and Spanish. Data were extracted into an MS Access database (Microsoft Corporation 1989-96). Tables showing baseline information and results were produced for each study and are presented in Appendix C.

2.5 Assessment of study validity

Study validity was formally assessed using validity checklists based on the checklist in NHS Centre for Reviews and Dissemination Report Number 4 (NHS CRD, 1996). The checklist was modified to address issues of water fluoridation. Separate checklists were devised for studies using a case-control design and all other study designs combined. These checklists are presented in Appendix D. Each study was assigned a ‘level of evidence’ using the definitions given above, and a validity score, based on the number of checks achieved on the checklist. The maximum score was 8 for all study designs except case control studies which had a total of 9 possible points. Study validity was assessed independently by two reviewers, with disagreements resolved through consensus.

The level of evidence (A, B, or C) is generic, and was used to classify studies for inclusion criteria based on overall quality and chance for bias. The validity assessment checklist is more specific to water fluoridation studies. Therefore, the validity checklist assessment is stricter.

2.6 Data analysis

Where the data were in a suitable format, measures of effect (with their 95% confidence intervals) for the major outcomes identified were shown on forest plots. This allowed a visual evaluation of the overall data set. The range of measures of effect for each outcome is also presented in the text.

Differences among studies may explain why individual studies report differing estimates of effect. These differences may relate to study design, geographic location, age of participants, type and duration of intervention, and methods of outcome assessment. Such differences between studies are known as heterogeneity, which may or may not be important. Some heterogeneity can be expected to occur by chance. A distinction is sometimes made between statistical heterogeneity (differences in the reported effects), methodological heterogeneity (differences in study design) and clinical heterogeneity (differences between studies in key characteristics of the participants, interventions or outcome measures). Statistical tests for heterogeneity are used to assess whether the observed variability in study results (measures of effect) is greater than that expected to occur by chance. If there is statistically significant heterogeneity between the estimates derived from different studies, this may result in a decision not to combine the studies in a meta-analysis. Statistical heterogeneity can exist even when all the studies included show an effect in the same direction (e.g. a protective effect), but there is variation in the estimate of the magnitude of the effect. Heterogeneity was investigated by visual examination of the forest plots and statistically using the Q-statistic. Even if the assessment of heterogeneity is not statistically significant there may be important heterogeneity.

Where no evidence of statistically significant heterogeneity was found, a meta-analysis was conducted to produce a pooled estimate of the measure of effect. The DerSimonian and Laird random effects model, which assumes that the study specific measures of effect come from a random distribution of measures of effect with a fixed mean and variance, was used to combine studies. It is a more conservative analysis, resulting in broader confidence intervals, used because some degree of underlying heterogeneity among the studies was assumed.

Tables indicating the general effect of fluoridation found in each study were created for each item, and, where possible, the point estimate and a measure of statistical significance (using the 95% confidence interval or p-value) of the finding was also included. Validity scores were included in these tables to allow assessment of the relationship between study quality and strengths of the association with fluoridation. Statistical analysis was carried out using StatsDirect (CamCode, England), Stata (Stata Corporation, USA), SAS (SAS institute Inc., USA) and Access (Microsoft Corporation, USA).

A table was not made for dental fluorosis, as the method of analysis used for this outcome differed from that used for other outcomes. The analysis used for fluorosis compared each fluoridated study area to each non-fluoridated study area, using a regression analysis, rather than comparing the differences found within each study to the differences found within other studies.

Where possible, meta-regression was used to investigate and explain sources of heterogeneity among studies. Meta-regression is an exploratory statistical analytical technique, which investigates the importance and nature of relationships between study results and study characteristics, and can be used to explore sources of heterogeneity. This is a modelling exercise that estimates the amount by which each identified ‘predictor variable’ (e.g. age) reduces the remaining heterogeneity. Dental caries and bone fracture results were analysed using meta-regression in order to assess the impact of potential sources of heterogeneity and estimate the underlying effect of water fluoridation. Meta-regression was carried out using Stata v. 6.0 (Stata Corporation, USA). The heterogeneity among fluorosis studies was explored by including variables that may account for the observed heterogeneity in the regression model.

Publication bias is defined as the failure to publish research on the basis of the nature and directional significance of the results. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. The data provided by the studies included in this review were not in a suitable format to allow investigation of publication bias using standard procedures (e.g. Funnel plots), and so a narrative approach was used to discuss publication bias.

3. GENERAL RESULTS

3.1 General results

The search identified over 3200 papers, of which 734 met relevance criteria. Upon closer inspection, 254 of these met full inclusion criteria for one or more of the objectives; these 254 papers relate to 214 studies (some papers refer to the same study). Among these there were 26 studies relevant to Objective 1, the effect of water fluoridation on dental caries; 9 of these also met inclusion criteria for Objective 2. For Objective 3, 13 studies were included. For Objective 4, a total of 176 studies were included. There were 88 studies on dental fluorosis, 29 on bone fractures, 26 on cancer, and 33 studying other possible adverse effects. These included studies came from 30 countries, were published in 14 languages and ranged in publication dates from 1939 to 2000. No randomised controlled trials of the effects of water fluoridation were found. The study designs used included 45 'before and after' studies, 102 cross-sectional studies, 47 ecological studies, 13 cohort (prospective or retrospective) studies and seven case-control studies. Several studies were reported in multiple papers over a number of years. For example, the original studies from Michigan were published in six papers, between 1942 and 1962.

3.2 Validity assessment

None of the included studies were of evidence level A. The reason for this among the studies evaluating dental caries was that none addressed three or more confounding factors. For Objectives 1 and 2, all studies that met inclusion criteria were evidence level B. All but three of the studies assessing Objective 3, were evidence level C, the others were evidence level B. Among the studies of possible adverse effects of water fluoridation, Objective 4, the majority were found to be level C evidence because they lacked a prospective, longitudinal design. Studies used to compare the effects of natural versus artificial water fluoridation, Objective 5, were evidence level B for possible positive effects and mainly level C for possible negative effects. The validity checklist scores and level of evidence are presented in D.

3.3 Extracted data

Data extracted from all of the included studies are presented in tables in Appendix C. Each outcome is presented in two separate tables, the first listing baseline data about the groups being studied, such as location and year of study, gender, and the methods used to assess outcome. The second table presents the results of each study by each outcome.

3.4 Protocol changes

Changes to the original protocol were minimal. The wording of the objective specific inclusion criteria was altered to clarify the intent of the criteria. The range of analyses undertaken was broader than had been described in the protocol. Due to extremely limited evidence, the inclusion criteria for Objective 3 were expanded to include studies of level C evidence, and limited to studies from the UK. These changes were made with the consultation of and agreement from the advisory panel. Full details of changes are included in Appendix M.

4. OBJECTIVE 1

What are the effects of fluoridation of drinking water supplies on the incidence of caries?

A total of 26 studies of the effect of water fluoridation on dental caries were found, reported in 73 articles published between 1951 and 2000. Five unpublished studies were located (Hobbs 1994, Wragg 1992, Gray 1999, Holdcroft 1999 and Gray, 2000). The before-after study design was used in all but three of the included studies. The three exceptions were two prospective cohort studies (Hardwick 1982, Maupomé 2000) of caries in children and one retrospective cohort study (Pot 1974) of adults with false teeth. An example of the before-after design is a study in which two groups of 12-year olds from two similar populations were examined for prevalence of caries prior to initiating water fluoridation in one of the groups. Five years after starting water fluoridation, 12 year olds were examined in the two areas (one fluoridated, the other not). The rates of caries in the first groups were then compared with the rates in the second groups. It is important to note that the children are different in the before and after periods. All before-after studies identified by the search met the inclusion criteria. Three of the studies met inclusion criteria but were not included in the main analysis and are discussed in section 4.3 (Klein 1946, Holdcroft 1999 and Gray 2000). The Hardwick cohort study examined two groups of British children at age 12 prior to the initiation of fluoridation in the water supply of one group, and followed these same children with annual examinations for four years.

Seven studies assessed the effect of discontinuing water fluoridation, including seven before-after analyses and one cohort study (Attwood 1988, Hobbs 1994, Kalsbeek 1993, Kunzel 1997, Maupomé 2000, Seppa 1998 and Wragg 1992). The Maupomé cohort study examined two groups of 8 and 14 year-old children within 14 to 19 months after fluoridation was stopped in one area and continued in the other. These same children were then re-examined three years later. This study also included a second group of children 8 and 14 years old at the follow-up examination, and so is both a before-after and cohort design. Only one of the 26 studies included examined adults (Pot 1974).

The studies assessing efficacy of water fluoridation all achieved evidence level B, and an average checklist score of 5 out of 8 (range 3.5 to 6.8). The checklist items most commonly missed by these studies were blinding of the examiners assessing outcomes to the children's exposure status, reliable measurement (or adequate reporting) of the fluoride concentration, and adequate investigation of confounding factors. None attempted to control for confounders using multivariate analysis (a technique commonly used since the early 1980s). The only method used to address confounding was by presenting data stratified by age or gender. Many additional studies were excluded because they failed to include a baseline examination prior to starting or stopping water fluoridation.

The measure of effect measure used in the main analysis was the difference of the *change* in caries from the baseline to the final examination in the fluoridated compared with the control area (Appendix E). For example, the change in DMFT in the fluoridated area (final survey minus baseline survey) minus the change in DMFT in the control (non-fluoridated) area (final survey minus baseline survey) is the *difference* in the change in DMFT for that study. The two main outcomes investigated by studies estimating the effect of fluoridation on caries were DMFT (and dmft) score and the proportion of caries-free children (in both primary and secondary dentition).

Tables 4.1 - 4.5 show the 26 studies that have been included in assessing objective 1. In these tables, the mean difference of the change in caries measurement between the fluoride and control areas is shown. If the reduction in dental caries between pre- and post-fluoridation periods was greater in the fluoridated group than in the non-fluoridated group the mean difference will be greater than zero. Thus, a mean difference greater than zero indicates a benefit of water fluoridation and a mean difference less than zero indicates no benefit of water fluoridation. If the 95% confidence intervals include zero the difference is not statistically significant at the 5% level.

4.1 Studies in which fluoridation was initiated

Figure 4.1 shows the mean difference of the change in the proportion (%) of caries-free children in the exposed (fluoride) group compared with the control group (low fluoride), for all ages extracted (colour coded by age), for studies in which fluoridation was initiated after the baseline survey.

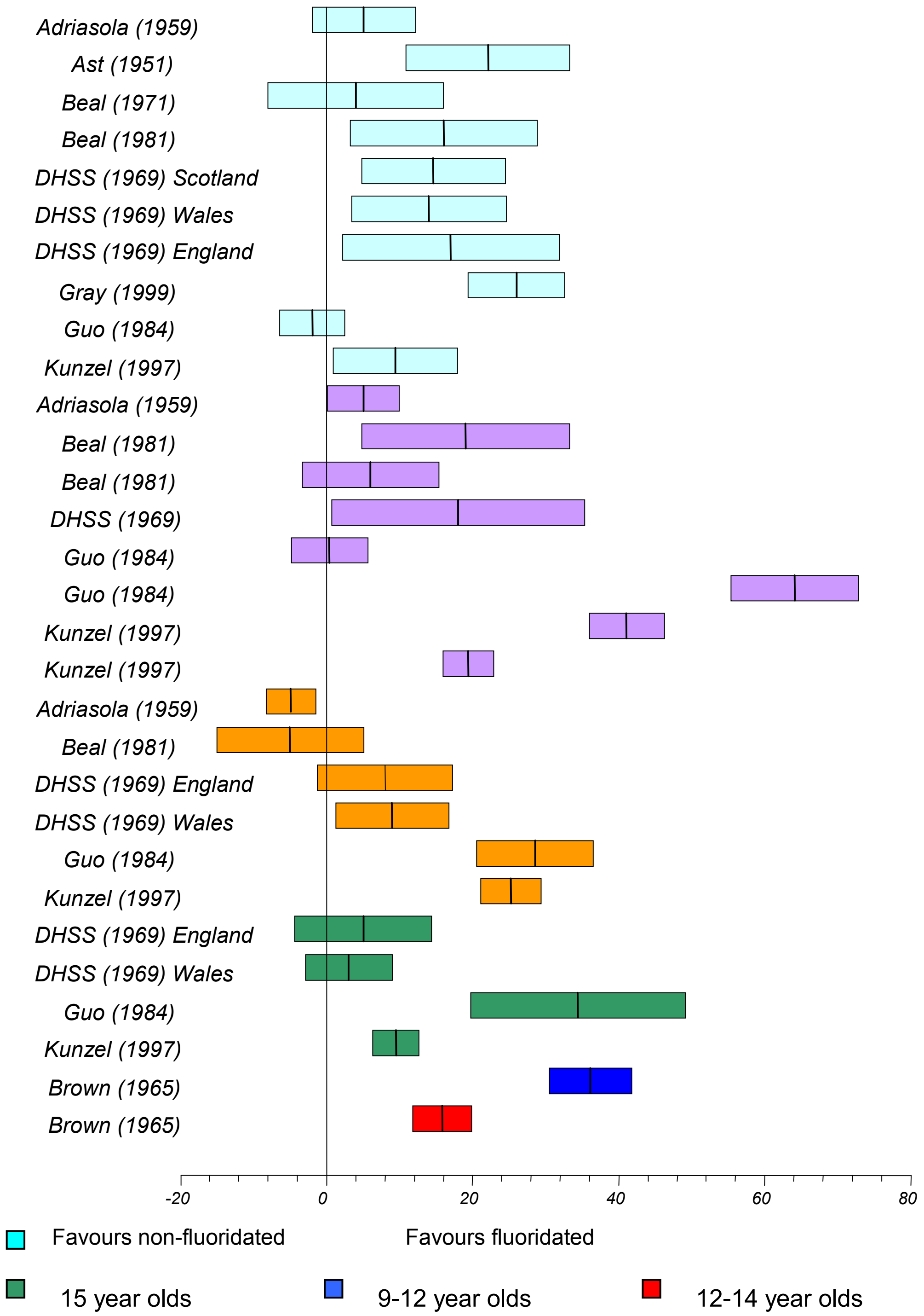


Figure 4.1: Increase in proportion (%) of caries-free children in fluoridated compared to non-fluoridated areas (mean difference and 95% CI)

The vertical line, at 0, is the 'no effect' line for measures of difference. Studies are indicated with a rectangle showing the 95% confidence intervals around the mean. The 95% confidence interval is the interval within which 95% of values of estimates derived from identified studies will fall. The rectangles are colour coded by age. If the rectangle crosses the 'no effect' line the difference is not statistically significant. If the rectangle is entirely to the right of the line the difference is statistically significant and fluoridation is associated with an increase in the proportion of children who are caries-free. If the rectangle is entirely to the left of the line the difference is statistically significant and fluoridation is associated with a decrease in the proportion of children who are caries-free.

The range of the mean difference in the proportion (%) of caries-free children is -5.0 to 64%, with a median of 14.6% (interquartile range 5.05, 22.1%). There was a statistically significant change, with a greater proportion of caries-free children in the fluoridated area, in 19 analyses. One analysis found a statistically significant greater decrease in the proportion of caries-free children exposed to fluoridated water compared with those exposed to non-fluoridated water. The remaining 10 analyses were unable to detect a statistically significant difference. It is estimated that a median of six people need to receive fluoridated water for one extra person to be caries-free (interquartile range of study NNTs 4, 9).

Figure 4.2 shows the mean difference of the change in dmft /DMFT in the exposed (fluoride) compared with the control group (low fluoride), separately by age (colour coded) for the four studies reporting dmft/DMFT, with 95% CIs.

Fifteen studies found a statistically significantly greater mean change in dmft/DMFT scores in the fluoridated areas than the non-fluoridated areas. The range of mean change in dmft/DMFT score was from 0.5 to 4.4, median 2.25 teeth (interquartile range 1.28, 3.63 teeth).

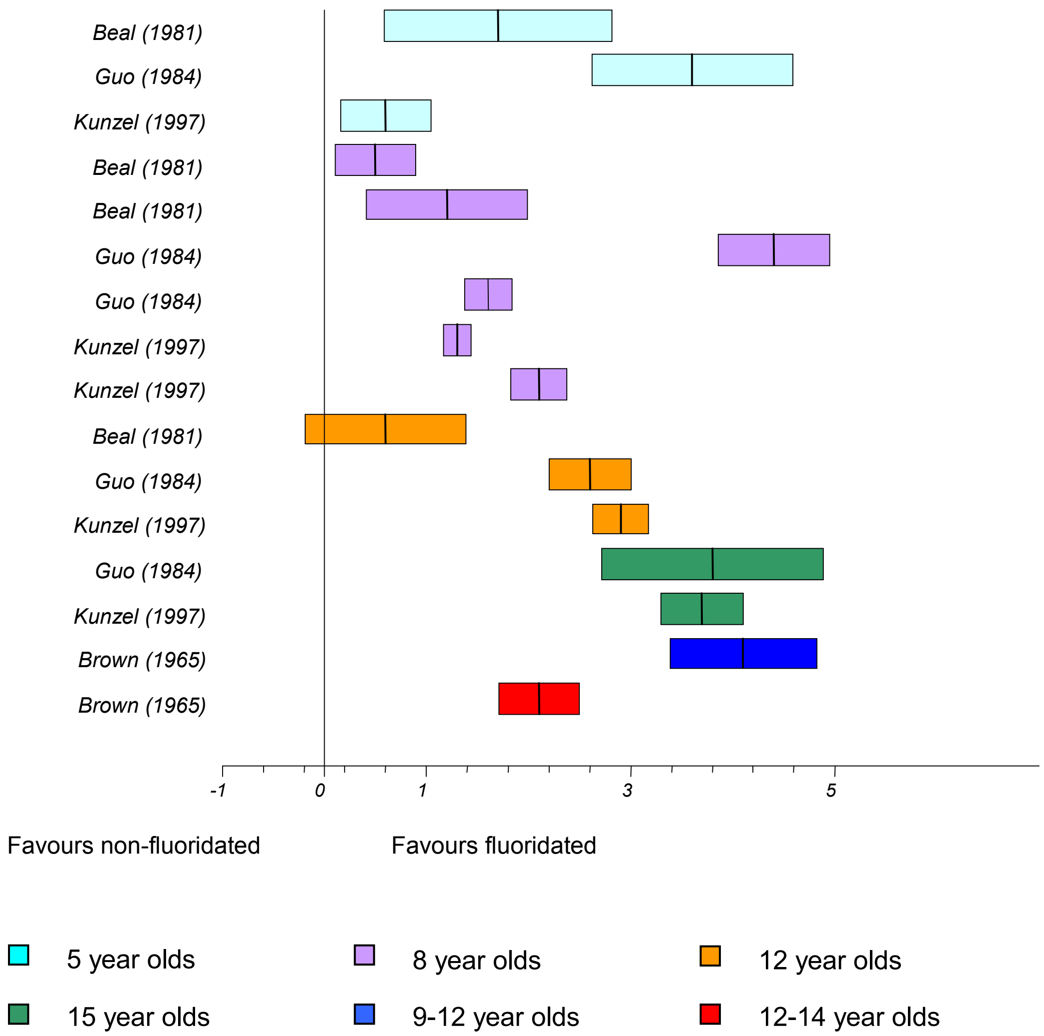


Figure 4.2: Change in dmft/DMFT Score (mean difference and 95% CI)

The Hardwick cohort study was plotted separately (figure 4.3) because the outcome measurements (increment in DMFT and DMFS) were too dissimilar to the others. In this study the effect of water fluoridation was assessed in the same children over a three-year period. This study showed a statistically significant mean difference in the increment in DMFT/DMFS score, with children in the fluoridated area having fewer *new* decayed, missing or filled teeth (or surfaces) after the three-year period. The examiners in this study were blind to the fluoridation status of the children.

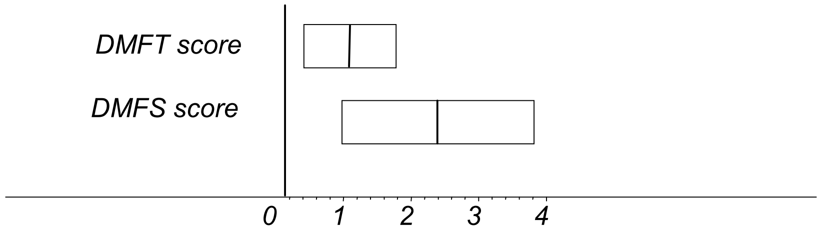


Figure 4.3 DMFT/DMFS increment over four years (mean difference and 95% CI)

Table 4.1 Mean difference of the change in the proportion of (%) caries-free children between the fluoride and control areas

Author (Year)	*Age*	**Teeth Type**	**Mean Difference** (95% CI)	**Validity Score**
Kunzel (1997)	5	Primary	**9.4** (0.9, 17.9)	**5.8**
	8	Permanent	**41.1** (36.0, 46.2)	
	8	Primary	**19.4** (15.9, 22.9)	
	12	Permanent	**25.2** (21.1, 29.3)	
	15	Permanent	**9.5** (6.3, 12.7)	
Beal (1981)	5	Primary	**16.0** (3.2, 28.8)	**5.5**
	8	Permanent	**19.0** (4.8, 33.2)	
	8	Primary	**6.0** (-3.4, 15.4)	
	12	Permanent	**-5.0** (-15.0, 5.0)	
DHSS (1969)	5	Primary	**17.0** (2.1, 31.9)	**5.5**
England	8	Not stated	**18.0** (0.7, 35.3)	
	12	Not stated	**8.0** (-1.2, 17.2)	
	14	Permanent	**5.0** (-4.4, 14.4)	
Wales	5	Primary	**14.0** (3.5, 24.5)	
	12	Not stated	**9.0** (1.2, 16.8)	
	14	Permanent	**3.0** (-2.9, 8.9)	
Scotland	5	Primary	**14.6** (4.79, 24.4)	
Adriasola (1959)	5	Primary	**5.1** (-1.9, 12.1)	**5.2**
	8	Not stated	**5.0** (0.1, 9.9)	
	12	Not stated	**-4.9** (-8.3, -1.5)	
Guo (1984)	5	Primary	**-2.0** (-6.4, 2.4)	**4.8**
	8	Permanent	**64.1** (55.4, 72.8)	
	8	Primary	**0.4** (-4.8, 5.6)	
	12	Permanent	**28.5** (20.5, 36.5)	
	15	Permanent	**34.4** (19.7, 49.1)	
Beal (1971)	5	Not stated	**4**(-8.0, 16.0)	**4.8**
Ast (1951)	5	Primary	**22.1** (10.9, 33.3)	**4.5**
Brown (1965)	12-14	Permanent	**15.8** (11.8, 19.8)	**4.5**
	9-11		**36.1** (30.5, 41.7)	
Gray (1999)	5	Primary	**26.0** (19.4, 32.6)	**3.5**

The associations that were found in the studies in which fluoridation was initiated are presented in Tables 4.1 and 4.2. Table 4.3 shows the results of studies using outcome measures other than the proportion of caries-free children or dmft/DMFT score. Some studies either did not provide data on the variance of the estimate of effect or the number of individuals studied. Further information was sought from the authors of these studies, however, only one author was contacted successfully.

Studies without variance data were not included in the plots or in the meta-regression. The reason for excluding data from further analysis is stated in the table.

Whilst in 27 of the 30 analyses the direction of association between water fluoridation and the change in the proportion of caries-free children was positive (fewer caries), in only 20 of these comparisons were the differences statistically significant. In three analyses the direction of association was negative (one in five-year-olds and two in 12 year-olds), but only one of these found a statistically significant effect (Table 4.1).

In all 31 analyses the direction of association of the dmft/DMFT scores with fluoridation status was positive. Standard error data were only available for 16 of these analyses, all but one of which showed a statically significant positive effect of fluoridation (Table 4.2).

Table 4.2 Mean difference of the change in dmft/DMFT between the fluoride and control areas

Author (Year)	**Age**	**Teeth Type**	**Mean Difference** ***(95% CI)***	**Included in Analysis**	**Reason not Included in Further Analysis**	**Validity Score**
Kunzel (1997)	5 8 8 12 15	Primary Primary Permanent Permanent Permanent	**0.6** (0.2, 1.0) **2.1** (1.8, 2.4) **1.3** (1.2, 1.4) **2.9** (2.6, 3.2) **3.7** (3.3, 4.1)	Yes		**5.8**
Beal (1981)	5 8 8 12	Primary Permanent Primary Permanent	**1.7** (0.6, 2.8) **0.5** (0.1, 0.9) **1.2** (0.4, 2.0) **0.6** (-0.2, 1.4)	Yes		**5.5**
DHSS (1969) England	5 8 12 14	Primary Permanent Permanent Permanent	**1.6** **0.8** **1.0** **1.5**	No	No standard error data	**5.5**
Wales	5 12 14	Primary Permanent Permanent	**2.1** **2.5** **2.3**			
Loh (1996)	7-9 7-9	Permanent Permanent	**3.1** **2.1**	No	No standard error data	**5.1**
Guo (1984)	5 8 8 12 15	Primary Permanent Primary Permanent Permanent	**3.6** (2.6, 4.6) **1.6** (1.4, 1.8) **4.4** (3.9, 4.9) **2.6** (2.2, 3.0) **3.8** (2.7, 4.9)	Yes		**4.8**
Alvarez-Ubilia (1959)	5	Primary	**2.2**	No	No standard error data	**4.5**
Arnold (1956)	12 15 8	Permanent Permanent Permanent	**1.2** **3.1** **1.2**	No	No standard error data	**4.5**
Blayney (1960)	12 8	Permanent Permanent	**3.4** **1.8**	No	No standard error data	**4.5**
Brown (1965)	12-14 9-11	Permanent Permanent	**4.1** (3.4, 4.8) **2.1** (1.7, 2.5)	Yes		**4.5**

The study with the highest validity score (Hardwick, 1982) showed a statistically significant difference in the increment in both DMFS and DMFT scores, with a lower increment in the fluoridated area compared with the control area. One study (Backer-Dirks, 1961) considered the average number of all dentinal lesions and the average number of approximal dental lesions. This study found the direction of association of fluoridation with caries to be positive (fewer caries) but no measure of the statistical significance of this effect was provided. Two studies (Beal, 1971 and Arnold, 1956) looked at deft score. Whilst both these studies found the direction of association to be positive, only one of these studies (Beal, 1971) provided standard error data. This study showed a statistically significant positive effect of fluoridation. One study (Ast, 1951) compared the number of erupted teeth per child before and after fluoridation was initiated and found the direction of association to be positive with fluoridation (more erupted teeth per child) in 12 year-olds but negative in 8 year-olds. No measure of the statistical significance of this association was provided, however, and the difference was so small that is unlikely that there was a statistically significant difference in the number of erupted teeth in the fluoridated compared with the control area. This same study also looked at the DMFT rate per 100 erupted teeth and found the direction of association to be positive (greater decrease in the DMFT rate in the fluoridated area compared with the control area) with water fluoridation. However no measure of the significance of this association was provided. One study (Pot, 1974) found the proportion of adults with false teeth to be statistically significantly greater in the control (low-fluoride) area compared with the fluoridated area.

Table 4.3 Mean difference of the change in other caries measurements between the fluoride and control areas

Author (Year)	Age	Mean Difference *(95% CI)*	Outcome	Validity Score
Hardwick (1982)	12 12	**2.5** (1.0, 3.9) **1.1** (0.4, 1.8)	Increment in DMFS score Increment in DMFT score	**6.8**
Backer-Dirks (1961)	11-15 11-15	**2.7** **1.4**	Average number of all approximal lesions Average number of approximal dentinal lesions	**5.0**
Beal (1971)	5	**2.5** (1.3-3.7)	deft score	**4.8**
Arnold (1956)	5 8	**1.6** **0.9**	deft score	**4.5**
Ast (1951)	12 8 12 8	**0.1** **-0.3** **10.5** **7.1**	Number of erupted permanent teeth per child DMFT rate per 100 erupted permanent teeth	**4.5**
Pot (1974)	5-55	**11.2** (3.8, 18.6)	% with false teeth	**4.0**

4.2 Studies in which fluoridation was discontinued

Figure 4.4 shows the mean difference of the change in the dmft/DMFT and DMFS score in children in the exposed (fluoride) group compared with the control group (low fluoride), in studies in which fluoridation was discontinued after the baseline survey.

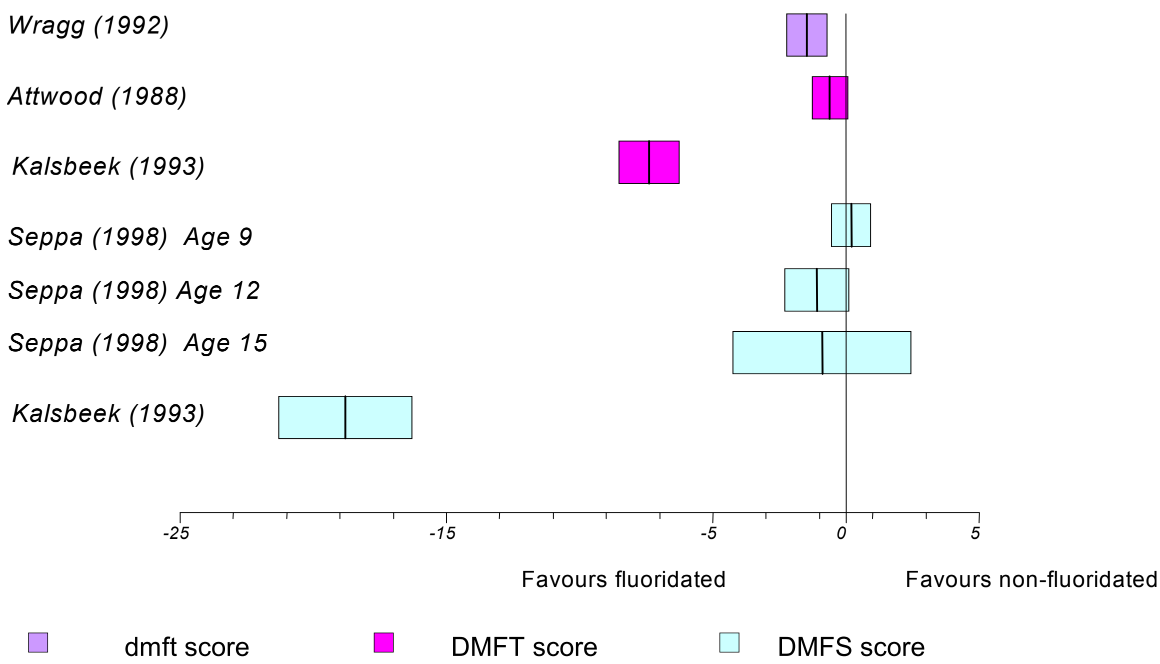


Figure 4.4: Stopping fluoridation: dmft/DMFT or DMFS score (mean difference and 95% CI)

The range of measures of effect in dmft/DMFT scores (Figure 4.4) is –7.4 to –0.6. Two of the three studies using dmft/DMFT show a statistically significant difference: when fluoridation was discontinued there was a greater increase in caries in the fluoridated compared with the control area suggesting that fluoridation had been beneficial. The range in measures of effect for DMFS score was –18.8 to 0.2, with all but one of the studies suggesting that stopping water fluoridation had led to a greater increase in caries in the previously fluoridated area than in the non-fluoridated area. Only one of the four analyses using DMFS found a statistically significant difference. The three analyses that did not find a statistically significant effect all came from the same study (Seppa, 1998), but relate to different age groups (ages 9, 12 and 15 shown in ascending order of age on the graph).

Table 4.4 shows the results of the studies that examined the effects of stopping water fluoridation. In this table a positive difference indicates that the difference between the fluoridated and non-fluoridated areas in the caries outcome became greater after the cessation of water fluoridation. A negative difference shows that the difference narrowed when fluoridation stopped.

Table 4.4 Mean difference in caries outcome measures in studies in which fluoridation was discontinued

Author (Year)	Age	Teeth Type	Mean Difference *(95% CI)*	Validity Score
Proportion of caries-free children				
Kunzel (1997)	8 12 15	Permanent	**8.6** **-5.3** **-2.5**	**5.8**
DHSS (1969)	5	Primary	**-2.7**	**5.5**
Wragg (1992)	5	Primary	**-21.6** (-37.1, -16.3)	**4.5**
Mean difference in dmft/DMFT				
Kunzel (1997)	12 15 8	Permanent Permanent Permanent	**0.1** **-0.4** **0.3**	**5.8**
Kalsbeek (1993)	15	Permanent	**-7.4** (-8.5, -6.3)	**5.5**
DHSS (1969)	5	Primary	**-16**	**5.5**
Attwood (1988)	10	Permanent	**-0.6** (-1.3, 0.1)	**4.8**
Hobbs (1994)	5	Primary	**-1.2**	**4.5**
Wragg (1992)	5	Primary	**-1.5** (-2.2, -0.7)	**4.5**
DMFS score				
Seppa (1998)	6 9 12 15	Not stated Permanent	**-0.1** **0.2** (-0.5, 0.9) **-1.1** (-2.3, 0.1) **-0.9** (-4.2, 2.4)	**5.8**
Kalsbeek (1993)	15	Permanent	**-18.8** (-21.3, -16.3)	**5.5**
Mean Difference in D1D2MFS* Scores				
Maupomé (2000)	8 14	Permanent	0.59 (0.41, 0.77) 1.39 (0.23, 2.55)	**6.0**
D1D2MFS* Incidence				
Maupomé (2000)	11 17	Permanent	0.13 (-0.07, 0.34) 0.47 (-0.02, 0.96)	**6.0**

*D1D2MFS is a modified DMFS score where D1 = an incipient lesion, D2 = a cavitated lesion

Of 22 analyses of stopping water fluoridation, 14 found the direction of association to be negative (that stopping water fluoridation led to an increase in caries in the previously fluoridated area compared to the never-fluoridated area). However only eight of these studies provided a measure of the significance of this association. Four of these analyses found that stopping water fluoridation had a statistically significant effect at the 5% level, while the other four did not. Eight analyses found the direction of association to be positive (that stopping fluoridation had not led to increases in caries in the previously fluoridated areas). Seven of these analyses (from Seppa 1998 and Maupomé 2000 of both before-after and cohort analyses), provided standard error data. Only the Maupomé before-after study found a statistically significant association, in both 8 and 14 year olds.

The Maupomé study also included a multiple regression on both the before-after and cohort data including age, sex, socio-economic status, site (still fluoridated or no longer fluoridated), use of snacks, swallowing of toothpaste, use of fluoride supplements and brushing/rinsing regime. For prevalence of D1D2MFS, higher age and lower socio-economic status were statistically significantly associated with caries prevalence. Higher scores were associated with the still-fluoridated site for the D1D2MFS score and D1 alone, but higher D2 alone scores were associated with the fluoridation ended site. For the cohort data, the regression analysis showed again that higher age and lower socio-economic status were associated with higher D1D2MFS scores. However, the association between score and site (still fluoridated or fluoridation ended) were less clear.

4.3 Studies which met inclusion criteria but were not included in the main analysis

Table 4.5 is a summary of the studies that met our inclusion criteria, but contained data in forms that could not be used in the pre-defined analysis. The data used in the reports by Holdcroft and Gray were derived from the British Association for the Study of Community Dentistry (BASCD) survey data. Each year the BASCD conducts an epidemiological survey of dental health in the UK. Every second year, 5-year-old children are examined in most regions of the UK (either a random sample or the whole population of a given health authority). These surveys are co-ordinated and published by the University of Dundee.

Table 4.5 Included studies from which relevant data could not be derived

Author (Year)	Outcome	Reason	Author's Conclusions
Klein (1946)	Caries	Different caries measurement at baseline and final surveys	Author states that the findings of this report support a beneficial role of fluoride in caries prevention
Holdcroft (1999)	dmft	Results presented for 14 areas, no pairing of exposed and control areas so could not make direct comparisons	The conclusion of this study was that significant improvements in dmft levels is possible in non-fluoridated districts. When measured against fluoridated districts, it implies that the effectiveness of fluoridation is at least exaggerated. Efforts to improve dental health outside of the influence of drinking fluoridated water will impact changes in dmft level.
Gray (2000)	dmft	Results presented for 10 areas, 6 areas fluoridated, no pairing of exposed and control areas so could not make direct comparisons	After 10 years of fluoridation dental decay was lower in the fluoridated than in the low fluoride areas.

4.4 Studies with more than two study areas

The majority of studies assessing caries compared one fluoridated area to one non-fluoridated area. However, there were five studies with more than two study areas, such as two fluoridated areas compared with one non-fluoridated area. In the DHSS Welsh studies (DHSS 1969), data from Holyhead were excluded from the analysis because although Holyhead usually received fluoridated water, occasionally the water supply was supplemented from a non-fluoridated source.

For two studies (Gray 1999, Wragg 1992) the data from the two areas with the same fluoride level in their water supplies were combined as no differences between the study areas were discussed. In the Beal (1971) study, two of the study areas were similar in social class structure (one fluoridated and one non-fluoridated area) while the other fluoridated area had a higher proportion of immigrants and was poorer on the basis of a number of indicators than the other two. Therefore, this area was dropped from the analysis and only the two similar areas were included. The comparison of the lower social class area with the higher social class area is considered under Objective 3.

The fifth study with more than two areas was the Canadian study of the Brantford-Sarnia-Stratford areas (Brown 1965), which included a non-fluoridated area, an artificially fluoridated area, and a naturally fluoridated area. The non-fluoridated and artificially fluoridated areas were used for the analysis of Objective 1, while the comparison of artificial and naturally fluoridated areas is considered under Objective 5.

4.5 Possible confounding factors

There are a number of potential confounding factors in assessing the development of caries within studies. Age, gender, social class, ethnicity, country, tooth type (primary or permanent), mean daily regional temperature, use of fluoride, total fluoride consumption, method of measurement (clinical exam, radiographs, or both), and training of examiners are all possible confounding factors. While most studies described the age of participants, data on other potential confounders were rarely available. Another possibly important confounding factor is the *number of erupted teeth per child*. It has been suggested that fluoridation may delay the eruption of teeth and thus caries incidence could be delayed as teeth would be exposed to decay for a shorter period of time. Only one study compared the number of erupted teeth per child. The difference was very small and in opposite directions in the two age groups examined, however no measure of the statistical significance of these differences was provided. Only one of the studies attempted to control for confounding factors using multivariate analysis (Maupomé 2000).

4.6 Meta-regression

A meta-regression analysis was undertaken to investigate possible sources of heterogeneity between studies. Variables that may account for the differences in measures of effect seen among different studies (or in this case each different measure of effect included in the analysis) were included in the regression model. Variables included in the analysis relate to study design and patient characteristics. The analysis aims to investigate why there is a difference in the measure of effect calculated from each study rather than why caries prevalence differs between study areas within studies.

The outcome measure used for this analysis is different from that used in previous analyses. The outcome measure used is taken from only the final survey data and corresponds to the mean difference (MD) for the dmft/DMFT data and the risk difference (RD) for the proportion of caries free children data. The reason for using only data from the final survey was to allow investigation of the effect of baseline caries levels by including this as a variable in the meta-regression. If the mean difference of the change in caries incidence was used as the outcome measure (as it has for the earlier analyses) this may lead to a spurious association being found, due to the correlation between the outcome variable and the baseline caries variable.

A paired t-test was carried out to investigate whether there were any statistically significant differences between caries prevalence (as measured by the proportion of caries-free children or dmft/DMFT) in the two study areas at baseline for each study (Appendix J). No statistically significant differences were found ($p= 0.97$ for proportion caries-free children and $p=0.77$ for dmft/DMFT), and so the final outcome measures could be taken as measures of the effect of fluoridation on caries incidence. This also permitted the calculation of the mean proportion of caries free children or dmft/DMFT at baseline for each study, this variable was included in the regression analysis as an estimate of caries experience at baseline for each study comparison.

The analysis was carried out separately for the two main caries outcome measurements: the proportion (%) of caries-free children and dmft/DMFT. Data on possible sources of heterogeneity were extracted from the studies where possible. If not described in the paper, data on altitude and mean daily temperature were obtained from published sources.

The studies included in this analysis contribute more than one estimate to the meta-regression, although different children contribute to the different estimates within studies. It has been assumed in this analysis that these subgroups of people are independent, and hence each estimate has been treated as though it came from a separate study. For example, most of the studies report results separately for children of more than a specific age, so the results for each age group were included separately in the analysis. The potential limitations of including this type of data are discussed in section 12.6.

Continuous measures were centred on the mean (the mean value of each variable was subtracted from each of the individual measures), before including them in the regression model. Centering continuous variables in this way results in the constant (or intercept) of the regression model pertaining to the pooled estimate of the measure of effect when the explanatory variable takes its mean value.

A univariate analysis was undertaken in which each of the variables was included individually in the regression model with the measure of effect. The random effects meta-regression models (mixed models) were implemented. to combine studies. Although age is related to tooth type (primary or permanent) both were included in the univariate analyses because the 8 year-old age group could have primary and/or permanent teeth. However, neither of the multivariate models included both terms.

A measure of the between study variance (heterogeneity) remaining after the variables included in the model had been accounted for was calculated using restrictive maximum likelihood estimation. Variables which showed a statistically significant association with the measure of effect (MD or RD) at the 15% statistical significance level ($p<0.15$) in the univariate analysis were included in the multivariate analysis. This significance level was chosen to conservatively identify variables that could potentially be important in the multivariate model. The multivariate analysis was carried out using a step-down analysis in which each variable was included in the initial model. Variables were dropped one by one, with the variable that showed the least evidence of a statistically significant association dropped first, until only variables which showed a statistically significant association at the 5% level were included in the analysis. The analysis was repeated using a step-up analysis to confirm the results of the step-down analysis. As a further exploratory analysis study validity was forced into the regression model as the effect of study validity was considered to be very important in these studies of variable quality. However, study validity was not found to be statistically significantly associated with the dependent variable in the analysis of dmft/DMFT score. The results of this analysis are presented in Appendix L.

4.6.1 Proportion (%) of caries-free children

A total of 31 RD estimates from 9 studies were included in the analysis. Several of these RD estimates came from the same study as each study provided estimates for more than one age group.

4.6.1.1 UNIVARIATE ANALYSIS

The results of the univariate analysis are shown in Table 4.6.

Table 4.6 Results of the univariate meta-regression analysis for the proportion of caries-free children

Variable	Category or mean	Constant (95%CI)	p-value of constant	Co-efficient (95%CI)	p-value of co-efficient	Between study variance
No variables (pooled estimate)		15.4 (10.8, 20.1)	<0.001			163.0
Baseline %caries-free subject *	19.4	15.5 (11.7, 19.3)	<0.001	0.4 (0.2, 0.6)	<0.001	105
Tooth type (n=29)*	Not stated	8.4 (0.4, 16.5)	0.039			136
	Permanent			13.4 (6.1, 23.6)	0.011	
	Primary			3.6 (-7.9, 15.2)	0.538	
Setting*	Taiwan	20.5 (9.6, 31.3)	<0.001			145
	Europe			-5.19 (-17.5, 7.1)	0.407	
	N. America			1.17 (-15.2, 17.6)	0.889	
	Chile			-20.3 (-37.9, -2.6)	0.025	
Study duration*	9.0	15.4 (10.9, 19.8)	<0.001	1.30 (0.0, 2.6)	0.049	147
Year of final survey	1969	15.4 (10.8, 20.1)	<0.001	0.24 (-0.2, 0.7)	0.279	162
Number of years since change in fluoridation status	0.5	13.3 (5.9, 20.7)	<0.001	-2.1 (-7.6, 3.5)	0.462	165
Age (years)	8.8	15.5 (10.7, 20.2)	<0.001	-0.23 (-1.6, 1.1)	0.739	167
Validity score*	5.2	15.5 (10.7, 20.2)	<0.001	-1.17 (-10.0, 7.7)	0.796	168
Average temperature (^{o}C)	11.7	15.4 (10.7, 20.2)	<0.001	0.11 (-0.7, 1.0)	0.795	168

*Included in multivariate analysis

The p-value shows whether the co-efficient is statistically significantly different from 0. If it is not statistically significantly different from 0 then this variable is not statistically significantly associated with the dependent variable (i.e. RD of proportion of caries-free children). The between study variance shows the estimate of the heterogeneity which is left between the estimates of the MD after that variable has been controlled for.

The model in which no variables (other than the risk difference) were included shows the pooled estimate of the risk difference of the change in the proportion of caries-free children to be 15.5% (95% CI: 10.8, 20.1). This is the same as the measure that would be produced by a standard meta-analysis. However, the measure of between study variance (heterogeneity) is large and highly statistically significant (p<0.001) and so this value should be interpreted with *extreme caution*.

At the 15% statistical significance level the following variables showed a statistically significant association with the risk difference: tooth type, study duration, setting, and baseline proportion of caries-free children. The risk difference increased with increasing proportion of caries-free children at baseline and study duration, and was greater in permanent teeth than in primary teeth and than in studies in which tooth type was not stated. The risk difference also varied according to setting and was greater in Taiwan and the North America and lower in Europe and Chile. Age, number of years since change in fluoridation status, average temperature, study validity and year of final survey did not show an association with the risk difference of caries incidence. Study validity was forced into the regression model for the reasons discussed above.

4.6.1.2 MULTIVARIATE ANALYSIS

The multivariate model shows the effect of each variable controlled for the possible effects of the other variables included in the model. The results of the multivariate analysis are shown in Table 4.7. All the variables were centered in the same way as in the univariate analysis.

Table 4.7 Results of the multivariate meta-regression analysis for the proportion of caries-free children

Variable	Category (mean)	Co-efficient (SE)	p-value	Between study Variance
Constant		14.3 (6.7, 21.9)	<0.001	53.1
Baseline %caries-free children	19.4	0.61 (0.43, 0.80)	<0.001	
Setting	Taiwan			
	Europe	-1.85 (-10.9, 7.2)	0.688	
	N. America	22.90 (10.7, 35.1)	<0.001	
	Chile	-4.71 (-17.1, 7.7)	0.456	
Validity score	5.2	16.78 (8.9, 24.7)	<0.001	

The proportion of caries-free children at baseline, setting and validity score show a statistically significant association at the 5% level with the risk difference of the proportion of caries-free children between fluoridated and control areas. These variables appear to account for a lot of the variation seen in the initial model where the measure of heterogeneity was 163. Including these variables in the regression model reduced the between study variance to 53. In this model the MD increases with increasing caries-free children at baseline, validity score and study duration, and is greatest in North America and Taiwan and is lowest in Europe and Chile. The model obtained using a step-up regression analysis was similar. The association of validity score with the risk difference is in the opposite direction in the univariate to that in the model presented above (negative association in the univariate, positive association in the multivariate). The reason for this is unclear but it is possible that this is related to the fact that setting, validity score and study duration will be the same for each analysis from the same study and thus some degree of colinearity is likely to exist between these three variables. It should also be noted that the association was not significant in the univariate analysis suggesting that one or more of the other variables included in the multivariate analysis act to confound the relationship between study validity score and the risk difference.

4.6.2 dmft/DMFT

4.6.2.1 UNIVARIATE ANALYSIS

A total of 16 MD estimates from 4 studies were included in the analysis. The results of the univariate analysis are shown in Table 4.8.

Table 4.8 Results of the univariate meta-regression analysis for dmft/DMFT score

Variable	Category or mean	Constant (95% CI)	p-value of constant	Co-efficient (95% CI)	p-value of co-efficient	Between study Variance
No variables (pooled estimate)		2.3 (1.8, 2.8)	<0.001			1.068
Baseline dmft/DMFT *	3.6	2.3 (1.9, 2.7)	<0.001	0.3 (0.1, 0.5)	0.006	0.713
Setting*	UK	1.3 (0.4, 2.2)	0.005			0.777
	Germany			0.9 (-0.3, 2.1)	0.135	
	N America			1.9 (0.4, 3.5)	0.014	
	Taiwan			1.5 (0.3, 2.8)	0.013	
Study duration (years)*	10.7	2.3 (1.9, 2.8)	<0.001	0.2 (0.03, 0.4)	0.018	0.815
Validity score*	5.3	2.3 (1.8, 2.8)	<0.001	-1.0 (-1.9, 0.0)	0.048	0.897
Age (years)*	9.5	2.3 (1.8, 2.8)	<0.001	0.1 (-0.01, 0.3)	0.062	0.903
Temperature (°C)	13.3	2.3 (1.8, 2.8)	<0.001	0.0 (-0.03, 0.1)	0.229	1.04
Number of years since change in fluoridation status	-0.6	2.2 (1.3, 3.0)	<0.001	-0.1 (-0.6, 0.4)	0.707	1.13
Year of final survey	1975	2.3 (1.8, 2.9)	<0.001	0.0 (-0.1, 0.1)	0.906	1.14
Tooth type	Primary	2.3 (1.5, 3.2)	<0.001			1.14
	Permanent			0.0 (-1.1, 1.1)	0.938	

*Included in multivariate analysis

The model in which no variables (other than the MD) were included shows the pooled estimate of the MD in dmft/DMFT between the fluoridated and control areas to be 2.3 (95% CI: 1.8, 2.8). This is the same as the measure that would be produced by a standard meta-analysis. However, the measure of between study variance (heterogeneity) is large and highly statistically significant (p<0.001) and so this value should be interpreted with *extreme caution*.

At the 15% statistical significance level the following variables showed a statistically significant association with the MD: baseline dmft/DMFT, setting, study duration, validity score and age. The MD was highest in Taiwan and North America, followed by Germany and the UK. Study duration, age, and baseline dmft/DMFT score showed a positive association with the MD – as the value of these variables increased so did the MD. Validity score showed a negative association with MD with the lowest validity studies showing a greater MD.

4.6.2.2 MULTIVARIATE ANALYSIS

Table 4.9 Results of the multivariate meta-regression analysis for dmft/DMFT score

Variable	*Mean*	Co-efficient	p-value	Variance
Constant		2.61 (2.31, 2.91)		0.111
Baseline dmft/DMFT	3.6	0.37 (0.26, 0.48)	<0.001	
Age (years)	9.5	0.11 (0.04, 0.18)	0.001	
Study duration (years)	10.7	0.26 (0.18, 0.34)	<0.001	
Setting*	UK			
	Germany	-0.74 (-1.20, -0.29)	0.001	
	N. America	-0.57 (-1.27, 0.13)	0.112	
	Taiwan	Droppped	dropped	

Age, baseline dmft/DMFT, setting and study duration show a statistically significant association at the 5% level with the MD in the dmft/DMFT. These variables appear to account for a lot of the variation seen in the initial model where the measure of heterogeneity was 1.07. Including these variables in the regression model reduced the between study variance to 0.111. All of the variables except study setting showed a positive association with the MD – as each variable increases so does the MD. Setting shows that the MD was smaller in Germany and North America than in the UK. There was insufficient data for the effects of Taiwan to be investigated and this was dropped from the analysis. The analysis was repeated using a step-up analysis and produced similar results. Validity score was did not show a significant association with the MD in the multivariate model. The model in which study validity was included is presented in Appendix L. Forcing study validity into the model had very little effect on the co-efficients and standard errors of the other variables.

4.7 Numbers needed to treat

The number needed to treat (NNT) represents the number of children that need to receive the intervention for one person to benefit from the intervention. The NNT can be calculated by taking the inverse of the risk difference. This is the measure that was calculated for the meta-analysis of the proportion of caries free children above. In this case it represents the number of people exposed to fluoridation for one additional child to be caries-free. An NNT is valid only for the comparison it is based on, for example water fluoride levels < 0.7 ppm versus 0.7 to 1.2 ppm.

The risk difference was calculated for each study comparison – for some studies more than one risk difference was calculated if caries measurement was made in more than one age group. A meta-analysis was conducted to provide a pooled estimate of the mean risk difference between the exposed and control groups. This was carried out for all teeth types combined (permanent, primary and not stated) and separately for permanent and primary teeth. Heterogeneity was investigated and found to be statistically significant in all models (the Q statistic) and so the results of these analyses should be interpreted with caution.

Table 4.10 Meta analysis of risk difference in the proportion (%) of caries-free children

Tooth type	Age	Number of studies	Risk Difference % (95% CI)	Q-statistic – measure of heterogeneity	P-value for heterogeneity at the 5% level	NNT (95% CI)
All	All	31	15.5 (10.7, 20.2)	1421.0	<0.001	6 (5, 9)
Primary	All	15	11.4 (6.5, 16.3)	354.4	<0.001	9 (6, 15)
Permanent	All	16	19.1 (11.4, 26.7)	751.3	<0.001	5 (4, 9)
Primary	5	11	13.2 (6.8, 20.0)	137.5	<0.001	8 (5, 15)
Primary	8	4	7.2 (-3.6, 18.0)	211.3	<0.001	14 (6, ∞)
Permanent	8	4	35.6 (22.4, 48.8)	39.1	<0.001	3 (2, 5)
Permanent	12	6	13.1 (0.8, 25.5)	215	<0.001	8 (4, 125)
Permanent	14 -15	4	8.8 (0.7, 16.9)	36.8	<0.001	11 (6, 143)

The numbers needed to treat with 95% confidence intervals are given in the final column of Table 4.10. For all teeth combined 6 people need to receive fluoridated water for one extra person to be caries-free, with a 95% confidence interval of between 5 and 9 people. Due to the heterogeneity the median risk difference was calculated for all teeth combined, for primary teeth and for permanent teeth. This was translated into a number needed to treat. The median NNT for all teeth combined was 6, for primary teeth was also 6 and for permanent teeth was 5. These numbers are very similar to those obtained using the meta-analysis suggesting that these figures are a relatively accurate estimation based on the data from the studies included in this analysis.

To investigate whether including estimates for multiple ages from one study in the meta-regression as if they were independent was leading to bias in the result, NNTs were calculated separately for each tooth type and age group (Table 4.10). The NNT was greater in primary than in permanent teeth and within permanent teeth increased with age. This would be expected as the univariate meta-regression showed that age had a negative association with the risk difference (and hence a positive association with the NNT), although this relationship was not significant in the multivariate analysis. The estimates of the risk difference were positive for all age groups reported. The variation in RD and NNT suggests that although there may have been some bias introduced by including estimates for multiple ages from the same study as if they were independent, this does not alter the conclusion that the overall effect is positive.

4.8 Publication bias

Although it is possible to create a funnel plot from the studies including the proportion (%) of caries-free children this has not been done because some studies would contribute several points, this would make the funnel plot difficult to interpret. It would be possible to take only one point from each study but this would only give nine points that would also lead to problems with regard to interpreting the plot. It is thus difficult to estimate whether publication bias is having an effect. It has been argued that it is easier to get a study published that shows a beneficial effect of water fluoridation. However, considering the broad approach to searching for studies and the inclusion of unpublished studies in this report it is unlikely that any major studies on the association of dental caries with water fluoridation have been missed. Importantly, any missed study would have to be very large, and very different to those that were included to overturn the overall result.

4.9 Discussion

Objective 1 attempts to assess the effect of water fluoridation on the development of caries. A small number of studies meeting the pre-defined criteria were found. While many cross-sectional studies exist, relatively few studies were designed to assess the effects of water fluoridation over time. Studying populations exposed or not exposed to water fluoridation longitudinally allows baseline dental health to be taken into account and differences developing over time to be assessed. Studies that assess dental caries at one point in time using an ecological or cross-sectional study design only show the differences in caries prevalence at that particular point in time. In such studies it is not possible to tell whether the observed differences have always existed between these populations or whether they are the result of the differing levels of water fluoride content between the study areas.

When diagnosing caries it is usual to have very specific written criteria. However, these criteria vary from study to study. In particular, they have changed over time as treatment philosophies have also changed. This means that there is likely to be inter-study variation in the threshold at which caries is diagnosed. What is more important is whether the diagnostic criteria have remained the same within studies. As this systematic review has used the difference in change between DMFT/dmft the intra-study variation is likely to be of minimal importance.

For this objective, the quality of studies found was only moderate (level B). A large number of studies were excluded because they were cross-sectional studies and therefore did not meet the inclusion criteria of being evidence level B or above. All but one of the studies included were before-after studies; three included studies used a cohort design, two prospective and one retrospective. The most serious defect of these studies was the lack of appropriate analysis. Many studies did not present an analysis at all, while others only did simple analyses without attempting to control for potentially confounding factors. Although the size of the differences found might be affected by confounding factors, the differences estimated in this review were sufficiently large that it is unlikely that confounding factors would account for them entirely. While some of these studies were conducted in the 1940's and 50's, prior to the common use of such analyses, studies conducted much later also failed to use methods that were commonplace at the time of the study. As an example, no study used an analysis that would control for the frequency of sugar consumption or the number of erupted teeth per child. Another defect of many studies was the lack of any measure of variance for the estimates of decay presented. This was not so much of a problem for the studies, which presented the proportion of caries-free children, as all these studies contained sufficient data to calculate standard errors for the data provided. However, for the studies that presented dmft/DMFT scores this was more of a problem with only four of the eight studies providing any estimate of variance.

To have clear confidence in the ability to answer the question in this objective, the quality of the evidence would need to be higher. The failure of these studies to deal with potential confounding factors or to provide standard error data means that the ability to answer the objective is limited.

Tables 4.1 to 4.3 and Figures 4.1 and 4.2 suggest, through a simple qualitative method of analysis, using means, and confidence intervals where available, that water fluoridation does appear to reduce caries. Table 4.4 shows that when water fluoridation is stopped, in 12 out of 16 studies the direction of the association is that the caries burden increases more in the previously-fluoridated groups than in the never fluoridated groups. Only eight of these studies provided a measure of the significance of this association and of these, four showed a statistically significant positive effect. When fluoridation is discontinued caries prevalence appears to increase in the area that had been fluoridated compared with the control area. Interpreting from this data the degree to which water fluoridation works to reduce caries is more difficult.

The meta-analysis showed a statistically significant effect of water fluoridation in reducing dental caries as measured by both dmft/DMFT and the proportion of caries-free children. However, the results showed statistically significant evidence of heterogeneity and thus the pooled estimates should be interpreted with caution. The meta-regression carried out to investigate the heterogeneity between studies showed that, for both dmft/DMFT and the proportion of caries-free children, the baseline caries measurement and study duration both accounted for a significant proportion of this heterogeneity. For both these outcome measurements, increased duration of follow up was associated with a greater difference in the change in caries measurement from baseline to final examination in the fluoridated compared with the control group.

The baseline measure of dental caries also showed a positive association with the mean difference. This is what would be expected for dmft/DMFT: the greater the population prevalence of tooth decay at the baseline examination the greater the effect of water fluoridation in decreasing this decay in the fluoridated area. However, the situation is slightly more complex for the proportion of caries-free children. The results suggest that the greater the proportion of caries-free children at baseline (i.e. the less decay in the population) the greater the change in the mean difference. This is possibly related to the distribution of caries-free children within a population. A population with a high proportion of caries-free children will also probably have more children with few decayed teeth than a population with a small proportion of caries-free children, which is likely to have more children with more decayed teeth. Such a population would only require a small decrease in decay for a noticeable increase in the proportion of caries-free children.

The meta-regression of the proportion of caries-free children found that setting accounts for a significant proportion of the heterogeneity. The results showed that the mean difference was highest in North America. However, this variable was the same for each analysis from the same study and so some caution should be exercised in interpreting these results. Average temperature and age were also statistically significantly associated with the mean difference in the meta-regression of the mean difference in dmft/DMFT. Both of these variables showed a positive association with the mean difference. Temperature was the same for each analysis from the same study; this may be a particular problem for these data as the 16 measures included in the analysis came from only four studies, and so the results for this variable should also be interpreted with caution.

5. OBJECTIVE 2

If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

Studies carried out after 1974 were selected to examine the effect of water fluoridation over and above the effect of other sources of fluoride, especially fluoridated toothpaste. As toothpaste containing fluoride was being widely used in industrialised countries by the early 1970's, examining the effect of water fluoridation after 1974 should allow for any modifying effect of fluoride toothpaste and other sources of dental fluoride (e.g. mouthrinses, tablets) to be apparent. Studies carried out post-1974 which were conducted in industrialised countries were considered to have included the effects of these sources of fluoride, unless the study stated otherwise. Of the 24 studies that met the inclusion criteria for Objective 1, ten were completed after 1974 (1978 – 1997). The mean validity score of these ten studies is 5.0 (range 3.5 to 6.8 out of 8). Five of these studies were conducted in the UK (Wragg 1992; Attwood 1988; Hardwick 1982, Hobbs 1994; Gray 1999). The others were from the Netherlands, Finland, Germany, and Taiwan. Among these were eight before and after studies and two cohort study (Hardwick 1982, Maupomé 2000). Six of the before and after studies examined the discontinuation of water fluoridation.

The results of the studies in which fluoridation was initiated and which were completed after 1974 are displayed in Table 5.1. The results of the studies in which fluoridation was discontinued during this time period are presented in Table 5.2. In addition to the ten studies outlined above, two studies (Gray, 2000 and Holdcroft, 1999) met inclusion criteria but direct comparison data could not be extracted and were excluded from this table. The results of these studies can be found in Table 4.5 in chapter 4.

Table 5.1 Caries studies of fluoridation initiation, completed after 1974

Author (Year)	*Age*	Teeth Type	Mean Difference *(95% CI)*	*Year of final survey*	Validity Score
% Caries-free					
Guo (1984)	5 8 8 12 15	Primary Permanent Primary Permanent Permanent	**-2.0** (-6.4, 2.4) **64.1** (55.4, 72.8) **0.4** (-4.8, 5.6) **28.5** (20.5, 36.5) **34.4** (19.7, 49.1)	1971 - 1984	**4.8**
Gray (1999)	5	Primary	**26.0** (19.4, 32.6)	1988 - 1997	**3.5**
dmft/DMFT Score					
Guo (1984)	5 8 8 12 15	Primary Permanent Primary Permanent Permanent	**3.6** (2.6, 4.6) **1.6** (1.4, 1.8) **4.4** (3.9, 4.9) **2.6** (2.2, 3.0) **3.8** (2.7, 4.9)	1971 - 1984	**4.8**
Cohort Study: Difference in Increment in DMFS/DMFT score (Control – Fluoridated)					
Hardwick (1982)	12 12	Permanent Permanent	DMFS **2.5** (1.0, 3.9) DMFT **1.1** (0.4, 1.8)	1974 - 1978	**6.8**

Of the six studies assessing the proportion of caries-free children, five studies found the direction of association of water fluoridation and caries to be positive. Four of these found a statistically significant benefit. One study found the direction of association to be negative, but this effect was not statistically significant. All of the five analyses investigating the mean difference in dmft/DMFT were from the same study (Guo, 1984). All found a statistically significant positive association between water fluoridation and the mean difference in the change in dmft/DMFT. The cohort study of water fluoridation initiation found a statistically significant difference in the increment in both DMFT and

DMFS scores between the fluoridated and control area with the control area showing the greatest increment (Hardwick, 1982).

Table 5.2 Caries studies in which fluoridation was discontinued completed after 1974

Author (Year)	*Age*	**Teeth Type**	**Mean Difference** *(95% CI)*	*Year of final survey*	**Validity Score**
proportion of caries-free children					
Kunzel (1997)	8 12 15	Permanent	**8.6** **-5.3** **-2.5**	1991 - 1995	**5.8**
Wragg (1992)	5	Primary	**-21.6** (-37.1, -16.3)	1985 – 1995	**4.5**
dmft/DMFT					
Attwood (1988)	10	Permanent	**-0.6** (-1.3, 0.1)	1980 – 1986	**4.8**
Hobbs (1994)	5	Primary	**-1.2**	1989 - 1993	**4.5**
Kalsbeek (1993)	15	Permanent	**-7.4** (-8.5, -6.3)	1968 – 1987	**5.5**
Kunzel (1997)	12 15 8	Permanent Permanent Permanent	**0.1** **-0.4** **0.3**	1991 - 1995	**5.8**
Wragg (1992)	5	Primary	**-1.5** (-2.2, -0.7)	1985 – 1995	**4.5**
DMFS score					
Kalsbeek (1993)	15	Permanent	**-18.8** (-21.3, -16.3)	1968 – 1987	**5.5**
Seppa (1998)	6 9 12 15	Not stated Permanent Permanent Permanent	**-0.1** **0.2** (-0.5, 0.9) **-1.1** (-2.3, 0.1) **-0.9** (-4.2, 2.4)	1992 - 1995	**5.8**
Mean Difference in D1D2MFS* Scores					
Maupomé (2000)	8 14	Permanent	0.59 (0.41, 0.77) 1.39 (0.23, 2.55)	**1993 – 1997**	**6.0**
			D1D2MFS* Incidence		
Maupomé (2000)	11 17	Permanent	0.13 (-0.07, 0.34) 0.47 (-0.02, 0.96)	**1993 – 1997**	**6.0**

*D1D2MFS is a modified DMFS score where D1 = an incipient lesion, D2 = a cavitated lesion

There were 20 analyses looking at the discontinuation of water fluoridation, four of which looked at the proportion of caries-free children, seven looked at the dmft/DMFT score, five looked at the DMFS score and four reported on the D1D2MFS score. Of these 20 analyses, 12 found the direction of association to be positive (ie a greater increase in caries in the area that had been fluoridated compared with the control area). Twelve of the 20 analyses provided a measure of the significance of the association, four of the studies found a statistically significant positive association. Four analyses from a single study (Maupomé 2000) found the direction of association to be negative (the level of caries improved more in the area that discontinued fluoridation than in the area that was never fluoridated). Two of these results (from the before-after study but not in the cohort study) were statistically significant.

In the development of both of the meta-regression models of caries for Objective 1, the baseline disease level was included and found to be statistically significant. At lower levels of disease the reduction of dmft/DMFT was less in fluoridated areas than in non-fluoridated areas but there was a larger increase in the number of children found to be caries-free. Both of these differences were statistically significant. If other sources of fluoride are shown to have an effect on dental caries then decay should drop, thus baseline levels of decay would be at lower levels than when many of the original studies looking at water fluoridation were started. Water fluoridation would thus be expected to have less of an effect on the severity of dental caries, as measured by the dmft/DMFT score, but would be expected to have a greater effect on the proportion of caries-free children (see discussion section of chapter 4). Year of final study was also included as an explanatory variable in the univariate meta-regression for both the caries-free and dmft/DMFT analysis. This variable did not show any evidence of a significant association with the mean difference and so was not included in the multivariate analysis.

5.1 Discussion

This objective assesses the impact of water fluoridation on caries after the advent of other sources of fluoride, especially toothpaste containing fluoride. Relatively few studies qualified to address this issue (10). None of these identified this objective as the purpose of the study, but were conducted in time periods and countries where fluoridated toothpaste use was widespread. No included study specifically measured fluoride exposure from sources other than water although Hardwick (1982) reported the use of fluoridated toothpaste in both groups. The studies included for Objective 2 are a subset of those in Objective 1. The studies included in Objective 2 are of moderate quality (level B). Aside from design issues, their major failing was lack of analyses controlling for exposure to other sources of fluoride, including toothpaste.

While only ten studies were included for Objective 2, these would be enough to provide a confident answer to the objective's question <u>if</u> the studies were of sufficient quality. Since these studies were completed after 1974, one might expect that the validity assessments would be higher than the earlier studies due to the introduction of more rigorous study methodology and analytic techniques. However, the average validity checklist score and level of evidence was essentially the same for studies completed after 1974 as the whole group of caries studies. Hence, the ability to answer this objective is similar to that in Objective 1.

In examining the post-1974 studies (Table 5.1), the evidence suggests that water fluoridation has an effect over and above that of fluoridated toothpaste (and other sources of fluoride). If fluoridated toothpaste was responsible for reducing the difference in baseline caries between fluoridated and non-fluoridated areas, then the meta-regression models created for Objective 1 suggest that at lower levels of caries the reduction in DMFT would be less but the proportion of caries-free children would be greater. The study included in the review with the highest validity score (Hardwick 1982) showed a statistically significant difference in caries increment between fluoridated and non-fluoridated areas. Those in the non-fluoridated area had the greatest increment, in spite of fluoridated toothpaste being used by both groups (94% vs 95% used only fluoride toothpaste in the fluoridated and non-fluoridated groups, respectively).

6. OBJECTIVE 3

Determination of whether fluoridation results in a reduction of caries across social groups and between geographical locations bringing equity

No level A studies, and very few level B studies for Objective 3 were identified by the search. Because the issue of social class effects of water fluoridation was considered highly important, studies of any level that were conducted in the UK were included. A total of 15 studies investigating the association of water fluoridation, dental caries and social class were identified, ranging in publication dates from 1969-1999. Among these were three unpublished studies (Holdcroft 1999; Gray 2000, Jones 2000). Details of baseline information and results from each study can be found in tables in Appendix C. All but three of the included studies were cross-sectional in design. These three were before-after study designs (DHSS, 1969; Holdcroft, 1999; Gray, 2000). Seven of the studies presented measures of caries experience (proportion (%) of caries-free children, DMFT and dmft) stratified according to the Registrar General's social class classification (see Appendix H). Of these studies, five examined caries experience in children aged five, and two also examined 8, 12 and 14 year-olds. One study studied 10 year-olds only and another 15-16 year-olds only. Two studies presented data in a similar way but used different methods of classifying social class (low versus high deprivation and urban ordinary versus social priority). Urban ordinary and social priority was a classification used by the education authority to classify its schools at the time of the study, with social priority indicating less privileged students. Two studies used a regression analysis to investigate the association of caries experience (dmft and DMFT) with a measure of social deprivation (Jarman and Townsend scores, section 6.3), separately for high and low fluoride areas. The remaining two studies presented dmft and proportion caries-free data for a sample of fluoridated and non-fluoridated areas together with the Jarman score for each area, before and after water fluoridation was introduced in some of these areas.

If water fluoridation results in a reduction in caries across social class, reducing social inequalities in dental health, these studies would be expected to show that caries experience is lower in fluoridated than non-fluoridated areas. Importantly, the difference in caries experience between the social classes would be less in the fluoridated than in the non-fluoridated areas.

All except two of the studies investigating the association between caries experience, water fluoridation and social class were of evidence level C. The only exceptions were the before-after studies, which were level B. The average checklist score was 1.6 out of 8 (range 0.8 to 5.3), with eight of the 12 studies scoring only 0.8. Only two of the studies were prospective, had a baseline survey and follow-up and so the remaining studies lost marks for these checklist items. Only one study reported reliable measurement (or adequate reporting) of the fluoride concentration. None of the studies attempted to control for confounding using multivariate analysis – the only confounders considered were age (most studies presented results for one age only or stratified on age) and ethnic group (two of the studies only included children from one ethnic group).

Because there were very limited data available in formats that allowed pooling of results using meta-analytic techniques a more simple approach was adopted. For studies in which caries experience was presented by social class, as measured by the Registrar General's grouping, some pooling was possible and the results of this are presented below. For the other studies a qualitative analysis has been presented.

6.1 Proportion (%) of caries-free children stratified by the Registrar General's classification of social class

The proportion of caries-free children for each age group was determined by calculating the total number of children with no caries experience (caries-free), summing this number across studies and dividing by the sum of the total number of children from all studies. This method also allowed the calculation of a standard error and confidence interval. The results of this analysis are presented in Table 6.1. The studies included were Bradnock, 1984; Carmichael, 1980; DHSS, 1969; Evans, 1996;

Murray, 1984; and Murray, 1991. If there were several studies from one geographical area the most recent study for that age group was included. This decision was made in order to minimise the effect of any confounding variables operating in this area.

Table 6.1 Proportion of caries-free children by social class and water fluoride level

Fluoride level	Studies Included	Age	Social Class I & II		Social Class III		Social Class IV & V	
			% Caries-free (95 % CI)	Number	% Caries-free (95% CI)	Number	% Caries-free (95% CI)	Number
High	Bradnock 1984,	5	73 (67, 79)	186	57 (52, 61)	453	53 (48, 57)	418
Low	Carmichael 1980, Evans 1996, DHSS 1969	5	55 (48, 63)	153	43 (37, 49)	289	37 (30, 44)	196
High	Murray 1984	10	43 (31, 55)	67	29 (23, 35)	249	30 (21, 39)	99
Low		10	26 (16, 36)	80	26 (20, 32)	225	23 (17, 29)	163
High	Murray 1991	15-16	31 (22, 40)	94	27 (20, 35)	135	23 (9, 37)	35
Low		15-16	23 (14, 32)	80	20 (13, 27)	140	25 (14, 36)	57

With the exception of one study of 15 to 16 year-old children (Murray 1991, social classes IV & V), these results show that for all age groups and all social classes the proportion of caries-free children is higher in the fluoridated than in the non-fluoridated areas. With the exception of the same study, caries experience is higher in the lower social classes (social class IV and V) than the higher social classes in both fluoridated and non-fluoridated areas. In most of the age groups, and for both high and low fluoride areas, a gradient relationship exists between social class and the proportion of caries-free children, this is illustrated graphically for children aged five in Figure 6.1. Data from children aged five years were graphed as four studies were included which looked at the association of water fluoride level, social class and caries experience in children of this age. Only two studies were found for other age groups, one each for ages 10 and 15-16.

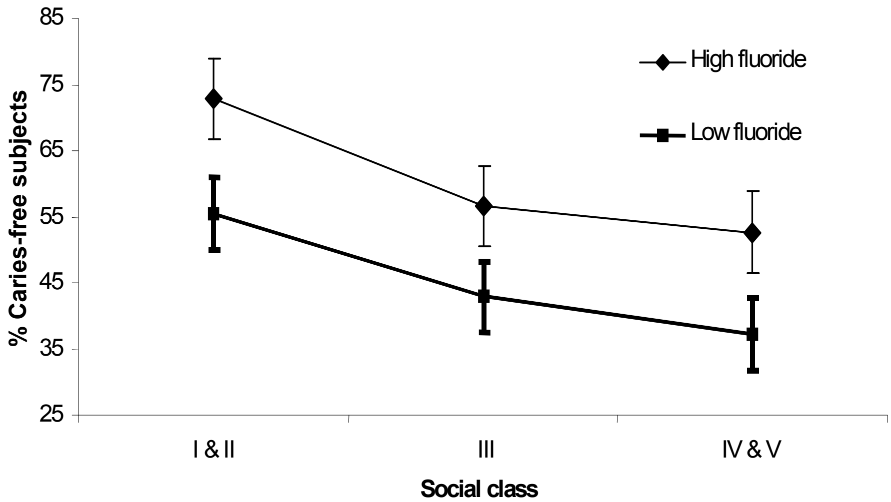


Figure 6.1 Proportion of (%) caries-free five-year-old children (95% CI) by social class in high and low fluoride areas

Figure 6.1 illustrates the higher proportion of caries-free children aged five years in the areas receiving fluoridated water compared with those receiving water with a low fluoride concentration. It also shows the increase in caries experience across the social classes for children aged 5 years. The absolute difference in the proportion (%) of caries-free children between Classes I & II and IV & V in the fluoridated group is 20%, while it is 18% in the non-fluoridated group. Thus there is no evidence from these studies to suggest that fluoridation reduces the social gradient.

6.2 dmft/DMFT stratified by the Registrar General's classification of social class

The mean number of dmft/DMFT per child for each age-group was determined by calculating the total dmft/DMFT in each study, summing this number across studies and dividing by the sum of the total number of children from all studies. This method did not allow the calculation of a standard error, and too many of the studies did not provide information on standard errors to allow this to be estimated. For children aged five, results from seven study analyses contributed to this analysis (from Bradnock 1984; Carmichael 1980; Carmichael 1989; DHSS 1969; and Evans 1996). For 8,12 and 14 year-olds, two analyses contributed (DHSS 1969, England and Wales data). However, for ages 10 and 15-16 data were only available from one study each (Murray 1984; Murray 1991). The results of this analysis are presented in Table 6.2.

Tables 6.2 dmft/DMFT by age, social class and water fluoride level

Fluoride level	Studies Included	Age	Social Class I & II		Social Class III		Social Class IV & V	
			DMFT	Number	DMFT	Number	DMFT	Number
High	Bradnock 1984; Carmichael 1980; Carmichael 1989; DHSS (England,) 1969; Evans 1996	**5**	1.1	343	1.9	388	1.8	227
Low		**5**	1.8	292	3.1	383	3.8	241
High	DHSS (England)	**8**	1.0	39	1.3	98	1.6	47
Low		**8**	1.2	49	2.0	88	2.2	37
High	Murray 1984	**10**	1.5	67	1.7	249	1.6	99
Low		**10**	1.8	80	2.0	225	2.0	163
High	DHSS (England)	**12**	3.6	15	3.5	47	3.5	17
Low		**12**	5.3	15	5.6	27	5.1	10
High	DHSS (England)	**14**	5.5	8	5.5	17	5.0	8
Low		**14**	6.8	13	7.8	29	6.5	8
High	Murray 1991	**15-16**	2.2	94	2.7	135	3.3	35
Low		**15-16**	2.9	80	3.4	140	3.9	57

These results show that for all age groups and all social classes the dmft/DMFT is lower in the fluoridated than in the non-fluoridated areas. On average there is more caries in the lower social classes (social class IV and V) than the higher social classes. In most of the age groups, and for both high and low fluoride areas, a gradient relationship exists between social class and the dmft/DMFT score, this is illustrated graphically for children aged five in Figure 6.2. As above children aged five were selected for further analysis as seven analyses were included for children of this age while data were only available from one or two analyses for each of the other age groups.

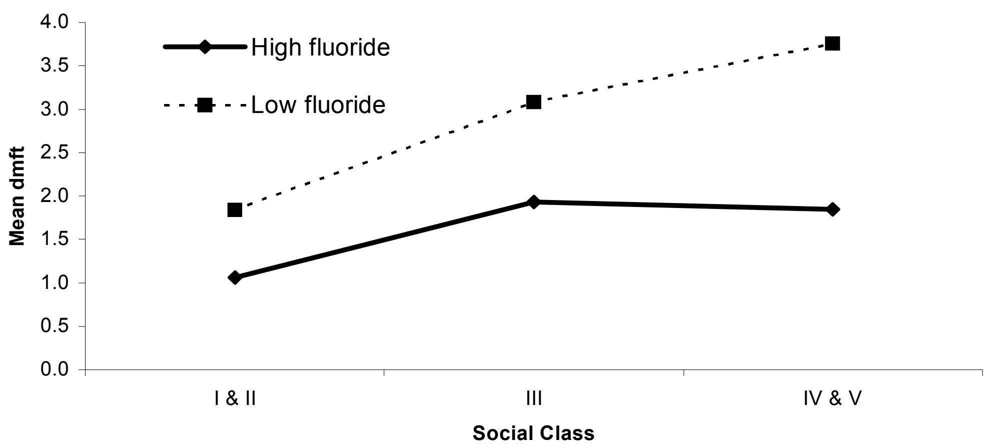


Figure 6.2 dmft by social class in high and low fluoride areas for children aged 5 years

Figure 6.2 illustrates the lower dmft in the areas receiving fluoridated water compared with those receiving water with a low fluoride concentration. It also shows the increase in caries experience across the social classes. The social class gradient is steeper in the low fluoride areas, in contrast to the proportion (%) of caries-free children graph. These data from 5-year-old children suggest that water fluoridation is leading to a decrease in dmft across the social classes and reducing the inequalities in dental health between the social classes. However this trend is not seen in the other age groups. It may be a finding peculiar to the younger age group or it may be because only a very small number of studies were included in the older age groups.

6.3 Other studies looking at dental decay, water fluoridation and social class

Two studies of five year-old children (Provart, 1995; and Rugg-Gunn, 1977) present results in a similar way to those outlined above but use different classifications of social class. The Provart study used the Townsend index (see Appendix H) to classify social deprivation, and then grouped the children into two groups, 'low' and 'high' deprivation. The cut-off used for this classification was not stated in the article. The Rugg-Gunn study used a classification system that was currently being used by the school system. Schools were classified as 'ordinary' or 'social priority'. Full details of these classifications were not given. These studies both show decreased caries experience in the fluoridated compared with the non-fluoridated areas. Comparing the fluoridated areas, Provart (1995) shows greater caries experience (measured by both dmft and proportion of caries-free children) in areas of 'high deprivation' compared with areas of 'low deprivation'. This finding is not confirmed by the Rugg-Gunn study, which did not find any difference in caries experience (deft and proportion of caries-free children) in areas defined as 'social priority' compared with areas defined as 'urban ordinary'.

A regression analysis approach was used in two studies, one of which was later re-analysed using a different measure of social deprivation (Riley, 1999; and Jones, 1997 and 2000). Riley selected five year-olds in seven fluoridated areas and seven non-fluoridated areas and calculated the slopes and intercept of the regression line, plotting mean dmft versus Townsend score for all fluoridated areas and all non-fluoridated areas. The slope of the regression line was positive in both groups of areas (the higher the deprivation scores the higher the dmft score) and the y intercept was lower in fluoridated areas (0.77 vs 1.7 for non-fluoridated areas). This means that the dmft experience is lower in fluoridated areas for all levels of deprivation. The slope of the regression line was statistically significantly less steep in the fluoridated areas than in the non-fluoridated areas (beta coefficient 0.08 vs 0.17, $p < 0.001$). This suggests that dental decay increases with increased social deprivation (as measured by the Townsend index), that dental decay is greater in non-fluoridated compared with fluoridated areas and that the *difference* in dental decay between the fluoridated and non-fluoridated areas increases with increased social deprivation.

The Jones 1997 study used data on five and 12 year-olds and calculated similar regression lines using the Jarman index. This study showed similar findings to the Riley study for dmft/DMFT scores. Dental decay had a significantly negative relationship with water fluoridation, and a significantly positive association with social deprivation. In this study, water fluoridation was also found to reduce the effect of deprivation. An unpublished report (Jones 2000) reassessed the impact of water fluoridation on caries by deprivation level using the same caries data for 12 year-old children, but classifying deprivation by the Townsend index rather than the Jarman index. The findings of the original study were confirmed, finding that the more deprived areas achieved greater reductions in tooth decay with water fluoridation than less deprived areas.

The Gray (2000) and Holdcroft (1999) reports present similar before-after data, comparing the dmft of children aged five before the introduction of water fluoridation in a selection of areas and 10 years after water fluoridation had been introduced. Jarman scores were presented for each area (based on the 1991 census). The authors have not presented enough suitable data for making comparisons. In particular, the areas that met inclusion criteria for having a baseline survey within one year of starting fluoridation were limited. In addition, none of the non-fluoridated areas presented had Jarman scores above zero, while the fluoridated areas had mixed Jarman scores. Matching fluoridated and non-fluoridated areas within these data sets is difficult due to the wide variation in Jarman scores, proportions of populations fluoridated, and starting dates of fluoridation.

The Beal 1971 study presents before and after data comparing the decayed, extracted and filled teeth (deft) and proportion of caries-free children aged five before the introduction of water fluoridation in two of three areas and three years later after water fluoridation had been introduced. One of the fluoridated areas is described as poorer and with a higher proportion of immigrants. The other two areas (one fluoridated, one not) are described as industrial areas. While there is no formal assessment of social class, the findings of this study are presented for comparison. The mean change in deft score in the poorer fluoridated area was larger than in the fluoridated industrial area (difference of 3.22 compared with 2.46). The change in the percent caries-free was also larger in the poorer group (difference of 39% compared with 13%). This implies that the effect is greater in the lower social classes.

6.4 Discussion

The number of UK studies with adequate social class data (15) was very small. Many other studies mentioned social class in some way, such as the typical occupations of the 'head of the house', or simply stated that social class in the areas being compared was similar. The quality of the evidence of the studies was low (all but 4 were level C), and the measures of social class that were used varied. Most of the studies that had enough information on social class to be evaluated were cross-sectional, with two before-after studies. Additionally, some of the included studies did not record individual exposure to water fluoride but were based on an ecological analysis, which is likely to be less accurate. Variance data were not reported for dmft/DMFT scores in these studies, so a statistical analysis was not undertaken. While these studies provide an indication of the effect, the ability to answer this question is low.

The effect of water fluoridation in reducing the difference in dental health between social classes classified by the Registrar General's classification shows varying effects. In the proportion of caries-free children analysis (Table 6.1 and Figure 6.1), a positive effect of water fluoridation is seen among children aged five years in all social classes. However, the difference between the classes does not vary between the high and low fluoride areas. In the mean change of dmft/DMFT analysis (Table 6.2 and Figure 6.2), water fluoridation does appear to be having an impact on reducing the differences between the social classes among children aged five years. In Figure 6.2 the slopes of the two lines are divergent, indicating a greater effect in the lower social classes (IV and V). This effect was not seen in 10 and 15-16 year-olds.

Two studies using regression analysis (presented in three analyses, Riley 1999; Jones 1997, Jones 2000) found similar effects on dmft/DMFT scores among five and 12 year-olds using measures of social deprivation (Townsend and Jarman indices) rather than the Registrar General's classification. These studies reported a statistically significant greater effect in the most deprived groups.

The meta-regression analysis reported in chapter 4 is also relevant to the discussion of the effect of water fluoridation on inequities in levels of dental caries. One of the findings of the social class studies is that people of lower social class had higher levels of dental caries. Thus their caries baseline score is higher. The results of the meta-regression analysis suggests that these children would have a higher reduction in mean dmft/DMFT but a lower reduction in the number of children who are caries-free. The meta-regression is based upon studies of stronger design than the majority of studies included in these analyses.

The small quantity of studies, differences between these studies, and their low quality rating, suggest *caution* in interpreting these results. There appears 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. This effect was not seen in the proportion of caries-free children among five year-olds. There were not sufficient data for the effects in children of other ages to be investigated fully.

Objective 4: Does water fluoridation have negative effects?

Any study of a potential negative effect of fluoridation that met inclusion criteria was reviewed. However, more studies were found and included on fluorosis, bone fracture, and cancer than other outcomes. This objective was broken down into four sections, fluorosis, bone fracture (and bone development effects), cancer and other possible adverse effects.

7. DENTAL FLUOROSIS

A total of 88 studies looking at the association of dental fluorosis with water fluoridation met inclusion criteria. Most of these studies examined children, but a few studied adults or did not state the age studied. Four of these studies used a before-after study design, one was a case-control study and the rest were cross-sectional studies in which the prevalence of dental fluorosis was measured at one point in time in areas with different water fluoride concentrations. Of these, 14 did not state whether the water was artificially or naturally fluoridated, 20 compared areas artificially fluoridated to a level of 0.6–1.2ppm with areas with low (<0.3ppm) or very high (4-7ppm) natural fluoride content. The remaining studies compared naturally fluoridated areas. These studies were conducted in 30 countries. For this analysis, study areas with natural fluoride levels above 5ppm were excluded. This is significantly above the level recommended for artificial fluoridation. The range of 0 to 5ppm is broad enough to be able to explore whether a dose-response relationship exists. Details of baseline information and results from each study can be found in the tables in Appendix C. Twelve studies met inclusion criteria but were not included in the main analysis for various reasons, the results of these studies and the reasons for their exclusion from the main analyses are presented in section 7.4.

One study achieved evidence level B, all of the remaining studies looking at dental fluorosis were of evidence level C. The validity scores ranged from 1.3 to 5.8 with a mean score of 2.8 out of a possible 8. Only one study included a baseline survey at the time of a change in the water fluoride level of one of the study areas (the level B study). Only four studies used a prospective study design and only 16 of the studies used any form of blinding.

Because the studies used different indices to assess fluorosis, the percentage prevalence of fluorosis was selected as the outcome of interest. Using this measure, all children with some degree of fluorosis were classified as 'fluorosed' as opposed to normal. Using the different indices, children with a TSIF, T&F or DDE score greater than zero and Dean's classification of 'questionable' or higher were classified as fluorosed. For the modified DDE index the number of children in the first category ('all') was taken as the number of children with dental fluorosis (see Appendix I). The term 'fluorosis' is used throughout this report, however it should be understood that the indices used to measure fluorosis also measure enamel opacities not caused by fluoride. Hence, the levels of fluorosis described here include some amount of overestimation of the prevalence of true fluorosis. This may be particularly true of those studies using the modified DDE index.

As there may be some debate about the significance of a fluorosis score at the lowest level of each index being used to define a person as 'fluorosed', a second method of determining the percent 'fluorosed' was selected. This method describes the number of children having dental fluorosis that may cause 'aesthetic concern'. The level at which fluorosis was judged to cause aesthetic concern was taken from a study by Hawley (1996). Children from Manchester aged 14 were shown pictures of fluorosis classified using the T & F index and asked to rate the appearance of each as either very poor, poor, acceptable, good or very good. The cut-off point for this analysis was taken as the level of fluorosis above which the children classified the photographs as "very poor" or "poor". This corresponded to a T & F score of three or more (Hawley, 1996). This was translated as being equivalent to Dean's score of "mild" or worse and a TSIF score of two or more. This additional analysis was restricted to these three indices, as the definition was not transferable to the other fluorosis indices.

A regression analysis was used to investigate the association of water fluoride level with the prevalence of dental fluorosis (the analysis was conducted separately for the two measures of fluorosis outlined above). A multilevel model was used to combine studies. Each area with a different fluoride concentration under observation within a study was included separately in the model. The log (odds) of having fluorosis/aesthetic fluorosis was modelled as a function of fluoride level. If the exact or average level of fluoridation was known this was included in the model. When a range of fluoridation level or an upper limit was provided the mid-value was used (for example if fluoridation was given as <0.7ppm, 0.35ppm was entered in the model for that group of people). When only a lower limit was given, 0.5ppm was added to this limit if it was less than 2ppm, and 1.0 was added if the limit was greater than 2ppm (e.g. if the level of fluoridation was given as >2.5ppm, then the level was entered as 3.5ppm). A sensitivity analysis was used to assess the robustness of the model's fit to the choice of values allotted to groups for which only lower limits were known. This was done by applying the lower limits themselves, and the lower limits +1.5ppm for levels with lower limits less than 2ppm, and 2ppm to groups with lower limits greater than 2ppm. The sensitivity analysis did not change the results of the analysis, so only the results of the main analyses are presented below.

The univariate regression model consisted of two parts. In the first, the standard fixed effect model, the log-odds of fluorosis was fitted as the outcome and the water fluoride level was fitted as the exposure variable. In the second, a random effects model was included to allow for the fact that some of the study areas came from the same studies (e.g. two low fluoride areas and four high fluoride areas from one study). Separate intercepts and slopes were permitted for each study by fitting these terms as random effects. In a similar fashion to more standard meta-analysis models, weighting of individual groups of people in the model was inversely proportional to the variance of the outcome estimate for that group. A normal distribution was assumed for the log odds for each group. Models were fitted using the 'PROC MIXED' procedure in the SAS software package, version 6.12 (SAS Institute Inc., USA). The algebraic form of the model used is presented in Appendix J.

The relationship between the *log* odds of aesthetic fluorosis and fluoride level appeared to be linear. However, the relationship between the *log* odds of fluorosis and the *log* of fluoride level appeared linear, and hence a log transformation of fluoride level was used in the model for this outcome. Both fluoride level and log fluoride level were centred before modelling.

A multivariate analysis was used to investigate possible sources of heterogeneity. This was similar to the univariate model in that it included two components, random and fixed effects. The effects of several potential factors were explored by including them as covariates in the above model. The effect of indices of fluorosis (e.g. Dean's), average age, source of fluoridated water (artificial, natural or both), mean altitude level, average temperature, type of teeth assessed (permanent, both, primary, not stated), method of assessment (clinical, photograph, both, not stated), study location (Europe, North America, S. America, Africa, Asia, Caribbean, Scandinavia, Australia), water source (public water, well, both, not stated), year of study report and study validity score were investigated.

The results of the analyses considering the proportion of people with any form of fluorosis and the proportion of people with fluorosis of aesthetic concern are presented separately.

7.1 Proportion of the population with dental fluorosis

7.1.1 Univariate analysis

The results of the univariate regression model are presented in Table 7.1

This model shows that log of the odds of the prevalence of dental fluorosis shows a positive linear association with the log of water fluoride level. Thus as water fluoride concentration increases so does the prevalence of dental fluorosis in the population. The random effects section of the model shows the variation between the intercepts and slopes fitted to the individual studies. Using this model, estimates with confidence intervals can be constructed for the proportion of persons in a population with fluorosis for a given level of water fluoridation.

Table 7.1 Results of the univariate analysis of the regression of water fluoride level against the proportion of the population with dental fluorosis

Variables	P-value individual parameters	Coefficient	Variance	Odds (95% CI)
Fixed effects				
Intercept	0.01	-0.440	0.030	0.644 (0.455 to 0.912)
Log fluoride level (centred by adding .526051)	0.0001	0.7155	0.0061	2.045 (1.750 to 2.390)
Random effects				
Between study (intercept)			2.024	
Between study (fluoride level – slope)			0.362	
Covariance of intercept and slope			-0.412	

This association is illustrated graphically in Figure 7.1. The size of the circles on the graph indicates the weighting of the study. Larger circles represent the larger studies.

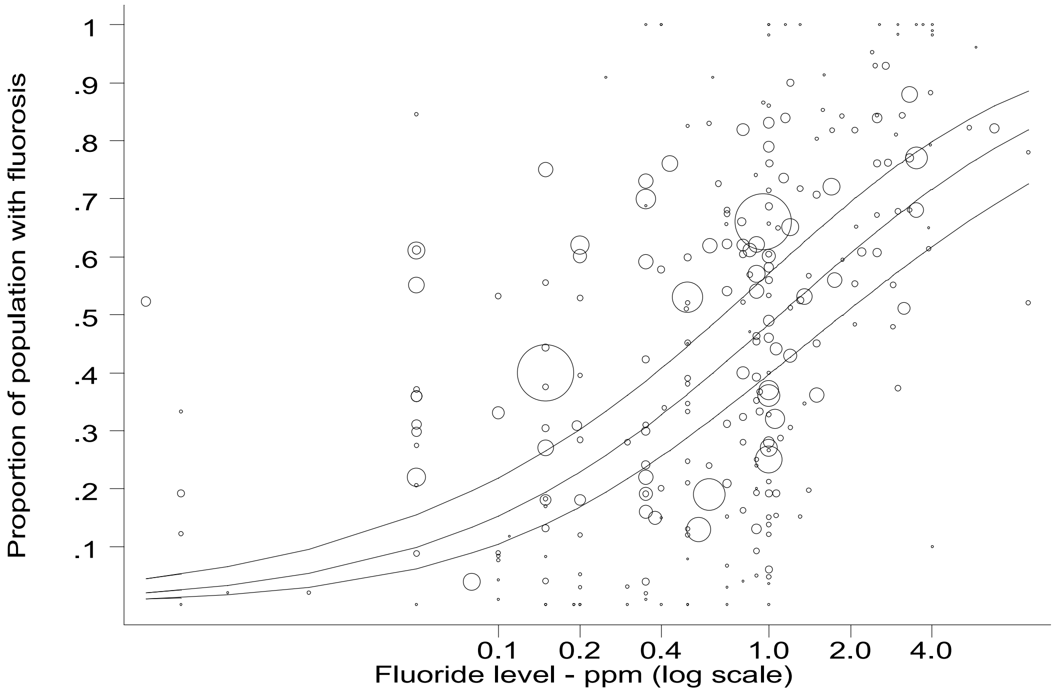


Figure 7.1 Proportion of the population with dental fluorosis by water fluoride level together with the 95% upper and lower confidence limits for the proportion

Examples of this model are illustrated in Table.7.2

Table 7.2 The estimated proportion (%) of the population with dental fluorosis at different water fluoride concentrations

Fluoride level	Proportion (%) of the population affected by dental fluorosis (95% CI)
0.1	15 (10, 22)
0.2	23 (17, 30)
0.4	33 (26, 41)
0.7	42 (34, 51)
1	48 (40, 57)
1.2	52 (43, 60)
2	61 (51, 69)
4	72 (62, 80)

These results show a strong association between water fluoride level and the proportion of the population with dental fluorosis. The model may not fit data at the extreme ends (low or high levels of fluoride) very well, due to the small numbers of data points. While many areas in Britain may have water fluoride levels lower than this, 0.4ppm has been chosen as the comparator (low fluoride) in subsequent analyses to ensure that the results are as reliable as possible. The effect of changing the water fluoride level of a low fluoride area with 0.4ppm fluoride in the water supply to an area with 0.7, 1.0 and 1.2ppm in the water supply is shown in Table 7.3

Table 7.3 Estimated difference in the proportion of the population with dental fluorosis at various levels of water fluoride concentration

Fluoride ppm	Difference in proportions (95% CI)
0.4 v 0.7	9.3 (-1.9, 20.6)
0.4 v 1.0	15.7 (4.1, 27.2)
0.4 v 1.2	18.9 (7.2, 30.6)

These results show that there are relatively large differences in the prevalence of dental fluorosis at the level of water fluoridation 0.7-1.2ppm when compared with an area with a relatively low water fluoride content (0.4 ppm). The differences in the prevalence of dental fluorosis at 1.0 and 1.2 compared with 0.4ppm are statistically significant (the confidence limits do not include 0). The numbers needed to harm (cause fluorosis) provide an estimate of the number of people that need to receive water fluoridated at the new level (compared to 0.4 ppm) for 1 extra person to have dental fluorosis. Increasing the level of water fluoride concentration from 0.4 to a slightly higher figure of 1.0 (the level which water is usually artificially fluoridated to) would lead to one extra person with dental fluorosis for every 6 people receiving the new higher level of water fluoride. In this case, the confidence interval ranges from 4 to 21 people. It must be remembered that these numbers are found when comparing to a theoretical low level of 0.4 ppm to 1.0 ppm, if the comparison level was lower the numbers needed to harm would be lower.

7.1.2 Multivariate analysis

The results of the multivariate analysis are presented in Table 7.4. All variables included in this model were statistically significant at the 5% level; all other variables which were investigated (see above) showed no statistically significant association at this level.

Table 7.4 Results of the multivariate analysis of the regression of water fluoride level against the proportion of the population with dental fluorosis

Variables	Parameter	P-value individual parameters	P-values Overall Variables	Coefficient	Variance	Odds (95% CI)
Fixed effects						
Intercept	Intercept	0.85		-0.069	0.146	0.933 (0.435 to 2.003)
Fluoride level	Fluoride level (ppm)	0.0001		0.718	0.006	2.050 (1.766 to 2.379)
Method of assessment	Clinical	0.77	0.0001	0.123	0.177	0.455 (0.220 to 0.943)
	Photograph	0.12		1.186	0.580	0.044 (0.007 to 0.275)
	Both	0.0001		2.582	0.432	0.005 (0.000 to 0.125)
	Not Stated	.		0	.	.
Teeth type	Permanent	0.04	0.0002	-0.787	0.138	1.131 (0.495 to 2.583)
	Both	0.001		-3.131	0.880	3.274 (0.736 to 14.571)
	Primary	0.002		-5.241	2.606	13.218 (3.642 to 47.977)
	Not Stated	.		0	.	.
Random effects						
Between study (intercept)					1.308	
Between study (fluoride level)					0.340	
Covariance of intercept & slope					-0.195	

These results show that the only variables to show a statistically significant association at the 5% level with the prevalence of dental fluorosis were water fluoride level, method of outcome assessment and teeth type. The odds of fluorosis were higher in studies using both a photographic and clinical assessment, compared with studies using a clinical or photographic examination and were slightly higher in studies using a photographic rather than a clinical assessment (in both high fluoride and low fluoride areas). This may be due to the drying of teeth before photographing them, allowing visualisation of more enamel defects. The odds of fluorosis were higher in permanent than primary teeth, and in studies looking at permanent teeth only compared with those looking at both permanent and primary dentitions. Controlling for these factors led to a small decrease in the between study variance for both the estimates of the intercept and slope. Some examples of the proportion of the population that would be predicted to have dental fluorosis at various levels of the exposures included in the final multivariate model are provided in Table 7.5.

Table 7.5 Multivariate model prediction of proportion of the population that would be expected to have dental fluorosis at various levels of exposure, method of measurement and teeth type

Fluoride level	Proportion (%) of the population with dental fluorosis (95% CI)
0.2ppm fluoride, identified clinically, both teeth types	2 (0, 11)
0.4ppm fluoride, identified clinically, both teeth types	3 (1, 17)
0.7ppm fluoride, identified using photograph, permanent teeth	61 (31, 85)
1.0ppm fluoride, identified using photograph, permanent teeth	67 (37, 88)
1.0ppm fluoride, identified using both methods of assessment, both teeth types	44 (12, 81)
2.0ppm fluoride, identified clinically, permanent teeth	54 (45, 62)

* both teeth types = permanent and primary teeth combined

7.2 Proportion of the population with dental fluorosis of aesthetic concern

7.2.1 Univariate analysis

The results of the model fitted in the univariate analysis are presented in Table 7.6

Table 7.6 Proportion of the population with dental fluorosis of aesthetic concern

Variables	P-value	Coefficient	Variance	Odds (95% CI)
Fixed effects				
Intercept	0.0001	-1.729	0.108	0.177 (0.091 to 0.346)
Fluoride level	0.0001	0.82985	0.0231	2.293 (1.685 to 3.120)
Random effects				
Between study (intercept) Sigma 2u			3.830	
Between study (fluoride level – slope) Sigma 2v			0.634	
Covariance of intercept and slope Sigmau v			0.113	

This shows that fluoride level has a statistically significant positive association with the prevalence of fluorosis of aesthetic concern. The between study variance in the estimate of the intercept slope of the regression line are higher than they were for the overall fluorosis analysis, indicating greater heterogeneity between studies. Using these model estimates, confidence intervals can be constructed for the proportion of persons in a population with fluorosis for a given level of water fluoridation (see Table 7.7).

Table 7.7 The proportion (%) of the population with dental fluorosis of aesthetic concern at different water fluoride concentrations

Fluoride level	% of the population affected by fluorosis of aesthetic concern (95% confidence interval)
0.1	6.3 (3.2, 12.4)
0.2	6.9 (3.5, 13.1)
0.4	8.2 (4.2, 14.9)
0.7	10.0 (5.0, 17.9)
1	12.5 (7.0, 21.5)
1.2	14.5 (8.2, 24.4)
2	24.7 (14.3, 39.4)
4	63.4 (37.9, 8.3)

This association is illustrated in Figure 7.2.

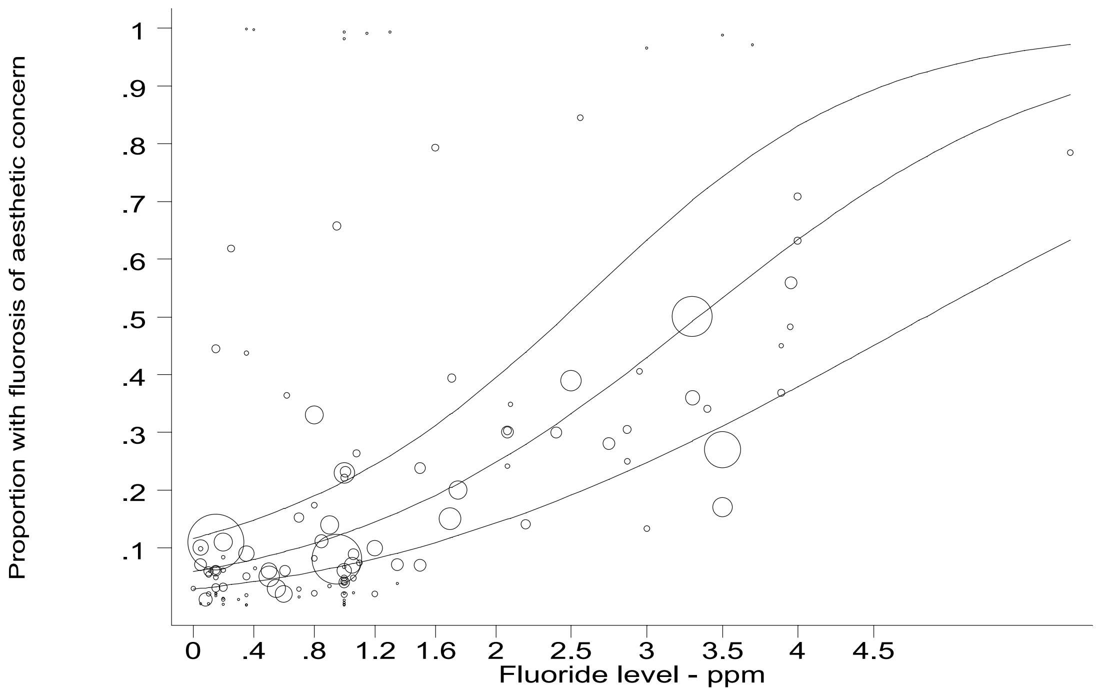


Figure 7.2 Proportion of the population with dental fluorosis of aesthetic concern by water fluoride level together with the 95% upper and lower confidence limits for the proportion

Figure 7.2 shows an increasing prevalence of fluorosis of aesthetic concern with increasing water fluoride level. The effect that changing the water fluoride level of a low fluoride area with 0.4ppm fluoride in the water supply to an area with 0.7, 1.0 and 1.2ppm in the water supply is shown in Table 7.8.

Table 7.8 Difference in the proportion of the population affected with fluorosis of aesthetic concern comparing a low level of water fluoride to levels around 1ppm

Fluoride ppm	Difference in proportions (%)
0.4 v 0.7	2.0 (-6 to 10)
0.4 v 1.0	4.5 (-4.5 to 13.6)
0.4 v 1.2	6.5 (-3.3 to 16.2)

The figures shown in Table 7.8 show that the difference between the proportion of the population affected with fluorosis of aesthetic concern at 0.4ppm compared with 0.7ppm is considerably lower than the difference in the proportion comparing 0.4ppm to 1.0ppm and 1.2ppm. Increasing the water fluoride level from 0.4 to 1.0ppm, the level to which water supplies are often artificially fluoridated, would mean that one additional person for every 22 people receiving water fluoridated to this level would have fluorosis of aesthetic concern. However, the confidence limits around this value include infinity, which means that it is possible that there is no risk. This is because the differences in proportions were not statistically significant (the confidence intervals include zero).

7.2.2 Multivariate analysis

The multivariate analysis of fluorosis of aesthetic concern is presented in Appendix K because the findings were similar to the findings on the primary analysis of fluorosis, section 7.1.2.

7.3 Sensitivity analysis

A sensitivity analysis of the regression analysis was conducted in which all data points above 1.5ppm were removed from the data set. It was suggested that the higher water fluoride levels were forcing the regression line to show a relationship that may not actually exist for the lower levels of fluoride. Restricting the analysis to levels less than 1.5ppm allowed the investigation of any association at these lower levels.

7.3.1 Fluorosis sensitivity analysis

The results of the univariate regression model are presented in Table 7.9.

Table 7.9 Results of the univariate regression of water fluoride level against the proportion of the population with dental fluorosis (sensitivity analysis)

Variables	P-value individual parameters	Coefficient	Variance	Odds (95% CI)
Fixed effects				
Intercept	0.01	-0.475	0.031	0.622 (0.437 to 0.885)
Log fluoride level (centred by adding .526051)	0.0001	0.5861	0.0070	1.797 (1.525 to 2.118)
Random effects				
Between study (intercept)			2.026	
Between study (fluoride level – slope)			0.349	
Covariance of intercept and slope			-0.338	

The model shows similar findings to the previous model (Table 7.1). The log of the odds of the prevalence of dental fluorosis continues to show a linear association with the log of water fluoride level. However, the gradient of the effect is slightly shallower (the increase in odds of fluorosis were 2.05 (95% CI: 1.75 to 2.39) in the first model and 1.80 (95% CI: 1.53 to 2.12) per unit increase of fluoride) in the sensitivity analysis.

Table 7.10 shows the estimates of the proportion (%) of the population with fluorosis at various water fluoride levels predicted by the model.

Table 7.10 Proportion of the population with dental fluorosis by water fluoride level together with the 95% upper and lower confidence limits for the proportion (sensitivity analysis)

Fluoride level	Proportion (%) of the population affected by fluorosis (95% CI)
0.1	18 (12, 26)
0.2	25 (18, 33)
0.4	33 (26, 41)
0.7	41 (33, 49)
1	46 (37, 55)
1.2	49 (40, 58)

The proportions of the population predicted to have fluorosis by this model are similar to the initial model in the lower water fluoride levels. However, the confidence intervals are larger. The graphical representation of this model is shown in Figure 7.3.

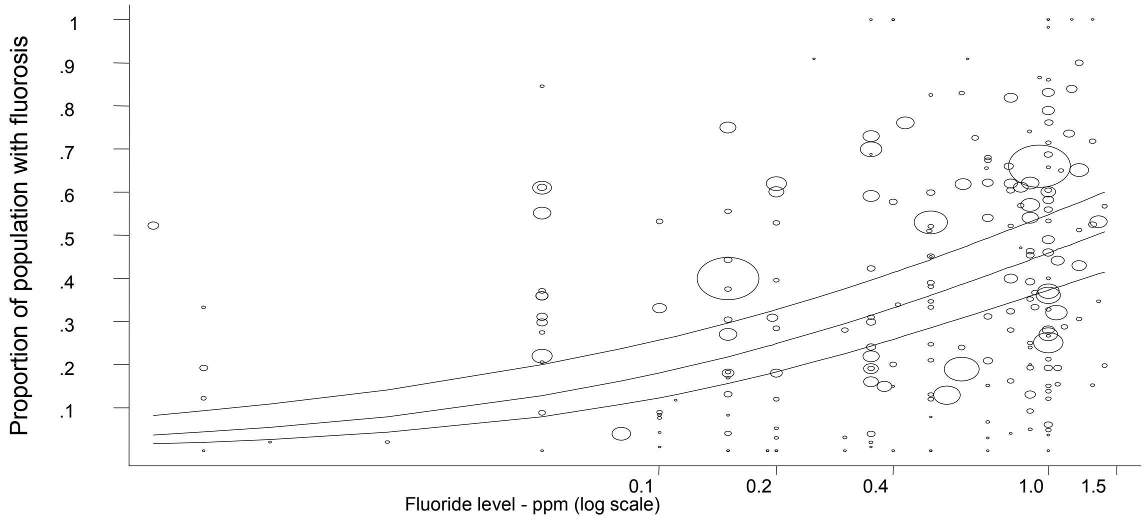


Figure 7.3 Proportion of the population with dental fluorosis by water fluoride level and predicted 95% confidence limits (sensitivity analysis)

7.3.2 Fluorosis of aesthetic concern sensitivity analysis

The results of the univariate regression model of fluorosis of aesthetic concern are presented in Table 7.11.

Table 7.11 Results of the univariate regression of water fluoride level against the proportion of the population with fluorosis of aesthetic concern (sensitivity analysis)

Variables	P-value	Coefficient	Variance	Odds (95% CI)
Fixed effects				
Intercept	0.0001	-1.953	0.130	0.142 (0.070 to 0.287)
Fluoride level (centred by subtracting 1.2565)	0.02	0.712	0.083	2.038 (1.159 to 3.583)
Random effects				
Between study (intercept)			4.117	
Between study (fluoride level – slope)			0.238	
Covariance of intercept and slope			1.657	

Similar to the original model, this model shows that fluoride level is statistically significantly associated with the prevalence of fluorosis of aesthetic concern. Again, the odds are slightly lower in this model, 0.14 (95% CI: 0.07 to 0.29), than in the original model, 0.18 (0.09 to 0.35). The predictions of the new model are given in Table 7.12.

Table 7.12 The proportion (%) of the population with dental fluorosis of aesthetic concern at different water fluoride concentrations

Fluoride level	% of the population affected by fluorosis of aesthetic concern (95% CI)
0.1	6 (2, 14)
0.2	6 (3, 14)
0.4	7 (3, 15)
0.7	9 (4, 17)
1	10 (5, 20)
1.2	12 (6, 22)

The point estimates here are slightly lower than in the original model (Table 7.6), but there is more uncertainty reflected in the larger confidence intervals. The graphical representation of the model is show in Figure 7.4.

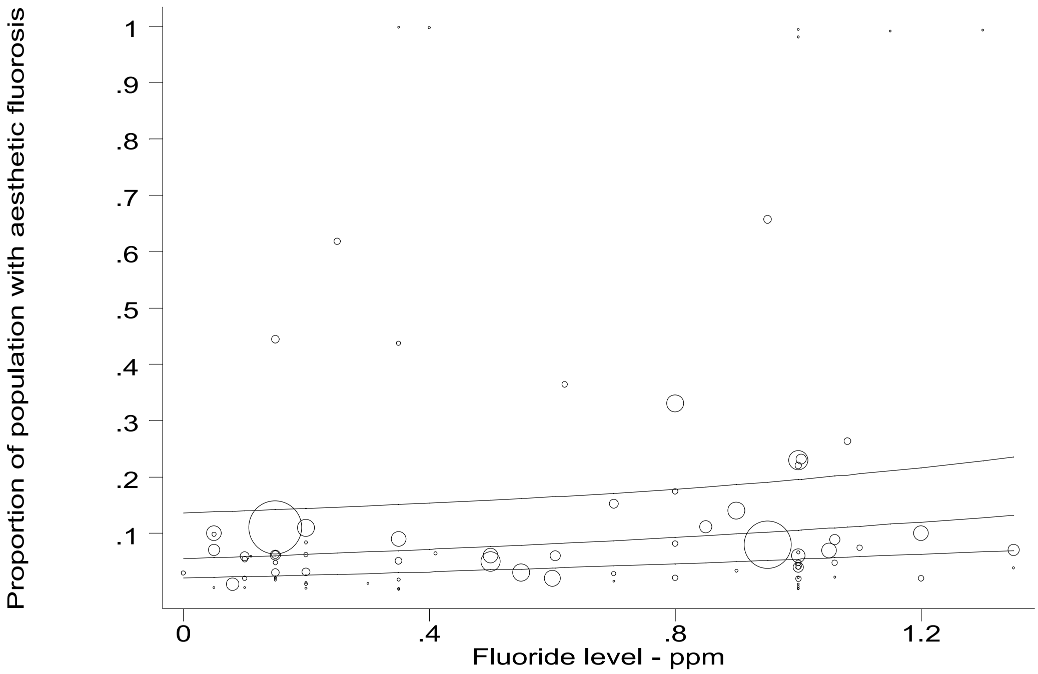


Figure 7.4 Proportion of the population with fluorosis of aesthetic concern by water fluoride level and predicted 95% Confidence Intervals

7.4 Studies that met inclusion criteria but were not included in the main analysis

The studies included in Table 7.13 were not included in the main analysis for the reasons outlined in the table. The conclusions of these studies appear to be compatible with the results of the main analysis of an increase in dental fluorosis with increased water fluoride concentration, so that their exclusion does not materially effect the result.

Table 7.13 Studies that met inclusion criteria but were not included in the main analysis

Author (Year)	Outcome	Reason for exclusion	Author's conclusions
Bhagan (1996)	Dental fluorosis	No separate results provided for control area – aggregate data only	The intensity of dental fluorosis is related to the concentration of fluoride in the water
Dissanayake (1979)	Dental fluorosis	The levels of fluoride in the **exposed groups** cover very wide ranges (0.3-3.8 and 0.3-4.6), which are very close to the levels of the control groups (< 0.2). These data can thus not be analysed in a meaningful way together with the other studies looking at fluorosis	Author does not make any conclusions regarding the incidence of dental fluorosis. Results indicate a considerably higher incidence of fluorosis in the areas with the higher ranges of fluoride concentrations in the water supplies
Forsman (1977)	Dental fluorosis	Different age groups are examined for the different fluoride exposure groups and so the results are not comparable between study areas	A greater proportion of children were affected by fluorosis in the higher fluoride area (2.75ppm) and fluorosis was also more severe in this area compared to the control areas (<1.5ppm)
Hellwig (1985)	Dental fluorosis	Children from naturally fluoridated areas combined with children from areas which changed from a low-fluoride supply to an optimally fluoridated supply 2 years prior to the examination– a significant proportion of the exposed group would not have been exposed to fluoride for enough time for a noticeable effect to have occurred	The incidence and severity of dental fluorosis was higher in the fluoridated areas compared to the control area
Larsen (1987)	Dental fluorosis	Measures of fluorosis are presented graphically for each tooth type. From these figures it is not possible to obtain an accurate reading.	The prevalence of dental fluorosis increases with the age during which the individual tooth is formed. The concentration of fluoride in the drinking water influenced the occurrence of fluorosis by resulting in a steeper profile of the prevalence from lower incisor to second molars rather than by increasing the prevalence for all teeth.
Latham (1967)	Dental fluorosis, nail mottling and prevalence of goitre	The results are not broken down as much as the water fluoride levels, giving very wide ranges of fluoride levels in some of the areas for which results are presented. All the areas are fluoridated at above 1ppm and some with fluoride levels as high as 45.5ppm	Author does not specifically relate results to water fluoride content of the area – he comments generally on the results seen in the whole sample studied, as all areas are exposed to comparatively high levels of fluoride. The incidence of dental fluorosis was high in all areas (>82%), as was the percentage of people with mottled nails (>26%), and the prevalence of goitre (12-41%). As these results are not specifically related to the water fluoride level and there was no control area it is difficult to link these findings to the water fluoride levels.

Author (Year)	Outcome	Reason for exclusion	Author's conclusions
Opinya (1991)	Dental fluorosis	Exposed area had fluoride level of 9ppm – considerably above level that would be encountered in artificially fluoridated area. Fluorosis data presented graphically for tooth type, not possible to obtain accurate data from the graphs	The incidence and severity of fluorosis was greater in the high fluoride area compared to the control area
Teng (1996)	Dental fluorosis	Areas selected because they were known to have a high incidence of fluorosis and then water fluoride level investigated. Reasons other than the fluoride content of the water are also investigated for the incidence of fluorosis.	Index of children's dental fluorosis has shown a decreased trend since the fluoride level of the water has been reduced
Gopalakrish-nan (1999)	Dental fluorosis	Areas selected because they were known to have a high incidence of fluorosis and then water fluoride level investigated. Reasons other than the fluoride content of the water are also investigated for the incidence of fluorosis.	Dental fluorosis is related to the high fluoride content of drinking water.
Morgan (1998)	Dental fluorosis and childhood behaviour problems	Children classified according to Dean's classification for fluorosis and then fluoride exposure examined. Childhood behaviour problems classified according to dental fluorosis levels not water fluoride levels.	The use of supplemental fluoride prior to age 3 was found to be a risk factor for dental fluorosis. No significant association was found between fluoride history variables in aggregate (including water fluoride level) and dental fluorosis. Dental fluorosis was not significantly associated with behaviour problems in the children studied

7.5 Prevalence of fluorosis over time

As with caries, the introduction of fluoride toothpaste in the 1970's could play a role in increasing the prevalence or degree of fluorosis occurring. Figure 7.5 presents the data on percent prevalence of fluorosis from 32 studies divided into before 1975 (23) and after 1985 (9), to allow sufficient time for fluorosis development after exposure to fluoridated toothpaste. These studies were conducted in nine countries (Australia, Canada, Finland, Ireland, Italy, New Zealand, Sweden, Britain, and the USA). Figure 7.5 is the main analysis measure of fluorosis; there were not enough data points to assess fluorosis of aesthetic concern. The bars represent different ranges of water fluoride (natural or artificial).

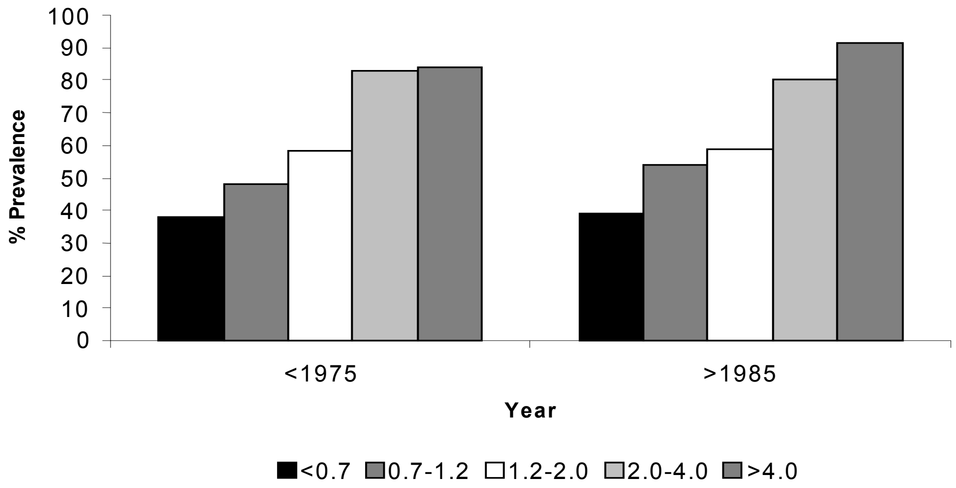


Figure 7.5 Prevalence of dental fluorosis at different water fluoride levels before 1975 and after 1985

Figure 7.5 shows similar patterns and prevalence of fluorosis both before 1975 and after 1985. An increase in the prevalence of fluorosis over time was not seen in this analysis of water fluoridation studies. While this finding is counterintuitive, no explanation is evident from these data. However, the measure of use of other fluoride sources was very crude.

Table 7.14 Studies that controlled for the effects of other fluoride use.

Author (Year)	Sources of fluoride	Other variables included in model	Classification of fluorosis	Results: Odds Ratio (95% CI)
Ismail (1990)	Fluoride tablet use	Type of school, city, sex, age	TSIF>=1	F tablet use = 1.70 (1.28, 2.27)
Riordan (1991)	Fluoride tablet use (short, medium and long term) versus no fluoride tablet use, likes toothpaste, started toothpaste < 1 year and 1-3 years versus >3 years, and swallowed toothpaste	Resident in fluoridated area for 1.2-4 years or 2.5-4 years versus <1 year	TF score >0	F tablets short: 1.55 (0.54, 4.42) F tablets medium: 0.87 (0.30, 2.52) F tablets long: 4.63 (1.97, 10.90) Likes toothpaste: 1.27 (0.75, 2.15) Started toothpaste <1 yr: 1.35 (0.72, 2.55) Started toothpaste 1-3 yr: 1.20 (0.63, 2.29) Swallowed toothpaste 1.02 (0.71, 1.45)
Szpunar (1988)	Fluoride rinse, use of fluoride supplements, dental attendance, age started brushing	Town, male education, age	Categorised as having fluorosis at TSIF>=1	Use of fluoride supplements, dental attendance, age started brushing not associated with fluorosis (no results presented). Fluoride rinse use = 1.57 (1.02, 2.41)
Brothwell (1999)	Fluoride supplements, fluoridated mouthwash, age parent brushed with fluoride paste,	Water fluoride level, breast feeding, highest level of education, household income	Categorised as having fluorosis at TSIF>=1	Fluoride supplements: 1.93 (1.02-3.62) Fluoride mouthwash: 2.73 (1.06-7.05) Age parent brushed: 0.93 (0.40-2.19)
Butler (1985)	Fluoride toothpaste, number of fluoride treatments, fluoride drops	Home air conditioning, race, total dissolved solids and zinc	CFI (Dean's community fluorosis index) stratified by exposure.	Use of fluoride toothpaste/drops and number of fluoride treatments almost identical in those that did and did not develop moderate fluorosis, therefore not included in multivariate analysis.
Heller (1997)	Fluoride drops, fluoride tablets, professional F treatment, school fluoride rinses	Water fluoride level, age	Fluorosis categorised as Dean's score of very mild or greater	Fluoride drops: 1.49 (1.11, 1.99) Fluoride tablets: 1.20 (0.96, 1.49) Professional F: 1.05 (0.85, 1.28) School fluoride rinse: 1.14 (0.84, 1.55)
Angelilo (1999)	Frequency of tooth brushing	Univariate analysis results presented	CFI (Dean's community fluorosis index) stratified by exposure.	Results presented as CFI (sd): Tooth-brushing < 1 day: 0.15 (0.31) > 1 day: 0.13 (0.37) No significant association so not included in multivariate analysis.
Kumar (1999)	Fluoride tablets and early brushing	Race and water fluoride level	Compared very mild or worse with normal.	Early brushing: 2.0 (1.2, 3.3) Fluoride tablet: 2.9 (1.3, 4.7) All compared to no fluoride exposure from any of these sources or from water fluoride.
Skotowski (1995)	Fluoride supplements, age started brushing, total toothpaste usage in 8 years, mouth rinse usage	Drinking water fluoride	Dental fluorosis present if received TSIF score>=1.	Fluoride-supplement use, mouth rinse use and age started brushing not significant in univariate analysis so not included in multivariate analysis. Fluoride exposure from toothpaste significant in univariate and multivariate analysis (adjusted OR not presented)

7.6 Possible confounding factors

There are likely to be many possible confounding factors in cross-sectional studies of dental fluorosis. Temperature and altitude are two that are frequently mentioned, but not controlled for in these studies. People living in climates with a higher mean temperature drink more water, thus being exposed to more total fluoride. Higher altitude has also been thought to be associated with the development of fluorosis, although the mechanism for this is unclear. Fluorosis can be difficult to distinguish from other developmental defects of enamel.

7.6.1 Studies which adjusted for the possible confounding effect of other sources of fluoride

Nine studies of the association between fluorosis and water fluoridation used multiple logistic regression analysis to control for the possible confounding effects of other sources of fluoride. The results of these analyses and the variables controlled for in the regression analysis are presented in Table 7.14. All results presented as adjusted odds ratios with 95% confidence intervals. These studies found mixed results, with no definite association between the other sources of fluoride studied and fluorosis.

7.7 Potential publication bias

The data were analysed in such a way that an measure of effect was not produced for each individual study thus it was not possible to investigate publication bias using standard methods.

7.8 Discussion

Fluorosis was the most widely and frequently studied of all the possible adverse effects considered. The fluorosis studies used cross-sectional designs, with a few before-after designs (again using different groups of people at each time point). The mean validity score was only 2.8 out of 8 and all but one of the studies were of evidence level C. Observer bias may be of particular importance in studies assessing fluorosis. Efforts to control for potential confounding factors, or reducing potential observer bias were infrequently undertaken. Seventy-two of 88 studies did not use any form of blinding of the assessor, and 50 of 88 did not control for confounding factors, other than by simple stratification by age or sex.

The primary fluorosis analysis was based on prevalence of ‘fluorosed’ people, including any degree of fluorosis. A conservative approach to defining fluorosis was used for this analysis, in that the ‘questionable’ category in Dean’s index was counted as fluorosis. Because there is evidence that very mild forms of fluorosis are not concerning to people (indeed some even preferred photographs of mildly fluorosed teeth) a secondary analysis assessed the prevalence of fluorosis of ‘aesthetic concern’.

With both methods of measuring the prevalence of fluorosis, a significant dose-response relationship was identified through the univariate regression analysis (Tables 7.1 and 7.6; Figures 7.1 and 7.2). The prevalence of fluorosis at a water fluoride level of 1.0ppm was estimated to be 48% (95% CI 40 to 57) for any fluorosis and 12.5% (95% CI 7.0, 21.5) for fluorosis of aesthetic concern. The numbers of additional people who would have to be exposed to water fluoride levels of 1.0 or 1.2ppm for one additional person to develop fluorosis of any level were quite low, 5 or 6 when comparing to a theoretical low fluoride level of 0.4ppm (Table 7.3). For fluorosis of aesthetic concern to occur in one additional person, however, the number was 22 at 1ppm, but the 95% CI included infinity (Table 7.8).

The multivariate analysis of fluorosis took into account variables potentially contributing to the heterogeneity between studies. This analysis found a statistically significantly higher risk in children with permanent teeth, compared with primary teeth or both types (Table 7.4). The multivariate analysis of fluorosis of aesthetic concern confirmed these findings (Appendix K). A sensitivity analysis limiting the range of water fluoride levels entered into the model did not alter the findings in any meaningful way.

The estimated NNT for one extra child to be caries-free (Chapter 4) was seven (95% CI 5 to 10), while the NNH for fluorosis is six (95% CI 4 to 21), with approximately a quarter of these being of aesthetic concern. These estimates are based on comparisons of specific levels of water fluoridation (e.g. < 0.7 ppm vs 0.7 to 1.2 ppm for caries, and 0.4 ppm vs 1.0 ppm for fluorosis). The numbers would change if different levels of fluoridation were compared.

Objective 4: Does water fluoridation have negative effects?

8. BONE FRACTURE AND BONE DEVELOPMENT PROBLEMS

A total of 29 studies of the effect of exposure to fluoridated water on bones met inclusion criteria. Among these were four prospective cohort studies, six retrospective cohort studies, 15 ecological studies, one case-control study, one study which used both a case-control and ecological design and two studies which met the inclusion criteria but was not included in the analysis for the reasons outlined in section 8.1. These papers studied a variety of fracture sites as well as slipped epiphysis in older children and young adults, and otosclerosis (malformation of bones in the ear). Hip fracture was included or was the only outcome in 18 studies. Details of baseline information and results from each study can be found in tables in Appendix C.

All but one of the studies looking at the association of water fluoride level with bone fractures were of evidence level C. The other study was of evidence level B, the average checklist score was 3.4 out of 8 (range 1.5 to 6.0). Only four of the 25 studies used a prospective study design, none used any form of blinding and only one study conducted a baseline examination prior to the introduction of fluoridation. The two lowest scoring studies did not address or control for any possible confounding factors. There were two case-control studies, both of which were of evidence level C, scoring 3.5 and 4 out of a possible 9 on the validity checklist.

Tables 8.1 to 8.4 present summaries of the findings of all eligible bone fracture studies included in the review, organised by fracture site or bone development problem. A point estimate of the size of the effect, the statistical significance of this measure and the study validity scores are also reported. In all calculations made by the review team, the area with the water fluoride level closest to 1.0 ppm was chosen and compared to the area with the lowest water fluoride level reported.

A forest plot of all the bone studies showing the measures of effect and their 95% confidence intervals was produced (Figure 8.1) for all studies that provided sufficient data to calculate a relative risk, odds-ratio or standardised rate-ratio and its 95% confidence interval. The majority of the measures of effect and their confidence intervals were distributed around 1, the line of no effect for related measures (suggesting no association), with no obvious outliers noted. The studies included in the forest plots differ from one another in a number of respects. Data are presented for both sexes, for different age groups and for different fracture sites (colour coded), using crude or adjusted outcomes and a variety of study designs.

In Figure 8.1, point estimates to the left of the vertical line indicate fewer fractures with exposure to fluoridated water, while those to the right side of the line indicate more fractures.

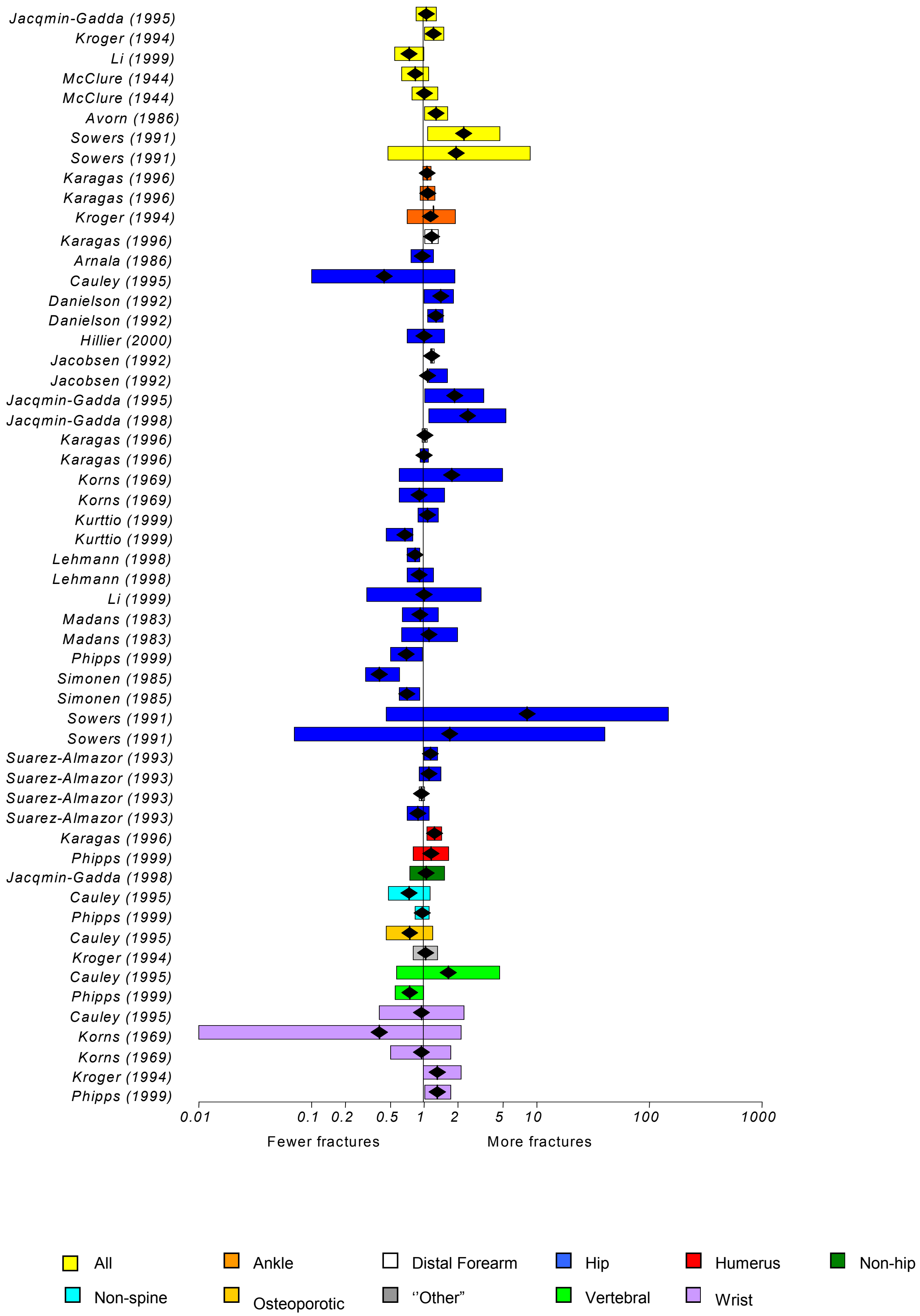


Figure 8.1 Bone fracture incidence (Measure of effect estimate and 95% CI)

Table 8.1 Effect of water fluoridation on hip fracture

Author (Year)	Age	Sex	RR (95% CI)	Validity score
Cauley (1995)	65+	Women	0.44 (0.1, 1.9)*	6.0
Jacqmin-Gadda (1998)	65+	Both	2.43 (1.1, 5.3)*	5.5
Sowers (1991)	20-35	Women	1.68 (0.07, 40.1)[1]	5.3
	55-80	Women	8.18 (0.46, 146.6)[1]	
Li (1999)	50+	Both	0.99 (0.3, 3.2)	5.0
Jacqmin-Gadda (1995)	65+	Both	1.86 (1.0, 3.4)*	5.0
Kurttio (1999)	50+	Women	1.08 (0.9, 1.3)*	4.5
	50+	Men	0.67 (0.5, 0.8)*	
Phipps (1999)	65+	Women	0.69 (0.5, 1.0)*	4.3
Hillier (2000)	50+	Both	1 (0.7, 1.5)*	4
Lehmann (1998)	35+	Women	0.83 (0.7, 0.9)	3.8
	35+	Men	0.91 (0.7, 1.2)	
Danielson (1992)	65+	Women	1.27 (1.1, 1.5)*	3.7
	65+	Men	1.41 (1.0, 1.8)*	
Jacobsen (1992)	65+	Women	1.08 (1.06, 1.10)	3.3
		Men	1.17 (1.13, 1.22)	
Cooper (1990)	45+	Both	R=0.41, p=0.009	3.3
Suarez-Almazor (1993)	45-64	Women	0.85 (0.7, 1.03)	3.0
	65+	Women	0.96 (0.9, 1.03)	
	45-64	Men	1.13 (1.0, 1.27)	
	65+	Men	1.07 (.087, 1.32)	
Madans (1983)	NS	Women	0.92 (0.6, 1.3)	2.8
	NS	Men	1.11 (0.6, 2.0)	
Simonen (1985)	50+	Women	0.7 (0.6, 0.9)*	2.5
	50+	Men	0.4 (0.3, 0.6)*	
Korns (1969)	40+	Men	1.75 (0.6, 4.9)	2.5
	40+	Women	0.91 (0.6, 1.5)	
Karagas (1996)	65+	Women	No association	1.5
Arnala (1986)	50+	Both	0.96 (0.8, 1.2)	1.5
	65+	Men	1 (0.9, 1.1)*	1.5

* = unadjusted **relative risk** ; RR = adjusted relative risk (see data extraction tables for further details of adjustment made in each study); [1] in the Sowers study there were no cases in the control group and so a Haldane approximation was used to estimate the relative risk.

A total of 18 studies (see Table 8.1) investigated the association of hip fracture with water fluoride level, making 30 analyses (e.g. men only, women only, both). Fourteen analyses found the direction of the association between water fluoridation and hip fracture to be positive (decreased hip fracture with increased water fluoride level). Five were statistically significant associations. Thirteen analyses found the direction of association to be negative (increased hip fracture), but only four of these found a statistically significant effect. Three additional analyses did not find any association. Three of the 18 studies found the direction of association positive in women but negative in men and one study found a negative effect in women and a positive effect in men.

There were no definite patterns of association for any of the fractures, for example, with all studies finding a positive effect for a particular fracture. A total of 30 analyses were conducted in 12 studies (see Table 8.2). Overall 14 analyses found the direction of association of water fluoridation and bone fracture to be negative (more fractures), of which one was statistically significant. Thirteen analyses found the direction of association to be positive (fewer fractures), of which one was statistically significant and two did not report variance data. Three analyses found no association. The two studies that found statistically significant effects were Li (1999), which found a small protective effect in both sexes for all fractures, while Karagas (1996) found a small negative effect in men for increased risk of fracture of the humerus. While both of these analyses were statistically significant, the 95% CI only just excluded 1.0.

Table 8.2 Effect of water fluoridation on other fractures

Author (Year)	Fracture	Age	Sex	RR (95% CI)	Validity Score
Sowers (1991)		20-35	Women	1.81 (0.5, 8.2)*	5.3
		55-80	Women	2.11 (1.0, 4.4)*	
Jacqmin-Gadda (1995)	All fractures	65+	Both	0.98 (0.8, 1.2)*	5.0
Li (1999)		50+	Both	0.69 (0.5, 0.9)	5.0
Avorn (1986)		65+	Women	1.2 (1.0, 1.5)	3.1
Kroger (1994)		47-56	Women	1.14 (0.9, 1.4)	2.8
McClure (1944)		19-23	Men	0.78 (0.6, 1.0)	2.8
		15-17	Men	0.95 (0.7, 1.2)	
Kroger (1994)	Ankle	47-56	Women	1.14 (0.7, 1.9)	2.8
Karagas (1996)		65+	Women	1 (0.9, 1.1)*	1.5
		65+	Men	1.01 (0.9, 1.2)*	
Bernstein (1966)	Collapsed vertebrae	45+	Women	0.26	3.5
		45+	Men	0.96	
Karagas (1996)	Distal forearm	65+	Women	Author states no association	1.5
		65+	Men	1.16 (1.0, 1.3)*	
Karagas (1996)	Humerus	65+	Women	Author states no association	1.5
		65+	Men	1.23 (1.1, 1.4)*	
Phipps (1999)		65+	Women	1.15 (0.8, 1.6)*	4.3
Jacqmin-Gadda (1998)	Non-hip	65+	Both	1.05 (0.7, 1.5)*	5.5
Cauley (1995)	Non-spine	65+	Women	0.73 (0.5, 1.1)*	6.0
Phipps (1999)		65+	Women	0.96 (0.8, 1.1)*	4.3
Cauley (1995)	Osteoporotic	65+	Women	0.74 (0.5, 1.2)*	6.0
Kroger (1994)	Other	47-56	Women	1.03 (0.8, 1.3)	2.8
Cauley (1995)	Vertebral	65+	Women	1.63 (0.6, 4.7)*	6.0
Phipps (1999)		65+	Women	0.74 (0.6, 1.0)*	4.3
Cauley (1995)	Wrist	65+	Women	0.95 (0.4, 2.3)*	6.0
Phipps (1999)		65+	Women	1.3 (1.0, 1.7)*	4.3
Kroger (1994)		47-56	Women	1.3 (1.0, 2.1)	2.8
Korns (1969)		40+	Men	0.4 (0.0, 2.1)	2.5
Korns (1969)		40+	Women	0.95 (0.5, 1.7)	

* = unadjusted relative risk ; RR = adjusted relative risk (see data extraction tables for further details of adjustment made in each study)

Three studies were included which examined the effects of water fluoridation on outcomes related to bone development (Table 8.3). Both studies of otosclerosis reported a beneficial effect of fluoridation, although no statistical analysis was presented. The study of slipped epiphyses found the direction of association to be positive (a protective effect) in girls and negative (increased risk) in boys, but neither of these was statistically significant at the 5% level.

Table 8.3 Effect of water fluoridation on bone development disorders

Author (Year)	Bone Development Defect	Age	Sex	RR (95% CI)	Validity Score
Karjalainen (1982)	Otosclerosis	All	Women	0.93	3.7
Daniel (1969)		All	Both	0.26	2.5
Kelsey (1971)	Slipped epiphysis	<25	Women	0.65 (0.4, 1.2)	3.8
			Men	1.2 (0.9, 1.6)	

8.1 Studies that met inclusion criteria but were not included in the main analysis

Two studies met inclusion criteria but were not included in the main analysis. Details of the studies and the reason for not including them in the main analysis are provided in Table 8.4.

Table 8.4 Studies which met inclusion criteria but were not included in the main analysis

Author (Year)	Outcome	Reason for exclusion	Author's Conclusions
Sowers (1986)	Bone fracture	The levels of fluoride in the control groups were similar to artificial levels of fluoridation. Women were classified according to water fluoride and calcium concentration. The high fluoride group (F level = 4ppm) was low in calcium and the lower fluoride groups (F level = 1pm) had very high and high levels of calcium in the water. This was likely to confound any association observed between water fluoride level and fracture incidence.	Intake of water providing ~4ppm of fluoride does not decrease fracture rate in young adult women or in postmenopausal women in a population-based setting. There was a history of more frequent fracture among women in the community with greater fluoride in drinking water as compared to women in the other 2 communities. Substantial fluoride intake may magnify the need for adequate dietary calcium and vitamin D intake, particularly in premenopausal women.
Horne (2000)	Bone fracture	Only the abstract was available. This did not provide sufficient details for inclusion of this study in the main analysis. The authors compared hip fractures and knee DJD joint replacements among those >65 years for 1991-1996 in a community with fluoridated water and 2 without. Directly standardised age-adjusted rates were calculated, these are not presented in the abstract. Only reports on one age-group which showed a significant association, results of other age-groups not presented and so it is not possible to draw conclusions from the limited results presented.	An association between fluoride and DJD of the knee was not supported, while a trend in the females for hip fracture was observed.

The level of water fluoride concentration examined in the Sowers (1986) study was higher than the level to which water supplies would be artificially fluoridated. The authors did not appear to find any significant association of fracture with water fluoride concentration, despite the possible confounding effect of the difference in calcium concentrations between the study areas. Full details of the Horne (2000) study were not available and the results presented in the abstract were insufficient for inclusion in the review or to draw any conclusions as to the results of this study.

8.2 Potential confounding factors

The incidence of hip fracture is strongly associated with age and sex, thus any study investigating the incidence of hip fracture should control for these variables. Other factors that may confound the association between water fluoride content and fracture incidence include body mass index (BMI), ethnicity, calcium intake, certain drugs, non-water fluoride exposure and the menopausal status of women. Of the 27 studies included in the analysis of water fluoridation and fracture incidence, 10 studies presented crude results only (some of these stratified on age and sex), 12 presented adjusted effect measures such as relative risks and odds ratios, and five studies presented standardised results. Of these, six studies failed to control for the effect of any possible confounding factors. Five studies presented results separately by sex and three studies controlled for age only (one of these controlled for age by only selecting people above a certain age). Five studies included only people within a certain age grouping and presented results by sex. Four studies controlled for the effects of both age and sex. Three studies controlled for age, sex and BMI and four studies controlled for other variables in addition to these three variables.

8.3 Meta-regression

Heterogenity was investigated using the Q statistic and found to be significant thus a meta-regression was carried out to investigate possible sources of heterogeneity between studies. Variables that may account for the differences in effect-size seen between studies were included in the regression model. The natural log of the outcome measure (relative risk, odds ratio or standardised rate ratio) was included as the dependent variable in the regression analysis. The results were then exponentiated to make the results more easy to interpret (see below for further details). The Haldane approximation was used to estimate variance where there were no cases in one of the groups. This involves adding 0.5 to the cells in a contingency table in which there are no cases.

Several of the studies included in the meta-regression contribute more than one estimate to the analysis. Some studies looked at different age groups or stratified results on sex and many of the studies looked at more than one fracture site. It has been assumed in this analysis that these subgroups of people are independent and hence each estimate has been treated as though it came from a separate study. The potential limitations of including these estimates in the same regression are discussed in section 12.6.

Continuous measures were centred on the mean (the mean value of each variable was subtracted from each of the individual measures), before including them in the regression model. Centring continuous variables in this way results in the constant (or intercept) of the regression model pertaining to the pooled estimate of the mean difference when the explanatory variable takes its mean value.

A univariate analysis was undertaken in which each of the variables was included individually in the regression model with the log of the relative risk, odds ratio or standardised rate ratio of the incidence of fracture in the fluoridated compared to the control study area. For studies that presented results for more than two study areas the comparison included in this analysis is the summary measure which compares the area with the fluoride level closest to 1ppm to the area with the lowest water fluoride level. If studies presented summary age-adjusted estimates in addition to age specific measures this estimate was included in the analysis, for studies in which no overall estimate was available age-specific or crude estimates were included.

A measure of the between study variance (heterogeneity) remaining after the variables included in the model had been accounted for was calculated using restrictive maximum likelihood estimation. Variables which showed a significant association with the outcome variable at the 15% significance level ($p<0.15$) in the univariate analysis were included in the multivariate analysis. The multivariate analysis was carried out using a step-down analysis in which each variable was included in the initial model. Variables were dropped one by one, with the variable that showed the least evidence of a significant association dropped first, until only variables which showed a significant association at the 5% level were included in the analysis. The analysis was repeated using step-up analysis to confirm the results of the step-down analysis. As a further exploratory analysis study validity was forced into the regression model as the effect of study validity was considered to be very important in these studies of variable quality.

8.3.1 Univariate analysis

The results of the univariate analysis are shown in Table 8.5. A total of 55 measure of effect estimates from 20 studies were included in the analysis.

At the 15% significance level the following variables showed a significant association with the summary measure: study duration and measure of exposure. These variables were included in the multivariate analysis. The model in which no variables (other than the outcome measure) were included shows the pooled estimate of the summary measure to be 1.00 (95% CI: 0.94, 1.06). This is the same as the measure that would be produced by a standard meta-analysis. The between study variance (heterogeneity) was investigated and found to be significant (Q statistic = 197 on 54 degrees of freedom, $p<0.001$). This pooled estimate suggests that there is no association between water fluoridation and fracture incidence. However, because of the significant heterogeneity this value should be interpreted with *extreme caution.*

Table 8.5 Results of the univariate meta-regression analysis for bone fractures

Variable	Category (number of analyses)	Constant (95% CI)	p-value of constant	Co-efficient (95% CI)	p-value of co-efficient	Between study variance
No variables (pooled estimate)		1.00 (0.94, 1.06)	0.926			0.029
Age	<35 (4)	0.89 (0.69, 1.14)	0.345			0.016
	35+ (6)			1.00 (0.73, 1.38)	0.983	
	45-65 (6)			1.21 (0.90, 1.62)	0.204	
	50+ (10)			0.91 (0.68, 1.21)	0.502	
	65+ (27)			1.20 (0.92, 1.56)	0.170	
	NS (2)			1.10 (0.71, 1.71)	0.660	
Study duration*	<5 (17)	1.04 (0.96, 1.13)	0.357			0.018
	5-10 (19)			1.03 (0.91, 1.17)	0.649	
	>10 (4)			0.69 (0.56, 0.84)	<0.001	
	Not stated (15)			0.90 (0.77, 1.04)	0.160	
Measure of* exposure	% exposed (10)	1.07 (0.95, 1.20)	0.271			0.028
	Water level (35)			0.92 (0.80, 1.07)	0.276	
	Years of exposure (10)			0.85 (0.69, 1.04)	0.118	
Highest estimate of water fluoride level	Low (2)	1.30 (0.84, 1.99)	0.236			0.030
	Optimum (49)			0.76 (0.20, 1.17)	0.214	
	High (4)			1.68 (0.75, 3.75)	0.205	
Outcome measure	Relative risk (48)	0.98 (0.91, 1.05)	0.512			0.030
	Odds Ratio (5)			1.19 (0.93, 1.52)	0.178	
	Standardised rate ratio (2)			1.15 (0.87, 1.53)	0.325	
Was an adjusted results presented?	No (18)	0.97 (0.86, 1.09)	0.594			0.030
	Yes (37)			1.04 (0.91, 1.20)	0.567	
Was the result adjusted for bmi?	No (45)	0.99 (0.93, 1.41)	0.855			0.031
	Yes (10)			1.03 (0.84, 1.27)	0.771	
Was the result adjusted for age?	No (20)	0.97 (0.86, 1.10)	0.652			0.031
	Yes (34)			1.03 (0.90, 1.19)	0.634	
	Matched (1)			1.03 (0.61, 1.74)	0.919	
Fracture site	Hip (27)	0.97 (0.89, 1.06)	0.549			0.032
	All (10)			1.03 (0.85, 1.25)	0.759	
	Wrist (5)			1.22 (0.90, 1.64)	0.200	
	Ankle (3)			1.05 (0.81, 1.36)	0.695	
	Distal forearm (1)			1.19 (0.81, 1.75)	0.374	
	Humerus (2)			1.23 (0.90, 1.69)	0.196	
	Non-hip (1)			1.08 (0.65, 1.79)	0.771	
	Non-spine (2)			0.90 (0.65, 1.25)	0.538	
	Osteoporotic (1)			0.76 (0.42, 1.38)	0.369	
	Other (1)			1.06 (0.68, 1.64)	0.800	
	Vertebral (2)			0.85 (0.55, 1.32)	0.472	
Was the result adjusted for sex?	No (5)	0.99 (0.81, 1.21)	0.917			0.032
	Yes (49)			1.01 (0.82, 1.24)	0.938	
	Matched (1)			1.01 (0.58, 1.76)	0.970	
Sex	Male (8)	1.00 (0.89, 1.11)	0.948			0.032
	Female (31)			1.00 (0.86, 1.15)	0.957	
	Both (16)			1.02 (0.82, 1.27)	0.832	
Validity*	3.65	0.99 (0.93, 1.06)	0.846	0.99 (0.94, 1.04)	0.748	0.030

*Included in multivariate analysis

8.3.2 Multivariate analysis

The multivariate model shows the effect of each variable controlled for the possible effects of the other variables included in the model. The results of the multivariate analysis are shown in Table 8.6. Study duration was the only variable to show a significant association at the 5% level with the summary measures (relative risk, odds ratio or standardised measure of effect) for the association of water fluoridation with bone fracture incidence. This variable reduced the between study variance from 0.029 to 0.018 in the final model. The analysis was repeated using a step-up analysis, this produced a similar model. This shows that the direction of association (non-significant) is negative (more fractures) for studies that last for less than five years and between five and 10 years and positive (fewer fractures) for studies in which duration is not stated. A statistically significant positive association was seen in studies that lasted for longer than 10 years, meaning that fewer fractures occur in fluoridated areas compared to non-fluoridated areas if they are studied longer than 10 years. Study validity did not show a statistically significant association with the measure of effect at the 5% level, and was not included in the multivariate model. The model with validity forced in is presented in Appendix L.

Table 8.6 Results of the multivariate meta-regression analysis for bone fracture studies

Variable	Category	Co-efficient (95% CI)	p-value	Between study variance
Constant		1.04 (0.96, 1.13)	0.357	0.018
Study duration	<5 (17)			
	5-10 (19)	1.03 (0.91, 1.17)	0.649	
	>10 (4)	0.69 (0.56, 0.84)	<0.001	
	Not stated (15)	0.90 (0.77, 1.04)	0.160	

8.4 Publication bias

A funnel plot to assess potential publication bias could not be constructed for bone fracture studies. The funnel plot graphs sample size versus measure of effect. The studies included in the meta-regression did not provide sufficient data on the sizes of the populations studied to make a plot. Because the measures of effect reported in these studies were distributed around 1, the line of no effect for relative measures, it would be unlikely that a funnel plot would be helpful in detecting potential publication bias. One additional study of osteoporotic bone fracture by Sowers, which included measurement of duration of residence, individual drinking water fluoride and serum fluoride levels, has been conducted. Communication with the author indicates that no association was found. However, while this study has been submitted to the Journal of Bone and Mineral Research, it has not yet been published.

8.5 Discussion

There were 29 studies included on bone fracture and bone development problems. Other than fluorosis, bone effects (not including bone cancers) were the most studied potential adverse effect. These bone studies also had low validity (3.4 out of 8) with all but one study being evidence level C. These studies included both retrospective and prospective cohort designs, some of which included appropriate analyses controlling for potential confounding factors. Observer bias could potentially play a role in bone fracture, depending on how the study is conducted.

The graph of estimates of association for all bone fracture studies (Figure 8.1) shows that the individual estimates of effect lie very close to a relative risk of 1.0. Most of the confidence intervals cross 1.0 (statistically non-significant). The only confidence intervals that do not include 1.0 (statistically significant) are evenly distributed, five indicating an increased risk of fracture and four indicating a decreased risk. The meta-regression showed that the pooled estimate of the association of bone fracture with water fluoridation was 1.00 (0.94, 1.06), however due to the significant heterogeneity between studies this value should be interpreted with extreme caution. The meta-regression showed that the only variable (out of 30 total) associated with the summary measure at the 5% significance level was study duration. Factors which would be expected to show an association with fracture incidence, such as fracture site, age and sex, were not associated with water fluoride level at the 5% significance level in either the univariate or multivariate models. This adds support to the result suggested by the pooled estimate of no association between water fluoridation and fracture incidence.

The evidence on bone fracture can be classified into hip fracture and other sites as there were a greater number of studies on hip fracture than any other site. Using a qualitative method of analysis, there is no clear association of hip fracture with water fluoridation (Table 8.5). Of 18 studies, three showed a statistically significant benefit, and two showed statistically significant harm, and three showed no effect of water fluoridation on hip fracture. One study found no cases of hip fracture in the low fluoride group, indicating harm from water fluoridation. The evidence on other fractures is similar (Table 8.2); of 30 study comparisons one found statistically significant benefit, one found statistically significant harm and three found no effect. The evidence on other bone outcomes was extremely limited. A negative association was suggested in the risk of slipped epiphysis in boys, but this finding was not statistically significant.

Objective 4: Does water fluoridation have negative effects?

CANCER STUDIES

A total of 26 studies examining the association between exposure to fluoridated water and cancer incidence and mortality met inclusion criteria; 10 before-after studies, 11 ecological studies, three case-control studies and two studies which met inclusion criteria but were not included in the main analysis for the reasons outlined in Table 9.4. These papers studied incidence and mortality from a variety of cancers, including all cancers, osteosarcoma, bone cancer, thyroid cancer and other site-specific cancers. Details of baseline information and results from each study can be found in tables in Appendix C.

Five of the studies of the association of cancer with water fluoride level achieved an evidence level of B (evidence of moderate quality, moderate risk of bias), the rest were of evidence level C (lowest quality of evidence, high risk of bias). The average validity checklist score was 3.8 out of 8 (range 2.8-4.8). For the three case-control studies the average score was 4.6 out of 9 (range 3.5 to 6.0). None of the included studies had a prospective follow-up or reported any form of blinding.

Analyses of cancer incidence and mortality data were identified for a variety of different cancers. The results of the studies considering all-cause cancer incidence and mortality and those that looked at osteosarcoma or bone and joint cancers, and thyroid cancer are presented below. All-cause cancer incidence is presented, as this is the outcome most commonly presented by the studies. The results of bone-cancer studies are also presented because if fluoride is linked to a site-specific cancer incidence, it is biologically plausible that this site would be affected because fluoride is taken up by bones. It has been suggested that fluoride may have an effect on the thyroid gland and for this reason studies which looked at cancer of the thyroid gland were also considered separately.

9.1 Cancer mortality from all causes

Table 9.1 shows the effect of fluoridation on all cause cancer incidence and mortality, a point estimate for this association, the measure used, and a measure of the significance of the association. Where studies presented an adjusted measure this is presented. For ecological or cohort studies that did not present an adjusted relative risk but did provide details on the number of cases and population at risk, an unadjusted relative risk was calculated. For studies that used an ecological or cohort study design that presented standardised mortality or incidence ratios (SMR/SIRs) the mean difference of the SMR/SIR was calculated together with the 95% confidence interval. For studies that used a before-after study design and presented relative risks or rate-ratios for two points in time the ratio of the summary measure comparing the final survey to the baseline survey was calculated. For studies that used a before-after study design and presented SMR/SIRs for both points in time, the difference of the change in SMR/SIRs from baseline to final survey between the fluoridated and control area was calculated. For studies that present a difference measure (e.g. mean difference) a negative result suggests a positive effect of fluoridation, and a positive result suggests a negative effect of fluoridation (i.e. greater cancer incidence in the fluoride group compared with the control group). For ratio measurements a ratio less than 1 suggests a positive effect of fluoridation and a ratio greater than one suggests a negative effect. If the confidence interval for this measure includes 1 or if the p-value is less than 0.05 then this suggests a statistically significant difference. In all calculations made by the review team, the area with the water fluoride level closest to 1.0 ppm was chosen and compared to the area with the lowest water fluoride level reported.

All cause cancer incidence and mortality was considered as an outcome in 10 studies, in which 22 analyses were made. Of these, 11 found the direction of association of water fluoridation and cancer to be positive (fewer cancers) and 9 found the direction of association to be negative (more cancers), 2 studies found no association of water fluoride exposure and cancer. One study (Lynch, 1985) found a statistically significant negative effect in 2 of the 8 sub-groups investigated; this was not confirmed when other sub-groups were considered (Appendix C). One study (Smith, 1980) found a statistically significant positive effect. There does not appear to be any association between validity and the direction of the association of water fluoride exposure and cancer incidence. Of the two studies with the highest validity scores (4.8 and 4.2) one found a statistically significant positive association (Smith, 1980) the other found a mixed effect (Lynch 1985); some analyses showed a statistically significant negative effect and others showing statistically non-significant associations in both directions. Overall these studies do not appear to show any association between overall cancer incidence and water fluoride exposure.

Table 9.1 Effect of fluoridation on cancer incidence and mortality

Author (Year)	Age	Sex	Summary measure	Results (95% CI)	Validity score
Smith (1980)	All ages	Both	Mean difference of change in SMRs	-4.4 (-7.5, -1.3)	4.8
Lynch (1985)	All ages	Male Female	Mean difference in SIRs	9.00 (p<0.001) 2.10 (p=0.592) -6.80 (p=0.057) -1.10 (p=0.500) 5.9 (p<0.001) 2.3 (p=0.565) 0.1 (p=1.000) 2 (p=0.630)	4.2
Chilvers (1983)	All ages	Both	Mean difference of change in SMRs	-0.1 (-3.8, 3.6)	3.8
Hoover (1976)	All ages	Male Female	Mean difference in SMRs	0 (-3.5, 3.5) 0 (-3.8, 3.8)	3.8
Chilvers (1985)	All ages All ages	Male Female	Mean difference in SMRs	-0.49 (-5.7, 4.8) -1.56 (-7.4, 4.3)	3.5
Goodall (1980)	Not stated	Male Female	Ratio of crude rate-ratios	0.85 0.90	3.5
Raman (1977)	All ages	Male	Mean difference of change in SMRs	6.9	3.3
		Female		18.9	
Cook-Mozaffari (1981)	All ages	Male	Ratio of Rate-Ratios	0.99	3.3
Richards (1979)	All ages	Both	Mean difference in SMRs	-3.3 (-18.7, 12.1)	3.1
Schlesinger (1956)	All ages	Male Female	Ratio of crude rate ratios	0.6 1.01	2.8

9.1.1 Studies of 20 US cities

Several studies presented analyses of data for the same set of cities in the USA, 10 fluoridated and 10 non-fluoridated cities (Table 9.2). These cities were originally selected and analysed by Yiamouyiannis (1977). The other studies present a re-analysis of the data included in this study, although some have selected slightly different years to investigate or have obtained data through different sources. All studies used before-after study designs comparing cancer incidence before and after the introduction of water fluoridation in 10 of the 20 study areas.

In the original study, Yiamouyiannis found a positive association between increased water fluoride and cancer incidence (more cancers). This study has been criticised for not taking into account demographic differences between the two groups of cities at baseline and inadequately accounting for changes in age (e.g. finer age bands) and gender structure between the baseline and final study years. Yiamouyiannis grouped men and women and whites and non-whites together into broad age groups (0-24, 25-44, etc) for the calculation of mortality ratios. The data show that the proportion of the populations that were non-white and over 65 years of age increased more rapidly in the fluoridated than in the non-fluoridated areas (Doll 1977).

The other studies use standardisation to control for age, sex and ethnic group. These studies did not find an association between cancer mortality and water fluoridation in the selected cities. Yiamouyiannis criticised the analysis used by Doll (1977) because the data used, supplied by the National Cancer Institute (NCI) contained a data transcription error which was repeated in the paper (Yiamouyiannis, 1977). Yiamouyiannis also argued that the analysis was inappropriate because 90-95% of the available data were omitted and that the selection of the year 1970 as one of the study years was inappropriate as fluoridation of the control group had already started. This had in fact only been started in two of the cities shortly (months) before the 1970 data were collected. Doll justified the choice of 1970 as a census year for which more accurate population data were available. Smith (1980) used the corrected NCI figures in a similar analysis and also failed to detect any association between water fluoridation and cancer mortality in the selected cities.

For the analysis presented here, the results of the four studies which analysed data for the same 20 US cities are presented together in Table 9.2. The study which scored the highest on the validity checklist, and did not include the error in the NCI data (Smith, 1980) is included in the main analysis in Table 9.1.

Table 9.2 Studies which present analyses of the same set of data for 20 cities in the USA

Author (Year)	Age	Sex	Summary measure	Results (95% CI)	Validity score
Doll (1977)	NS	Both	Mean difference of change in SMRs	-7.0 (-10.6, -3.4)	4.8
Chilvers (1982)	NS	Both	Mean difference of change in SMRs	-1.8 (-7.9, 4.2)	4.8
Smith (1980)	All ages	Both	Mean difference of change in SMRs	-4.4 (-7.5, -1.3)	4.8
Yiamouyiannis (1977)	0-24	Both	Ratio of crude rate ratios	1.01	4.1
	25-44			1	
	45-64			1.03	
	65+			1.03	

9.2 Osteosarcoma and bone cancer

Table 9.3 shows the association of osteosarcoma, bone and joint cancer incidence and mortality with water fluoride level, a point estimate of variance for this association, the measure used, and a measure of the significance of the association. Where studies presented an adjusted measure this is presented. For studies that did not present an adjusted relative risk but did provide details on the number of cases and population at risk, an unadjusted relative risk was calculated.

Table 9.3 Association of osteosarcoma, bone and joint cancer incidence and mortality with water fluoride level

Author (Year)	Age	Sex	Cancer	Summary measure	Results (95% CI)	Validity score
Kinlen (1975)	All ages	Both	Bone	Mean difference in SMRs	6 (-50.8, 62.8)	4.0
Hoover (1976)	All ages	Male	Bone	Mean difference in SMRs	0 (-35.9, 35.9)	3.8
		Female			20 (-22.6, 62.6)	
Hoover (1991)	All ages		Bone and joint	Mean difference of change in SIRs	1 (-30.2, 32.2)	3.3
Mahoney (1991)	<30	Male	Bone	Crude RR	0.93	2.8
	<30	Female			0.96	
	30+	Male			0.84	
	30+	Female			1.1	
Moss (1995)	Not stated	Both	Osteosarcoma	OR	1.0 (0.6, 1.5)	6.0
Gelberg (1995)	<24		Osteosarcoma	OR	2.07 (0.5, 8.0)	4.3
	<24			OR	1.84 (0.8, 4.2)	
Hrudey (1990)	All ages		Osteosarcoma	Crude RR	0.93 (0.6, 1.6)	4.0
Hoover (1991)	All ages		Osteosarcoma	Mean difference of change in SIRs	-11 (-44.6, 22.6)	3.8
McGuire (1991)	0-40	Both	Osteosarcoma	OR	0.33 (0.0, 2.5)	3.5
Mahoney (1991)	<30	Male	Osteosarcoma	Crude RR	0.98	2.8
	<30	Female			0.78	
	30+	Male			0.88	
	30+	Female			0.91	
Cohn (1992)	0- 20	Male Female	Osteosarcoma	Crude RR	3.4 (1.4, 8.1) 1.0 (0.3, 3.5)	2.5

Four studies considered the association of bone related cancer and water fluoride exposure, performing eight analyses. Of these, the direction of association of water fluoridation and bone cancer was found to be positive in three, negative in four and one did not detect a relationship. None of the studies found a statistically significant association, however one study (Mahoney 1991) contributed five of the nine analyses with no variance data.

Seven studies of osteosarcoma, presenting 12 analyses were included. Of these, the direction of association between water fluoridation and osteosarcoma incidence or mortality was found to be positive (fewer cancers) in seven, negative (more cancers) in threeand two found no relationship. Of the six studies that presented variance data, one (Cohn 1992) found a statistically significant association between fluoridation and increased prevalence of osteosarcoma in males. This study however, also had the lowest validity score, 2.5 out of 8. One study (Mahoney 1991) contributed four of the 12 analyses but did not provide variance data.

9.3 Cancer of the thyroid gland

Two studies (Kinlen 1975, Hoover 1976) investigated the association of water fluoride level with cancer of the thyroid gland. Both studies used indirect standardisation to control for the effects of age and sex and did not find any association between water fluoride level and thyroid cancer (Appendix C).

9.4 Studies that met the inclusion criteria but were not included in the main analysis

The studies in table 9.4 met the inclusion criteria but were not included in the main analysis for the reasons outlined in the table. Both of these studies appear to confirm the results of the main analysis: a lack of association between water fluoride content and cancer incidence and mortality.

Table 9.4 Studies that met the inclusion criteria but were not included in the main analysis

Author (Year)	Outcome	Reason	Authors Conclusions
Hoover (1990)	Cancer Mortality	Non-fluoridated areas grouped together with areas fluoridated within the past five years.	The relative risk of death from cancers of the bones and joints was the same after 20-35 years of fluoridation as it was in the years immediately preceding fluoridation. A similar lack of relationship to timing of fluoridation was noted for the incidence of bone and joint cancers and osteosarcomas. The relative risk of developing these cancers 20 or more years after fluoridation was lower than the risk associated with less than five years of fluoridation among both males and females. For no type of malignancy was there consistent evidence of a relationship with patterns of fluoride. In a study of over 2300000 cancer deaths in fluoridated counties across the US, and over 125000 incident cancer cases in fluoridated counties covered by two population based cancer registries, no trends in cancer risk that could be ascribed to the consumption of fluoridated drinking water could be identified.
Swanberg (1953)	Cancer Mortality	Cancer mortality compared between fluoridated area and the whole of the US - includes areas with fluoride in the water supplies and so not a suitable control area	The death rate from cancer in the study area decreased during the study period whereas the death rate from cancer in the whole of the US (the control area) increased over the same period.

9.5 Possible confounding factors

There is a dramatic increase in cancer with age and a considerable difference in cancer mortality between men and women and among different ethnic groups, thus even small differences in the age, sex and ethnic structure of a population can lead to noticeable differences in cancer incidence. Any study looking at the association of cancer with different exposures should therefore control for these confounding factors in the analysis. There are numerous other factors that may also lead to differences in cancer incidence between populations if the exposure of populations differ, for example, smoking, social class, diet and environmental factors, including exposure to other sources of fluoride. Of the 26 cancer studies in the main analysis, 12 used standardisation (11 used the indirect and one the direct method) to control for age and sex (some studies presented results separately by sex) and four of these also controlled for ethnic group. One study presented an age adjusted rate, and five studies presented crude data only. Of the three case-control studies, one presented a crude odds ratio matched on age, gender and county of residence, one presented an odds ratio with cases and controls matched on sex and year of birth (age). The third matched cases and controls on age, sex and race and then presented an odds ratio adjusted for population size, age radiation exposure and gender.

9.6 Discussion

The evidence of the effect of water fluoridation on cancer was of the highest quality available under Objective 4 (3.8 out of 8 compared with a mean of 2.7 for other possible negative effects) but was still only low to moderate. Twenty-one of the 26 studies presented are from the lowest level of evidence (level C) with the highest risk of bias. While prospective study designs may be more difficult to conduct in cancer studies due to long incubation periods and rarity of some cancers, they are possible. Blinding of outcome assessment to exposure is certainly possible in such studies, for example outcomes assessed using published sources could blind investigators to fluoride levels in the study areas.

There is no clear picture of association between water fluoridation and overall cancer incidence and mortality (Table 9.1). Whilst there were 11 analyses that found the direction of association of water fluoridation and cancer to be positive (fewer cancers), a further nine analyses found a negative direction of association (more cancers), and two studies found no effect. Only two studies found statistical significance, both suggesting an association in different directions. One of these studies contained eight analyses of which only two found a statistically significant adverse effect of water fluoridation.

While a broad number of cancers were represented in the included studies, osteosarcoma, bone/joint and thyroid cancers were of particular concern due to fluoride uptake by bone and thyroid. Again, no clear association between water fluoridation and increased incidence or mortality was apparent. Of eight analyses from the six studies of osteosarcoma and water fluoridation reporting variance data, none found statistically significant differences. Thyroid cancer was also considered but only two studies examined this and neither found a statistically significant association with water fluoride level.

The findings of cancer studies were mixed, with small variations on either side of no effect. Individual cancers examined were bone cancers and thyroid cancer, where once again no clear pattern of association was seen. Overall, from the research evidence presented no association was detected between water fluoridation and mortality from any cancer, or from bone or thyroid cancers specifically.

Objective 4: Does water fluoridation have negative effects?

10. OTHER POSSIBLE NEGATIVE EFFECTS

A total of 33 studies of the association of water fluoridation with other possible negative effects were included in the review. There were six before and after studies, one retrospective cohort study, 12 ecological studies, five cross sectional, one case control study and eight studies which met inclusion criteria but were not included in the main analysis for reasons outlined below (Table 10.3 and section 10.2). These studies examined a variety of different outcomes including Down's syndrome, mortality, senile dementia, goitre and IQ. Details of baseline information and results from each study can be found in tables in Appendix C. Two studies (Briner 1966 and Schatz 1976) presented data from the same two cities in Chile from similar time periods. To avoid duplication, only the Schatz study is presented in the tables below, but both studies are included in the data tables in Appendix C. Although some authors (Spittle 1993) have reported cases of hypersensitivity to fluoridated water, no studies meeting the inclusion criteria were found.

The quality of these studies was generally low; all studies were of evidence level C (lowest quality of evidence, high risk of bias). The average validity checklist score was 2.7 out of 8 (range 1.5-4.5). None of the studies had a prospective follow up or incorporated any form of blinding. Whilst the one case control study (Dick, 1999) achieved a validity checklist score of 7 out of 9, it should be noted that this study was also of evidence level C.

Table 10.1 shows the effect of water fluoridation on all potential adverse outcomes (other than fluorosis, bone fracture and cancer) reported in the studies included. A point estimate for this association, the measure used and a measure of the significance of the association is presented. Where studies reported an adjusted measure, this is presented. For studies that did not present an adjusted relative risk but did provide details on the number of people studied and population at risk, an unadjusted relative risk was calculated from these data.

For studies that present a difference measure (e.g. mean difference) a negative result suggests a benefit of fluoridation, and a positive result suggests harm from fluoridation (i.e. greater cancer incidence in the fluoride group compared with the control group). For ratio measurements a ratio less than 1 suggests a benefit of fluoridation and a ratio greater than one suggests harm. If the confidence interval for this measure includes 1 or if the p-value is less than 0.05 then this suggests a statistically significant difference.

Only three studies showed a statistically significant effect at the 5% level. Forbes (1997), found a statistically significant negative effect of water fluoride on Alzheimer's disease (increased incidence) and a statistically significant positive effect on impaired mental functioning (decreased incidence). Erickson (1976) found a statistically significant positive association with congenital malformations in one of two sets of data but not in the other. Lin (1991) found statistically significant negative association of combined low-iodine/high fluoride with goitre and mental retardation. Age at menarche, anaemia during pregnancy and sudden infant death syndrome (SIDS) did not show statistically significant associations with water fluoride exposure. The direction of association of primary degenerative dementia (Still 1980) and cognitive impairment (Jacqmin-Gadda 1994) with water fluoridation was positive (fewer cases) but no measure of the statistical significance of this effect was provided. Skeletal fluorosis and IQ both found the direction of association with water fluoride to be negative, but again no measure of the statistical significance of this association was presented.

Five studies examined the association between all cause mortality and water fluoride exposure. Three studies found the direction of association of water fluoridation and mortality to be negative (more deaths), one found the direction of association to be positive (fewer deaths) and one found no association. Once again, no measures of the statistical significance of these associations were provided. However, for two of the studies that found a negative direction of association, the point estimate was 1.01, which is unlikely to have reflected a statistically significant effect. Three studies examined the association between infant mortality and water fluoride level. All three studies found a negative direction of association, but again no measure of the statistical significance of this association was presented and so it is difficult to draw conclusions from these results.

Table 10.1 Association of various adverse effects with water fluoride level

Author (Year)	Outcome	Age	Sex	Summary measure	Results (95% CI)	Validity score
Forbes (1997)	Alzheimer's disease	76	Both	Adjusted odds ratio	1.22 (1.0-1.5)	4.0
	Impaired mental functioning				0.49 (0.3-0.9)	
Still (1980)	Primary degenerative dementia	55+	Both	Crude RR	0.18	3.0
Jacqmin-Gadda (1994)	Cognitive impairment	>= 65	Both	Crude RR	0.93	4.5
Griffith (1963)	Anaemia during pregnancy	Not stated	Women	Rate difference	2.03 (-5.0-9.0)	2.3
Farkas (1983)	Age at menarche	7-18	Girls	Mean difference	0	1.5
Erickson (1976)	Congenital malformations		Both	Crude RR	1.08 (p>0.05) 0.95 (p<0.05)	3.5
	Down's syndrome				1.16 (p>0.05) 0.96 (p>0.05)	
Erickson (1980)	Congenital malformations		Both	Crude RR	1.00 (0.9-1.1)	3.5
	Down's syndrome				0.93 (0.7, 1.2)	
Berry (1958)	Down's syndrome		Both	Crude RR	0.84-1.48	1.8
Needleman (1974)	Down's syndrome		Both	Crude RR	1.14	2.0
Rapaport (1957)**	Down's syndrome		Both	Crude RR	1.5	2.0
					2.3	
					2.2	
					2.2	
Rapaport (1963)	Down's syndrome		Both	Crude RR	3.0	2.0
	Infant mortality				1.3	
Dick (1999)	Sudden Infant Death Syndrome	Not stated	Both	Odds ratio	1.19 (0.8, 1.7)	7 (of 9)
Overton (1954)	Infant mortality		Both	Difference in RR	0.06	2.8
Erickson (1978)	Mortality	All	Both	Adjusted rate-ratio	1.01	3.8
Hagan (1954)	Mortality	Not stated	Both	Adjusted rate-ratio	1.01	3.5
Rogot (1978)	Mortality	Not stated	Both	Difference in RR	0	4.1
Schatz (1976)*	Mortality	Not stated	Both	Difference in RR	-0.1	2.8
	Infant mortality	Not stated	Both	Difference in RR	0.5	
Weaver (1944)	Mortality	Not stated	Both	Difference in RR	0	1.8
Zhao (1996)	IQ	7-14	Both	Mean difference	-7.7	2.5
Lin (1991)	IQ	7-14	Not stated	Mean difference	-6	1.5
	Mental retardation	7-14	Not stated	Crude RR	1.6 (1.15, 2.34)	
Jolly (1971)	Skeletal fluorosis	Not stated	Both	Increased prevalence of skeletal fluorosis at higher fluoride concentrations		2.7
Gedalia (1963)	Goitre	7-18	Female	Crude RR	0.16-1.80	2.5
Jooste (1999)	Goitre	6,12 & 15	Both	Crude RR	0.3-1.2	1.8
Lin (1991)	Goitre	7-14	Not stated	Crude RR	1.11 (1.04, 1.20)	1.5

* Briner (1966) reported data from the same areas and some of the same years but is not presented here because Schatz reported more years and included infant mortality.
** Multiple areas studied, for details on see Appendix C

Six studies looked at the association between Down's syndrome and water fluoride level. Three studies found a negative direction of association (Needleman 1974, Rapaport 1957, Rapaport 1963), one found a positive direction of association, one found no association (Berry 1958) and the other found a positive direction of association for one set of data and a negative direction of association for the other. None of the three studies that found a negative direction of association presented any measure of statistical significance. The one study that found a positive direction of association

(Erickson 1980) did present variance data and failed to find a statistically significant association. The study that found a positive direction of association in one set of data and a negative direction of association in the other did not find a statistically significant association in either direction (Erickson 1976).

10.1 Possible confounding factors

All the studies looking at other possible negative effects used study designs that measured population rather than individual exposures to fluoridated water, and because of this they are susceptible to confounding by exposure. If the populations being studied differed in respect to other factors that are associated with the outcome under investigation, then the outcome may differ between these populations leading to an apparent association with water fluoride level. Which factors may act as confounding factors depends on the outcome under investigation and will thus differ for all the different outcomes discussed above. Nineteen analyses looking at other possible negative effects discussed potential confounding factors (Table 10.2). Twelve of these analyses did not control for any of these confounding factors in the results presented.

Table 10.2 Other possible negative effects associated with water fluoride and the confounding factors controlled for in the analysis.

Author (Year)	Outcome	Confounding factors discussed in study	Controlled for
Forbes (1997)	Alzheimer's disease	Water quality variables	Yes
	Impaired mental functioning		
Still (1980)	Primary degenerative dementia	Chloride, magnesium and calcium content of water	No
Griffith (1963)	Anaemia during Pregnancy	Parity and stage of pregnancy	No
Dick (1999)	Sudden Infant Death Syndrome	Age, region, sex, time, season, gestation, ethnicity, etc	Yes
Erickson (1976)	Down's syndrome	Maternal age, white births only	Yes
Erickson (1980)	Congenital malformations	Maternal age, white births only	No
	Down's syndrome		
Needleman (1974)	Down's syndrome	Maternal age	No
Rapaport (1957)	Down's syndrome	Maternal age	No
Rapaport (1963)	Down's syndrome	Maternal age effect of other minerals in water, iron, magnesium, manganese calcium	No
	Infant mortality		
Overton (1954)	Infant mortality	Ethnicity, social and economic conditions	No
Erickson (1978)	Mortality	Age, sex and ethnicity	Yes
Hagan (1954)	Mortality	Age, sex and ethnicity	Yes
Rogot (1978)	Mortality	Age, sex and ethnicity	Yes
Schatz (1976)	Mortality	Soil and climate	No
	Infant mortality		
Weaver (1944)	Mortality	Age, sex and area compatibility	No
Zhao (1996)	IQ	Educational level of parents	No
Jolly (1971)	Skeletal fluorosis	Sex	Yes
Jooste (1999)	Goitre	Use of iodised salt, height, weight, urinary, water, & salt levels	No
Gedalia (1963)	Goitre	Iodine water level	No

For Down's syndrome, maternal age is of particular importance as a possible confounding factor because the incidence of Down's syndrome is associated with maternal age. This means that if the average maternal age of the fluoridated population is higher than that of the non fluoridated population, an association with water fluoridation would most likely be found. All but one of the six Down's syndrome studies considered the effects of maternal age, however only two of these studies attempted to control for this possible confounding factor. The two studies by Erickson (1976, 1980) included white births only and presented results separately for five-year maternal age groups and one of these studies (1976) presented age-adjusted rates. Both of these studies found a non-significant association of water fluoride level with Down's syndrome at the 5% significance level.

Rapaport (1957) did not control for the effects of confounding factors but did look at the difference in maternal age between the two study areas. He found that maternal age was higher in the low fluoride areas than the high fluoride areas, this would be expected to lead to a higher rate of Down's syndrome in these areas when in fact the reverse was found. Rapaport (1963) also considered maternal age and found that the number of Down's syndrome births to mothers over the age of 40 was greater in the fluoride areas than the low-fluoride areas, however no measures of the significance of this association was presented. Needleman (1974) compared the mean age of mothers in the two study areas and found that maternal age was 34.0 in the high fluoride group and 33.2 in the low fluoride group. The author suggested this was enough to account for the observed differences in the incidence of Down's syndrome found in this study.

Three of the five studies looking at the association between mortality and water fluoridation used standardisation to control for the influence of age, sex and ethnicity (Erickson 1978, Hagan 1954, Rogot 1978). Two of these studies found a negative direction of association; no association was found in the other. None of these studies presented variance data.

Table 10.3 Studies that met inclusion criteria but were not included in the main analysis

Author (Year)	Outcome	Reason	Authors Conclusions
Gupta (1995)	Congenital malformation	No adequate control area - the control area contains <1.5ppm which would be considered a high fluoride area in most studies	There was an increased incidence of spina bifida occulta in children expose to high fluoride (4.5 or 8.5ppm) compared to those expose to low fluoride (<1.5ppm)
Karthikeyan (1996)	Skeletal fluorosis	Areas selected because they were known to have a high incidence of fluorosis and then water fluoride level investigated. Reasons other than the fluoride content of the water are also investigated for the incidence of fluorosis	Skeletal fluorosis was only present in one of the fluorosis regions, the area which had the highest water fluoride content (3.8-8.0)
Latham (1967)	Nail mottling and prevalence of goitre	The results are not broken down as much as the water fluoride levels, giving very wide ranges of fluoride levels in some of the areas for which results are presented. All the areas are fluoridated at above 1ppm and some with fluoride levels as high as 45.5ppm.	Author does not specifically relate results to water fluoride content of the area - he comments generally on the results seen in the whole sample studies, as all areas are exposed to comparatively high levels of fluoride. The percentage of people with mottled nails was high in all areas (>26%) as the prevalence of goitre (12-41%). As these results are not specifically related to the water fluoride level and there was no control area it is difficult to link these findings to the water fluoride levels.
Freni (1994)	Birth rates	The way fluoride exposure is classified` is unclear and misleading; the mean fluoride level in the control areas is sometimes higher than the mean fluoride level in the exposed areas.	A negative association was found between high fluoride levels in drinking water and lower birth rates.
Heasman (1962)	Mortality	The range of water fluoride levels in some of the areas classified as exposed overlaps with the fluoride range in the areas classified as control areas.	The results indicate that the overall mortality was the same in the fluoride and control areas, specific causes of death differences reaching significance at the 5% level. These were conflicting and it was considered very unlikely that fluoride was the cause.
Morgan (1998)	Dental fluorosis and childhood behaviour problems	Children classified according to Dean's classification for fluorosis and then fluoride exposure examined. Childhood behaviour problems classified according to dental fluorosis levels not water fluoride levels	the use of supplemental fluoride prior to age 3 was found to be a risk factor for dental fluorosis. No significant association was found between fluoride history variables in aggregate (including water fluoride level) and dental fluorosis. Dental fluorosis was not significantly associated with behaviour problems in the children studied
Packington (2000)	Fetal, perinatal and infant mortality, congenital malformations and Down's syndrome	Years of data used not the same. No description of methods, unclear exactly how data presented were calculated. Graphs unclear	Fetal, perinatal and infant mortality, congenital malformations and Down's syndrome are higher in fluoridated areas of England than in non-fluoridated areas.
Mitchell (1991)	Sudden Infant Death Syndrome	Data presented graphically. No figures presented in the text. Data could not be read accurately from the graph.	There is no indication of a relationship between fluoridation of the water supply and SIDS in New Zealand.

10.2 Studies that met inclusion criteria but were not included in the main analysis

The eight studies in Table 10.3 were not included in the main analysis of other possible negative effects of water fluoridation for the reasons listed. In three of these studies (Gupta 1995; Freni 1994; Heasman 1962) the control areas included areas that would be considered fluoridated, making interpretation of the results impossible. Data from the other studies were not extracted because of the way the data were presented. Four of these studies conclude that they found a negative relationship with the outcome studied and water fluoridation, two found no association and two did not present clear conclusions.

10.3 Discussion

Interpreting the results of the other possible negative effects is very difficult because of the small number of studies that met inclusion criteria on each specific outcome, the study designs used and the low study quality.

The quality of the research on these topics was generally low, evidence level C (mean of 2.7 out of 8 on validity assessment). Given that all the studies are from lowest the level of evidence with the highest risk of bias, the conclusions should be treated with caution.

A major weakness of these studies generally was the lack of control for any possible confounding factors, many of which were highlighted by the study authors. If the populations being studied differed in respect to other factors that are associated with the outcome under investigation then the outcome may differ between these populations leading to an apparent association with water fluoride level. What is clear is that any further research in these areas needs to be of a much higher quality and should address and use appropriate methods to control for confounding factors.

Overall, the studies examining other possible negative effects provide insufficient evidence on any particular outcome to reach conclusions.

11. OBJECTIVE 5

Are there differences in the effects of natural and artificial water fluoridation?

In order to investigate whether there are differences in the effects of artificially and naturally fluoridated water on positive (caries) and negative (e.g. cancer) outcomes, each of these outcomes will be considered separately. Unfortunately studies of artificially fluoridated areas rarely report what form of fluoride had been used (e.g. sodium fluoride or silicated fluoride). Consequently, identifying the effects of the various forms of fluoride used in artificial fluoridation schemes separately was not possible.

11.1 Caries studies

Only one study compared a naturally fluoridated area, an artificially fluoridated area and a control area using a before and after study design. This was the Brantford-Sarnia-Stratford study (Brown, 1965) in which Brantford was artificially fluoridated, Stratford was naturally fluoridated and Sarnia was the control area. The proportion of caries-free children and the DMFT was measured at baseline (3 years after fluoridation was introduced in Brantford) and then again seven years later, in children aged 9-11 and 12-14 years. Table 11.1 shows the results of this study.

Table 11.1 Caries experience in naturally, artificially and non-fluoridated areas.

Age	Outcome	Brantford (artificial F)		Stratford (natural F)		Sarnia (control)	
		Baseline	Final	Baseline	Final	Baseline	Final
9-11	% caries-free	5.7	43.8	52.1	49.9	6.1	8.1
12-14	% caries-free	1.2	18.7	27.2	28.1	0.6	2.3
9-11	DMFT	4.1	1.5	1.1	1.2	4.2	3.7
12-14	DMFT	7.7	3.2	2.6	2.3	7.9	7.5

At the baseline survey, caries experience, as measured by the proportion of caries-free children and the DMFT score in both age groups, was relatively high in the control area and the area that had recently started to receive fluoridated water. In the survey conducted seven years later, caries experience remained high in the control area and low in the naturally fluoridated area. In the artificially fluoridated area, decay had declined to levels approaching those seen in the naturally fluoridated area. This suggests that naturally and artificially fluoridated water have similar effects on dental decay.

11.2 Possible negative effect studies

11.2.1 Dental fluorosis

A total of 88 studies investigating the association of dental fluorosis and water fluoridation were identified. Of these, 14 did not state whether the water was artificially or naturally fluoridated, 20 compared an area artificially fluoridated (0.6-1.2ppm) with areas of low (<0.3ppm) or very high (4-7ppm) natural fluoride content. The remaining studies only considered naturally fluoridated areas. There were no studies in which an area with water naturally fluoridated to around 1ppm was compared with an area artificially fluoridated to this level. It was therefore not possible to make a direct comparison of the difference in the effect of the naturally fluoridated water compared with artificially fluoridated water.

A term for type of fluoridation (artificial or natural) was included in the regression analysis. This variable did not show an association with fluorosis incidence, suggesting that there is no difference in the effects of artificially and naturally fluoridated water on the incidence of dental fluorosis.

11.2.2 Bone fracture and bone development problems

A total of 29 studies were identified which looked at fracture incidence. Nine compared areas naturally fluoridated at 1ppm with areas of a low natural fluoride level. Eight studies compared areas with different levels of naturally occurring fluoride in the water. Five studies compared areas with mixed (artificial and natural) water fluoride exposure (for example, considering the number of years or proportion of the population exposed to fluoridated water). Seven studies did not state whether the water was artificially or naturally fluoridated. There were no studies in which an area with water naturally fluoridated to around 1ppm was compared with an area artificially fluoridated to this level. It was therefore not possible to make a direct comparison of the effects of naturally fluoridated compared with artificially fluoridated water.

11.2.3 Cancer studies

A total of 26 studies looking at the association of cancer incidence with water fluoridation were found. Twelve studies compared areas with artificially fluoridated water with areas with a low natural fluoride content. Three compared areas with different natural water fluoride levels; one compared areas with mixed (both artificially and naturally fluoridated) water fluoridation; and eight studies did not state whether the water was artificially or naturally fluoridated. There were no studies in which an area with natural fluoride levels around 1ppm was compared with an area artificially fluoridated at this level. It was therefore not possible to make a direct comparison of the difference in effects of naturally fluoridated compared with artificially fluoridated water.

Table 11.2 shows the direction of the association of the water fluoride level with osteosarcoma or bone, joint and overall cancer incidence and mortality for each of these studies, and whether the study compares areas with artificial, natural or mixed water supplies.

There were only two studies that considered areas containing only naturally fluoridated water and so it is difficult to draw conclusions from these results. However, the data suggest that there is no statistically significant association between water fluoridation and cancer incidence, irrespective of whether the fluoridated area is artificially or naturally fluoridated.

Table 11.2 Association of cancer incidence and mortality with water fluoride level by method of fluoridation (artificial, natural, not stated)

Artificially or Naturally fluoridated	Author (Year)	Cancer	Statistically significant association
Artificial	Chilvers (1983)	All cause	No
Artificial	Cook-Mozaffari (1981)	All cause	Not stated
Artificial	Smith (1980)	All cause	Yes (positive effect)
Artificial	Goodall (1980)	All cause	Not stated
Artificial	Richards (1979)	All cause	No
Artificial	Schlesinger (1956)	All cause	Not stated
Artificial	Raman (1977)	All cause	Not stated
Artificial	Mahoney (1991)	Bone	Not stated
Artificial	Hoover (1991)	Bone and joint	No
		Osteosarcoma	No
Artificial	Hrudey (1990)	Osteosarcoma	No
Artificial	Mahoney (1991)	Osteosarcoma	No
Natural	Chilvers (1985)	All cause	No
Natural	Hoover (1976)	All cause	No
		Bone	No
Other	Lynch(1985)	All cause	Yes (negative effect) in 2 of 6 analyses
Other	Kinlen (1975)	Bone	No
Other	Gelberg (1995)	Osteosarcoma	No
Other	McGuire (1991)	Osteosarcoma	No
Other	Moss (1995)	Osteosarcoma	No

11.2.4 Other possible negative effects studies

A total of 31 studies were included in the main analysis assessing the association of other possible adverse effects of water fluoride concentration. Of these, five studies compared areas artificially fluoridated to the 1ppm level with areas with a low natural fluoride level, 11 studies compared areas with different levels of naturally occurring water fluoride levels, and 13 studies did not state whether the areas were artificially or naturally fluoridated. There were two studies in which an area with water naturally fluoridated at around 1ppm was compared with an area artificially fluoridated to this level (Schatz 1976, Rogot 1978). Both studies looked at mortality using a before-after study design, with the baseline survey carried out before water fluoridation was introduced into one of the three study areas. If water fluoride level had a statistically significant effect on mortality, then at the baseline examination mortality would be expected to be higher in the naturally fluoridated area than in the two other, low fluoride study areas. At the final survey, after fluoridation had been artificially introduced into one of these areas, the mortality rate in the artificially fluoridated area would be expected to show an increase in mortality rate to a level approaching (or surpassing) that seen in the naturally fluoridated area. Neither of these studies showed such an association, and neither study showed a statistically significant difference in mortality rates between the study areas. These data have thus not found any association.

A wide range of outcomes was considered with many outcomes only discussed in one or two studies. There is thus insufficient evidence for any of these outcomes to compare the effects of artificially and naturally fluoridated water.

11.3 Discussion

The assessment of natural versus artificial water fluoridation effects is greatly limited due to the lack of studies making this comparison. Very few studies included both areas with low natural fluoride and areas with high natural or artificial fluoride in their studies. In addressing the question of Objective Five for caries studies there was only one study that could be included. The validity assessment (4.5) of this evidence level B study was slightly below the average (5.0) for the caries studies overall. This study was done in Canada and did not control for potential confounding factors in the analysis. The confidence with which the question can be answered by a single study of moderate validity is low.

The ability to address the question of Objective Five with respect to the effect of natural versus artificial fluoridation on negative effects is also low, as there were no direct comparisons of artificial versus natural water fluoride presented.

As the measure of effect estimates reported in all of the bone fracture studies were similar, no difference in the effect based on artificial or natural fluoridation was expected.

There were not enough studies on cancer incidence and mortality reporting the use of only a natural source of fluoride to adequately compare to those reporting only artificial sources (Table 11.2). There were also no studies using mixed (artificial/natural) water supplies that stratified on this basis. From the data presented, no differences are apparent.

For other potential adverse effects, it was not possible to determine the effects of natural versus artificial sources of water fluoridation. In addition to the overall low quality of studies, there were not enough studies on any particular outcome with subjects exposed to different sources of water fluoride to make adequate comparisons.

12. CONCLUSIONS

The conclusions of this systematic review of water fluoridation are as follows:

12.1 Objective 1: What are the effects of fluoridation of drinking water supplies on the incidence of caries?

The best available evidence (level B) from studies on the initiation and discontinuation of water fluoridation suggests that fluoridation does reduce caries prevalence, both as measured by the proportion of children who are caries-free and by the mean dmft/DMFT score. The degree to which caries is reduced, however, is not clear from the data available. The range of the mean difference in the proportion (%) of caries-free children is -5.0 to 64%, with a median of 14.6% (interquartile range 5.05, 22.1%). The range of mean change in dmft/DMFT score was from 0.5 to 4.4, median 2.25 teeth (interquartile range 1.28, 3.63 teeth). It is estimtaed that a median of six people need to receive fluoridated water for one extra person to be caries-free (interquartile range of study NNTs 4, 9). The best available evidence on stopping water fluoridation indicates that when fluoridation is discontinued caries prevalence appears to increase in the area that had been fluoridated compared with the control area. Interpreting from this data the degree to which water fluoridation works to reduce caries is more difficult. The studies included for Objective 1 were of moderate quality (level B), and limited quantity.

12.2 Objective 2: If fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

An effect of water fluoridation was still evident in studies completed after 1974 in spite of the assumed exposure to fluoride from other sources by the populations studied. The meta-regression conducted for Objective 1 confirmed this finding. The studies included for Objective 2 were also of moderate quality (level B), but of limited quantity.

12.3 Objective 3: Does fluoridation result in a reduction of caries across social groups and between geographical locations?

The available evidence on social class effects of water fluoridation in reducing caries appears to suggest a benefit in reducing the differences in severity of tooth decay (as measured by dmft/DMFT) between classes among five and 12 year-old children. No effect on the overall measure of proportion of caries-free children was detected. However, the quality of the evidence is low (level C), and based on a small number of studies. The association between water fluoridation, caries and social class needs further clarification.

12.4 Objective 4: Does fluoridation have negative effects?

The possible negative effects of water fluoridation were examined as broadly as possible. The effects on dental fluorosis are the clearest. There is a dose-response relationship between water fluoride level and the prevalence of fluorosis. Fluorosis appears to occur frequently (predicted 48%, 95% CI 40 to 57) at fluoride levels typically used in artificial fluoridation schemes (1 ppm). The proportion of fluorosis that is aesthetically concerning is lower (predicted 12.5%, 95% CI 7.0 to 21.5). Although 88 studies of fluorosis were included, they were of low quality (level C). The best available evidence on the association of water fluoridation and bone fractures (27 of 29 studies evidence level C) show no association. Similarly, the best available evidence on the association of water fluoridation and cancers (21 of 26 studies evidence level C) show no association. The miscellaneous other adverse effects studied did not provide enough good quality evidence on any particular outcome to reach conclusions. The outcomes related to infant mortality, congenital defects and IQ indicate a need for further high quality research, using appropriate analytical methods to control for confounding factors. While fluorosis can occur within a few years of exposure during tooth development, other potential adverse effects may require long-term exposure to occur. It is possible that this long-term exposure has not been captured by these studies.

12.5 Objective 5: Are there differential effects of natural and artificial fluoridation?

The evidence on natural versus artificial fluoride sources was extremely limited, and direct comparisons were not possible for most outcomes. While no major differences were apparent in this review, the evidence is not adequate to reach a conclusion regarding this objective.

12.6 Limitations of this systematic review

In conducting a large systematic review that extends back to the late 1930's, limitations are inevitable. The primary limitation of the review is the quality of the research included.

The first limitations revolve around the search strategies. More non-English language databases (particularly Russian and Chinese) could have been searched. The impact of failing to search such databases is unknown and the logistic and financial impact of trying to do so would be significant. Some reports were difficult to obtain. However, out of over 730 articles, only 14 were not retrieved. Attempts were made to contact authors to assist in locating further reports, but due to the age of the research were not successful. Additional difficulties were encountered in obtaining some theses and dissertations. Given the comprehensive nature of the search, the completeness of retrieval, and the openness of the review process to the public, the review team feels that it is unlikely that a key study of sufficient size and quality to change any of the findings was missed.

Even comprehensive searches such as that used here may result in a biased collection of studies. Since studies showing a statistically significant result are more likely to be published, the set of published studies located may represent a biased sample and over-estimate an effect (positive or negative).

The validity assessment of the included studies (Appendix D) used a checklist scoring system. This approach can be criticised for lack of sensitivity, in that studies are assessed for having done the items on the list, but not necessarily how well they were conducted. For example, a study could receive points for controlling for confounding factors, but the analysis may not have been performed correctly.

The lack of variance data in some studies, particularly for Objectives 1 and 2, limited the amount of data that could be included in the analyses. Insufficient data prevented statistical pooling of data on social class effects, cancer, other adverse effects, and natural versus artificial fluoride effects. Generally, low to moderate study qualities limit the strength of the possible inferences that can be made.

Some of the studies included in the meta-regression analyses contribute more than one observation to the meta-analysis. It has been assumed in the meta-regression analyses that these observations are independent, and hence each estimate has been treated as though it came from a separate study. For example for studies that report results stratified by age but present no summary measure, results for all strata are included separately in the analysis. However, this approach may introduce bias in the results. Any confounding factors not controlled for, or bias in the study design is likely to be similar for all estimates coming from the same study. Including these estimates as separate estimates in the regression analyses could have the effect of compounding these sources of bias. Study level variables, such as study length and validity score, will also be the same for all the estimates that come from a single study. The direction or degree of any effect of this potential bias is unknown.

12.7 Other factors to be considered

The scope of this review is not broad enough to answer independently the question 'should fluoridation be undertaken on a broad scale in the UK'? Important considerations outside the bounds of this review include the cost-effectiveness of a fluoridation program, total fluoride exposure from environmental and non-environmental sources other than water, environmental and ecological effects of artificial fluoridation and the ethical and legal debates. This review did not include animal or laboratory studies because studies on humans were available and would give more reliable estimates of any potential benefits and harms.

12.7.1 Economic analysis

If a benefit of water fluoridation on caries occurrence was demonstrated, the cost-effectiveness of such an intervention relative to other strategies would need to be carefully considered. The search strategies used in this review did not specifically identify research related to the cost-effectiveness of water fluoridation. A search of the NHS Economic Evaluation Database did not identify any recent studies meeting the criteria for a full economic evaluation.

This review is presenting new information on the effectiveness of water fluoridation in preventing caries and the effects on fluorosis, which previous economic analyses would not have had.

12.7.2 Total fluoride exposure

There is some suggestion that total fluoride exposure has increased over recent years, particularly in industrialised nations. Exposure to fluoride from sources other than water may alter the amount required in water for optimum caries reduction and is thus a potential confounding factor in studies of the association between water fluoridation and negative effects. Because sources of fluoride exposure vary, this may be a difficult issue to examine, in that exposure would need to be measured at the person level, rather than at the population level. However, if two study areas are comparable, in all respects, the fluoride exposure from non-water sources (e.g. tea) should also be similar. There are studies that have measured total fluoride exposure in people exposed to fluoridated and non-fluoridated water, but these did not meet inclusion criteria for this review (Guha-Chowdhury, 1996, Mansfield, 1999). Because of potential toxicity of very high doses of fluoride, it would seem sensible that any future studies should attempt to measure total fluoride exposure in areas being researched.

12.8 Information to guide practice

The available evidence shows that water fluoridation reduces the prevalence of caries. The median difference between fluoridated and non-fluoridated areas in the proportion of children who are caries-free is 14.6%, while the reduction in the number of teeth affected (dmft/DMFT score) is 2.3. The available evidence shows that fluorosis occurs in approximately 48% of the population at water fluoridation levels of 1.0ppm. The proportion who have teeth that are affected enough to cause aesthetic concern is approximately 12.5%. The quality of these data on benefit and harm is in general only low to moderate, and should be interpreted with caution, especially considering the significant heterogeneity between studies. The benefit and harm data need to be considered in conjunction when making decisions about water fluoridation.

12.9 Implications for research

Although there has been considerable research in this area, the quality is generally low. The research needs that have been identified through this systematic review are described below.

12.9.1 Caries studies

The two most important factors missing from the current set of studies are adjusting for confounding factors using standard analytic techniques, and reporting variance data. In addition to the potential confounding factors noted in section 4.2.2, frequency of sugar consumption, measurement of total exposure to all sources of fluoride, the number of erupted teeth per child, and the level of spending on dental health in intervention and control areas should be included. Blinding of observers should be attempted and at least standardisation of the assessment would be essential to reduce the potential impact of observer bias. Studies should also consider changes in social class structure over time. Only one included study addressed the positive effects of fluoridation in the adult population. Assessment of the long-term benefits of water fluoridation is needed.

It would be logical to include an assessment of adverse effects alongside any future study of caries. While fluorosis may be evident in young populations within a few years of starting fluoridation, other potential adverse effects may take longer to occur, or may occur largely in an adult population.

Most of the evidence on social class effects of fluoridation was from cross-sectional studies of low quality. If further studies are considered, social class effects could be incorporated into a study of fluoridation efficacy. More research into the most appropriate tool to measure social class in relation to dental health is also needed.

12.9.2 Adverse effects studies

The results of this review suggest that a dose-response relationship exists between water fluoride level and the prevalence of fluorosis. Future studies should address the impact of using lower levels of water fluoride content, such as 0.8ppm in a formal way in conjunction with an efficacy study. The potential confounding factors and causes of between study heterogeneity identified in this review should be controlled for in the analysis.

With bone fracture and cancer studies, the evidence is very balanced around the 'no effect' mark. If any further research is considered, controlling for confounding factors and ensuring adequate blinding should be a priority.

The other possible adverse effect studies suffered greatly by not sufficiently controlling for important confounding factors, many of which were discussed by authors in the study reports, but not controlled for. Very few of the possible adverse effects studied appeared to show a possible effect. High quality research that takes confounding factors into account is needed.

12.9.3 Economic evaluations

When evaluating the cost-effectiveness of an intervention such as water fluoridation, there are key factors to be considered. The costs of the intervention are weighed against the benefits. A full economic evaluation of water fluoridation should include a complete accounting of the potential costs of the intervention (cost of fluoridating, administration costs, and quality assurance costs) and the benefits. Examples of the benefits that should be included are the reduction in caries that is assumed, any changes in the number of dental visits, procedures, and long-term effects such as changes in the need for dentures. The quality of life (QOL) of those who receive the intervention should be measured, in comparison to those not receiving the intervention (such as the effect of not losing teeth to caries, the effect of having fluorosed teeth, anxiety associated with dental visits, and dental pain). Indirect costs of travel time and time off work for parents to take children to the dentists could also be included. Such an economic evaluation could be done along side an intervention study measuring actual resource use and costs, or as a modelling exercise using the most accurate efficacy data (e.g. from this systematic review). Differences in dental resource use among social classes should also be investigated.

13. BIBLIOGRAPHY

Dental effects of water fluoridation. Seventh report on the Brantford fluoridation caries study. *Med Serv J Canada* 1960;16:590-607.

The conduct of the fluoridation studies in the UK and the results achieved after five years. Report to the Ministry of Health 1965.

Adair SM, Hanes CM, Russell CM, Whitford GM. Dental caries and fluorosis among children in a rural Georgia area. *Pediatr Dent* 1999;21(2):81-5.

Adriasola G. First evaluation of the program of fluoridation of drinking water in Curico-San Fernando, Chile, 1956. *Bol Ofic Sanit Panamer* 1959;47:412-20.

Al-Alousi W, Jackson D, Crompton G, Jenkins O. Enamel mottling in a fluoridated and a non fluoridated community. *Br Dent J* 1975;138:9-15.

Alvarez-Ubilla A. primera evluacion del programa de fluoacion del agua potable Curico-San Fernando. *Odontologica Chilena* 1959;41:1277-1283.

Angelillo IF, Torre I, Nobile CG, Villari P. Caries and fluorosis prevalence in communities with different concentrations of fluoride in the water. *Caries Res*1999;33(2):114-122.

Arnala I, Alhava E, Kivivouri R. Hip fracture incidence not affected by fluoridation, Ostreofluorosis studied in Finland. *Acta Orthop Scand* 1986;57:344-8.

Arnold F, Dean HT, Knutson J. Effect of fluoridated water supplies on caries prevalence. *Pub Health Rep* 1953;68:141-148.

Arnold FJ, Dean HT, Jay P, Knutson J. Effect of fluoridated public water supply on dental caries prevalence. *Pub Health Rep* 1956;71:652-658.

Arnold F. Grand Rapids fluoridation study; results pertaining to the eleventh year of fluoridation. *Am J Pub Health* 1957;47(5):539-545.

Ast D, Finn S, McGaffrey I. Newburgh-Kingston caries fluoride study: dental findings after three years of water fluoridation. *Am. J. Public Health* 1950;40(June):716-724.

Ast D, Finn S, Chase H. Newburgh-Kingston caries fluorine study; further analysis of dental findings including permanent and diciduous dentitions after 4 years of water fluoridation. *J Am Dent A*. 1951;42:188-195.

Ast D, Chase H. Newburgh-Kingston caries fluoride study; dental findings after six years of water fluoridation. *Oral Surg* 1953;6:114-123.

Ast D, Buschel A, Wachs B, Chase H. Newburgh Kinston caries fluorine study; combined clinical and roentgen dental findings after 8 years of water fluoridation. *J Am Dent Assoc.*1955;50(June):680-685.

Attwood D, Blinkhorn AS. Trends in dental health of ten-year-old schoolchildren in South-West Scotland UK after cessation of water fluoridation. *Lancet* 1988;2(8605):266-267.

Avorn J, Niessen L. Relationship between long bone fractures and water fluoridation. *Gerodontics* 1986;2:175-9.

Azcurra AI, Battellino LJ, Calamari SE, de Cattoni ST, Kremer M, Lamberghini FC. [Dental health status of students living in places supplied with drinking water of very high and very low levels of fluorides]. *Rev Saude Publica* 1995;29(5):364-75.

Backer-Dirks O, Houwink B, Kwant GW. The results of 6 1/2 years of artificial fluoridation of drinking water in the Netherlands. The Tiel-Culemborg experiment. *Arch Oral Biol* 1961;5:284-300.

Backer-Dirks O. The relation between the fluoridation of water and dental caries experience. *Int Dent J* 1967;17/3:582-605.

Beal J, James P. Dental caries prevalence in 5 year old children following five and a half years of water fluoridation in Birmingham-288. *Brit Dent J* 1971;130(7):284.

Beal JF, Clayton M. Fluoridation a clinical survey in Corby and Scunthorpe England UK. *Public Health* 1981;95(3):152-160.

Bernstein D, Sadowsky N, Hegsted D. Prevalence of osteoporosis in high- and low-fluoride areas of North Dakota. *JAMA* 1966;198:499-504.

Berry W. A study of the incidence of mongolism in relation to the fluoride content of water. *Am J of Ment Defic* 1958;62(4):634-636.

Bhagan VU, Rajam R, Renganathan PS. Endemic fluorosis in Azhagappapuram village of Kanyakumari District of Tamil Nadu, India. *Asian Journal of Chemistry* 1996;8(3):536-538.

Blayney J, Tucker W. Evanston dental caries study; purpose and mechanism of study. *J Dent Research* 1948;27:279-286.

Blayney JR. A report on thirteen years of water fluoridation in Evanston, Ill *J Am Dent Assoc* 1960;61:76-9.

Blayney J, Hill I. Fluorine and dental caries. *J Am Dent Assoc*.1967;74:233-302.

Blayney JR, Hill IN. Evanston dental caries study. XXIV. Prenatal fluorides--value of waterborne fluorides during pregnancy. *J Am Dent Assoc* 1964;69:291-4.

Booth I, Mitropoulos C, Worthington H. A comparison between the dental health of 3-year old children living in fluoridated Huddersfield and non-fluoridated Dewsbury in 1989. *Comm Dent Health* 1991;9:151-157.

Bowling A. *Research methods in health: Investigating health and health services*. Buckingham: Open University Press; 1997.

Bradnock G, Marchment M, Anderson R. Social background fluoridation and caries experience in 5 year old population. *Br Dent J* 1984;156:127-131.

Bransby E, Forrest J. The dental condition of children in seven areas in England and Wales as shown by the base-line dental examinations made in connection with the fuoridation demonstration studies. *Mon Bull Min Health, Great Britain* 1958;17:26-34.

Bransby ER, Forrest JR, Mansbridge JN. Dental effects of fluoridation of water with particular reference to a study in the United Kingdom. *Proc Nutr Soc* 1963;22:84-91.

Briner A, Carmona I. Fluoracion y mortalidad en Chile. *Odontolgia Chilena* 1966;83:7-21.

Brothwell DJ, Limeback H. Fluorosis risk in grade 2 students residing in a rural area with widely varying natural fluoride. *Community Dent Oral Epidemiol* 1999;27(2):130-136.

Brown H, McLaren H, Stewart B. Brantford fluoridation study - 1954 report. *J Canad Dent Assoc* 1954(20):585.

Brown HK. The Brantford-Sarnia-Stratford fluoridation caries study--1961 report. *Canad J Public Health* 1962;53:401-8.

Brown H, Poplove M. The Brantford-Sarnia-Stratford Fluoridation Caries Study: Final Survey, 1963. *Can J Pub Health* 1965;56(8):319-324.

Brown HK, Poplove M. The Brantford-Sarnia-Stratford fluoridation caries study: Final survey, 1963. *J Canad Dent Assoc* 1965;31(8):505-511.

Butler WJ, Segreto V, Collins E. Prevalence of dental mottling in school-aged lifetime residents of 16 Texas communities. *Am J Public Health* 1985;75(12):1408-12.

Campbell DA, Radford JM, Burton P. Unemployment rates: an alternative to the Jarman index? [see comments]. *BMJ* 1991;303(6805):750-5.

Carmichael C, French, Rugg-Gunn A, Furness.JA The relationship between social class and caries experience in five year old children in Newcastle and Northumberland after 12 years fluoridation. *Comm Dent Health* 1984;1:47-54.

Carmichael C, Rugg-Gunn A, Ferrell R. The relationship between fluoridation, social class and caries experience in 5 year old children in Newcastle and Northumberland in 1987. *Br Dent J* 1989;167:57-61.

Carmichael C, Rugg-Gunn A, French A, Cranage J. The effect of fluoridation upon the relationship between caries experience and social class in 5-year old children in Newcastle and Northumberland levels. *Br Dent J* 1980;150:9-12.

Cauley J, Murphy P, Riley T, Black D. Public health bonus of water fluoridation: Does fluoridation prevent ostoporosis and its related fractures? *Am J Epidemiol* 1991;134:768.

Cauley J, Murphy P, Riley T, Buhari A. Effects of fluoridated drinking water on bone mass and fractures: the study of osteoporotic fractures. *J Bone Min Res* 1995;10(7):1076-86.

CDC. Water fluoridation and costs of Medicaid treatment for dental decay - Louisiana 1995-1996. *MMWR* 1999;48(34) :753-757.

Chen B. An epidemiological study on dental fluorosis and dental caries prevalence in communities with negligible, optimal and above-optimal fluoride concentrations in drinking water supplies. *Chin Dent J* 1989;8:117-27.

Chen W, Xu R, Chen G, Zao J, Chen J, Institution: health and Epidemic Prevention Station of Guangdong Province G. Changes in the prevalence of endemic fluorosis after changing water sources in two villages in Guangdong, China. *Bulletin of Environmental Contamination and Toxicology* 1993;51(4):479-482.

Chilvers C. Cancer mortality by site and fluoridated water supplies. *J Epidemiol Community Health* 1982;36:237-42.

Chilvers C. Cancer mortality and fluoridation of water supplies in 35 USA cities. *Int J Epidemiol* 1983;12(4):397-404.

Chilvers C, Conway D. Cancer mortality in England in relation to levels of naturally occurring fluoride in water supplies. *J Epidemiol Comm Health* 1985;39:44-7.

Clark DC, Hann HJ, Williamson MF, Berkowitz J. Aesthetic concerns of children and parents in relation to different classifications of the tooth surface iIndex of fluorosis. *Community Dent Oral Epidemiol* 1993;21(6):360-364.

Clarkson J, O'Mullane D. A modified DDE index for use in epidemiological studies of enamel defects. *J Dent Res* 1989;68(3):445-450.

Clarkson JJ, O'Mullane DM. Prevalence of enamel defects-fluorosis in fluoridated and non-fluoridated areas in Ireland. *Community Dent Oral Epidemiol* 1992;20(4):196-199.

Cohn P. *An epidemiological report on drinking water*. Trenton: New Jersey Department of Health, Environmental Health Service, Trenton; 1992 November 8.

Colquhoun J. Disfiguring dental fluorosis in Aukland, New Zealand. *Fluoride* 1984;17:234-242.

Cook-Mozaffari P, Bulusu L, Doll R. Fluoridation of water supplies and cancer mortality 1: a search for and effect in the UK on risk of death from cancer. *J Epidemiol Comm Health* 1981;35:227-32.

Cooper C, Wickham C, Lacey R, Barker D. Water fluoride concentration and fracture of the proximal femur. *J Epidemiol Comm Health* 1990;44:17-19.

Cooper C, Wickham C, Barker D, Jacobsen S. Water fluoridation and hip fracture. *JAMA* 1991;266:513-514.

Correia Sampaio F, Ramm von der Fehr F, Arneberg P, Petrucci Gigante D, Hatloy A. Dental fluorosis and nutritional status of 6- to 11-year-old children living in rural areas of Paraiba, Brazil. *Caries Res* 1999;33(1):66-73.

Cutress T, Suckling G, Pearce E. Defects in tooth enamel in children in fluoridated and non-fluoridated water areas of the Auckland Region. *NZ Dent J* 1985;81:12-19.

Daniel H. Stapedial otosclerosis and fluorine in the drinking water. *Arch Otolaryngol* 1969;90:69.

Danielson C, Lyon JL, Egger M, Goodenough GK. Hip fractures and fluoridation in Utah's elderly population. *JAMA* 1992;268(6):746-748.

de Crousaz P. Observations on enamel opacities in Switzerland in relation to water or salt fluoridation. *SSO Schweiz Monatsschr Zahnheilkd* 1982;92(4):332-44.

Dean HT. Studies on mass control of dental caries through fluoridation of the public water supply. *Public Health Reports* 1950;65:1403-1408.

DHSS. *The fluoridation studies in the United Kingdom and results achieved after 11 years. A report of the Committee on Research into Fluoridation*. London: Her Majesty's Stationary Office; 1969. Reports on Public Health Medical Subjects No. 122.

Dick A, Ford R, Schluter P, Mitchell E, Taylor B, Williams S, et al. Water fluoridation and sudden infant death syndrome. *N Z Med J* 1999;112(1093):286-9.

Dissanayake C. Geochemical provinces and the incidence of dental disease in Sri Lanka. *Science of the Total Environment* 1979;13(1):47-53.

Doll R, Kinlen L. Fluoridation of water and cancer mortality in the U.S.A. *Lancet* 1977;1:1300-1302.

Downer MC, Blinkhorn AS, Holt RD, Wight C, Attwood D. Dental caries experience and defects of dental enamel among 12-year-old children in north London, Edinburgh, Glasgow and Dublin. *Community Dent Oral Epidemiol* 1994;22(Pt 1):283-5.

Downer M, Blinkhorn A, Attwood D. Effect of fluoridation on the cost of dental treatment among urban Scottish schoolchildren. *Community Dent Oral Epidemiol* 1981;9:112-6.

Driscoll WS, Horowitz HS, Meyers RJ, Heifetz SB, Kingman A, Zimmerman ER. Prevalence of dental caries and dental fluorosis in areas with optimal and above-optimal water fluoride concentrations. *J Am Dent Assoc* 1983;107(1):42-7.

Eklund S, Ismail A, Burt B, Calderon J. High-fluoridated drinking water, fluorosis and dental caries in adults. *J Am Dent Assoc* 1987;114(March):324-328.

Ellwood RP, O'Mullane DM. Dental enamel opacities in three groups with varying levels of fluoride in their drinking water. *Caries Res* 1995;29(2):137-42.

Elwood, JM. *Critical Appraisal of epidemiological studies and clinical trials*. 2nd edition 1998 Oxford, Oxford Univ Press

Ellwood RP, Omullane D. The association between developmental enamel defects and caries in populations with and without fluoride in their drinking water. *J Pub Health Dent* 1996;56(2):76-80.

Erickson JD. Mortality in selected cities with fluoridated and nonfluoridated water supplies. *N Engl J Med* 1978;298:1112-1116.

Erickson JD. Down syndrome, water fluoridation, and maternal age. *Teratology* 1980;21(177-180).

Erickson JD, Oakley GP, Flynt JW, Hay S. Water fluoridation and congenital malformation: No association. *J Am Dent Assoc* 1976;76(981).

Evans DJ, Rugg-Gunn AJ, Tabari ED. The effect of 25 years of water fluoridation in Newcastle assessed in 4 surveys of 5-year-old children over an 18-year period. *Br Dent J* 1995;178(2):60-64.

Evans D, Rugg-Gunn A, Tabari E, Butler T. The effect of fluoridation and social class on caries experience in 5-year-old Newcastle children in 1994 compared with results over the previous 18 years. *Comm Dent Health* 1996;13(Suppl 2):27-37.

Farkas G, Fazekas A, Szekeres E. The fluoride content of drinking water and menarcheal age. *Acta Univ Szeged Acta Biol* 1983;29(1-4):159-168.

Forbes WF. Geochemical risk factors for mental functioning, based on the Ontario Longitudinal Study of Aging (LSA) .6. The effects of iron on the associations of aluminum and fluoride water concentrations and of pH with mental functioning, based on results obtained from the LSA and from death certificates mentioning dementia. Canadian Journal On Aging-Revue *Canadienne Du Vieillissement* 1997;16(1):142-159.

Forrest J. Mottled enamel and caries experience in fluoride and non-fluoride areas. *Proc Roy Soc Med* 1955;48:989.

Forrest J. Caries incidence and enamel defects in areas with different levels of fluoride in drinking water. *Br Dent J* 1956;100:195-200.

Forrest JR, James PM. A blind study of enamel opacities and dental caries prevalence after eight years of fluoridation of water. *Br Dent J* 1965;119(7):319-22.

Forsman B. Early supply of fluoride and enamel fluorosis. *Scand J Dent Res* 1977;85(1):22-30.

French AD, Carmichael CL, Rugg-Gunn AJ, Furness JA. Caries preventive effect of 12 years water fluoridation in Newcastle and Northumberland 5 Year old children. *J Dent Res* 1982;61(4):537.

French AD, Carmichael CL, Rugg-Gunn AJ, Furness JA. Fluoridation and dental caries experience in 5-year-old children in Newcastle and Northumberland in 1981. *Br Dent J* 1984;156(2):54-57.

French. Relationship between social class and dental health in 5-year old children in the North and South of England. *Br Dent J* 1984;156:83-86.

Freni SC, Gaylor DW. International trends in the incidence of bone cancer are not related to drinking water fluoridation. *Cancer* 1992;70(3):611-618.

Freni SC. Exposure to high fluoride concentrations in drinking water is associated with decreased birth rates. *J Toxicol Environ Health* 1994;42(1):109-21.

Gaspar McR, Armbruster LM, Pereira AnC, Moreira BHW. Opacidades de origem n„o-fluorotica e fluorose dent ria em reas com baixa (0, 2ppm F) e otima (0, 7 ppm F) concentra"es de fluor na gua de abastecimento Non-fluorosis and dental fluorosis opacities in aereas with lower (0, 2 ppm F0 and good (0, 7 ppm F) fluoride concentration in drinking water. *Rev Bras Odontol* 1995;52(2):13-8.

Gedalia I, Brand N. The relationship of fluoride and iodine in drinking water in the occurrence of goiter. *Arch Int Pharmacodyn* 1963;142:312-5.

Gelberg K, Fitzgerald E, Hwang S, Dubrow R. Fluoride exposure and childhood osteosarcoma: a case-control study. *Am J Pub Health* 1995;85(1678-1683).

Gessner BD, Beller M, Middaugh JP, Whitford GM. Acute fluoride poisoning from a public water system. *N Engl J Med* 1994;330(2):95-9.

Glattre E, Wiese H. Inverse relationship between fluoride and cancer in mouth and throat? *Acta Odentol Scand* 1979;37:9-14.

Goodall C, Foster F, Fraser J. Fluoridation and cancer mortality in New Zealand. *NZ Med J* 1980;92:164-7.

Gopalakrishnan P, Vasan R, Sarma P, Nair K, Thankappan K. Prevalence of dental fluorsis and associated risk factors in Alappuxha district, Kerala. *Natl Med J India* 1999;12(3):99-103.

Goward PE. Mottling on deciduous incisor teeth. A study of 5-year-old Yorkshire children from districts with and without fluoridation. *Br Dent J* 1982;153(10):367-9.

Gray M, Langford K. Notes on the results of the studies of 5 year old children conducted in the West Midland since 1985. Unpublished report 2000.

Gray M. Report to the District Dental Advisory committee of Dudley: Changes in the level of dental disease in fluoridated and non-fluoridated areas of Dudley. 1999.

Griffith GW. Anaemia in pregnancy in relation to the fluoride content of domestic water supplies. *Mon Bull Min Health* (London) 1963;22:30-8.

Grimaldo M, Borja Aburto VH, Ramirez AL, Ponce M, Rosas M, Diaz Barriga F. Endemic fluorosis in San Luis Potosi, Mexico. I. Identification of risk factors associated with human exposure to fluoride. *Environ Res* 1995;68(1):25-30.

Grobler SR, Vanwyk CW, Kotze D. Relationship between enamel fluoride levels, degree of fluorosis and caries experience in communities with a nearly optimal and a high fluoride level in the drinking-water. *Caries Res* 1986;20(3):284-288.

Groeneveld A. A longitudinal study of the effect of water fluoridation on progression and reversion of caries lesions. 31st Orca (European Organization for Caries Research) Congress, Noordwijkerhout, Netherlands, July 4-7, 1984. *Caries Res* 1985;19(2):159.

Groeneveld A. Longitudinal study of prevalence of enamel lesions in a fluoridated and non-fluoridated area. *Community Dent Oral Epidemiol* 1985;13(3):159-63.

Guha-Chowdhury N, Drummond B, Smillie AC. Total fluoride intake in children aged 3 to 4 years--a longitudinal study. *J Dent Res* 1996;75(7):1451-7.

Guo M, Hsieh C, Hong Y. Effect of water fluoridation on caries prevalence in Chung-Shin Village after 3 years. *The Formosan Science* 1978;32:111-119.

Guo MK, Hsieh CC, Hong YC, Chen RS. Effect of water fluoridation on prevalence of dental caries in Chung-Hsing New Village Taiwan after 9 years. *J Formosan Med Assoc* 1984;83(10):1035-1043.

Gupta SK, Gupta RC, Seth AK, Chaturvedi CS. Increased incidence of spina bifida occulta in fluorosis prone areas. *Acta Paediatrica Japonica* Overseas Edition 1995;37(4):503-506.

Haavikko K, Helle A. The prevalence and distribution of enamel defects in with different fluoride contents in the drinking water. *Proceedings of the Finnish Dental Society* 1974;70(5):178-185.

Hagan T, Pasternack M, Scholz G. Water-borne fluorides and mortality. *Pub Health Rep*. 1954;69:450-454.

Hardwick J, Teasdale J, Bloodworth G. Caries increments over 4 years in children aged 12 at the start of water fluoridation. *Br Dent J* 1982;153:217-222.

Harty F. *Concise illustrated dental dictionary*. Second edition ed. Oxford: Wright; 1994.

Hawley G, Ellwood, RP, Davies, RM. Dental caries. fluorosis and the cosmetic implications of different TF scores in 14-year old adolescents. *Comm Dent Health* 1996;13:189-192.

Heasman M, Martin A. Mortality in areas containing natural fluoride in their water supplies. *Mon Bull Min Health* 1962;21:150.

Heifetz SB, Driscoll WS, Horowitz HS, Kingman A. Prevalence of dental caries and dental fluorosis in areas with optimal and above-optimal water-fluoride concentrations: a 5-year follow-up survey. *J Am Dent Assoc* 1988;116(4):490-5.

Heintze SD, Bastos JR, Bastos R. Urinary fluoride levels and prevalence of dental fluorosis in three Brazilian cities with different fluoride concentrations in the drinking water. *Community Dent Oral Epidemiol* 1998;26(5):316-23.

Heller KE, Eklund SA, Burt BA. Dental caries and dental fluorosis at varying water fluoride concentrations. *J Pub Health Dent* 1997;57(3):136-143.

Hellwig E, Klimek J. Caries prevalence and dental fluorosis in German children in areas with different concentrations of fluoride in drinking water supplies. *Caries Res* 1985;19(3):278-283.

Hill I, Blayney J, Wolf W. Evanston dental caries study VI; a comparison of the pre-fluoride with post-fluoride caries experience of 6, 7 and 8 year old children in the study area. *J Dent Res* 1950;29:549-555.

Hill I, Blayney J, Wolf W. Evanston dental caries study; effect of artificially fluoridated water on dental caries experience of 12, 13 and 14 year old school children. *J.Dent.Res* 1951;30:670-675.

Hill I, Blayney, Wolf N. Evanston dental caries study; caries experience rates of 6, 7 and 8 year old children with progressively increasing periods of exposure to artificially fluoridated water. *J Dent Research* 1952;31:346-353.

Hill I, Blayney J, Wolf W. Evanston dental caries study; caries experience rates of 12, 13 and 14 year old children after exposure to fluoridated water for 59 to 70 months. *J. Dent Res* 1955;34:77-88.

Hill I, Blayney J, Wolf W. Evanston dental caries study, reduction in dental caries attack rates in children 6 to 8 years old. *J Am Dent Assoc* 1956;53:327-333.

Hill IN, Blayney JR, Wolf W. The Evanston dental caries study. XIX. Prevalence of malocclusion of children in a fluoridated and control area. *J Dent Res* 1959;38:782-94.

Hill I, Blayney J, Wolf W. Evanston fluoridation study: twelve years later. *Dental Progress* 1961;1 (2):95-99.

Hill IN, Blayney JR. The Evanston dental caries study. 23. Oral lactobacilli and decayed tooth surface rates among children in a fluoridated area. *J Dent Res* 1965;44:718-33.

Hillier S. Water fluoridation and fracture of the proximal femur. *J Bone and Mineral Res* 1997;12:1533.

Hillier S, Copper C, Kellingray S, Russell G, Hughes H, Coggon D. Fluoride in drinking water and risk of hip fracture in the UK: a case control study. *The Lancet* 2000;335:265-269.

Hobbs D. Annual report of the Director of Dental Public Health to Powys Health Authority. Powys; 1994.

Holdcroft C. Five year old dental health in England, 1993-94. Unpublished report 1999.

Holdcroft C. Dental Health Expenditure in England, 1998 to 1999: Unpublished report; 2000.

Hong CY, Hong YC, Guo MK, Hsieh CC, Chen RS. Prevalence of mottled enamel after 12 years of water fluoridation in Chung-Hsing New Village (Taiwan). *J Formosan Med Assoc* 1990;89(3):225-230.

Hoover RN, McKay FW, Fraumeni JFJ. Fluoridated drinking water and the occurrence of cancer. J *Natl Cancer Inst* 1976;57(4):757-768.

Hoover R, DeVessa S. *Fluoridation of drinking water and subsequent cancer incidence and mortality*: Report to the Director of the National Cancer Institute; 1990 June, 1990.

Hoover R, Devesa S, Cantor K, Fraumeni J. *Review of Fluorides Benefits and Risks*, *Appendix F:* Department of Health and Human Services, USA; 1991 February 1991.

Horne BD, Gren LH, Hegmann KT, et al. The effects of fluoridation on degenerative joint disease and hip fractures. Society for Epidemiological Research , Abstracts of the 33rd Annual Meeting, Seattle Washington. June 15-17. Am J of Epidemiol 2000, 151:S18

Hrudey SE, Soskolne CL, Berkel J, Fincham S. Drinking water fluoridation and osteosarcoma. *Can J Public Health* 1990;81(6):415-416.

Hsieh C, Guo M, Hong Y. Effect of water fluoridation on prevalence of dental caries in Chung-Hsing New Village after 6 years. *J Formosan Med Assoc* 1979;78:168-176.

Hsieh CC, Guo MK, Hong YC, Chen RS. An evaluation of caries prevalence in Chung-Hsing New Village Taiwan after 12 years of water fluoridation a final report. *J Formosan Med Assoc* 1986;85(8):822-831.

Hutton W, Linscott B, Williams D. Final report of local studies on water fluoridation. *Canad. J. Pub. Health* 1956;47:89-92.

Ibrahim Y, Affan A, Bjorvatn K. Prevalence of dental fluorosis in Sudanese children from two villages with 0.25 and 2.56 ppm fluoride in the drinking water. *Int J Paediatr Dent* 1995;5(4):223-9.

Ismail AI, Brodeur JM, Kavanagh M, Boisclair G, Tessier C, Picotte L. Prevalence of dental caries and dental fluorosis in students, 11-17 years of age, in fluoridated and non-fluoridated cities in Quebec (Canada). *Caries Res* 1990;24(4):290-297.

Jablonski S. *Illustrated dictionary of dentistry*. London: W.B. Saunders; 1982.

Jackson D, James PM, Wolfe WB. Fluoridation in Anglesey. A clinical study. *Br Dent J* 1975;138(5):165-71.

Jackson RD, Kelly SA, Katz BP, Hull JR, Stookey GK. Dental fluorosis and caries prevalence in children residing in communities with different levels of fluoride in the water. *J Pub Health Dent* 1995;55(2):79-84.

Jackson RD, Kelly SA, Katz B, Brizendine E, Stookey GK. Dental fluorosis in children residing in communities with different water fluoride levels: 33-month follow-up. *Pediatr Dent* 1999;21(4):248-54.

Jacobsen S, Goldberg J, Miles T, Brody J, Stiers W, Rimm A. Regional variation in the incidence of hip fracture: US white women aged 65 years and olders.*JAMA* 1990;264(4):500-2.

Jacobsen S, Goldberg J, Cooper C, Lockwood S. The association between water fluoridation and hip fracture among white women and men aged 65 years and older; a national ecologic study. *Ann Epidemiol* 1992;2:617-626.

Jacqmin-Gadda H, Commenges D, Leteneur L, Barberger-Gateau P, Dartigues J-F. Components of drinking water and risk of cognitive impairment in the elderly. *Am J Epidemiol* 1994;139:48-57.

Jacqmin-Gadda H. Fluorine concentration in drinking water and fractures in the elderly. *JAMA* 1995;273:775-776.

Jacqmin-Gadda H, Fourrier A, Commenges D, Dartigues J. Risk factors for fractures in the elderly. *Epidemiology* 1998;9(4):417-423.

Jarman B. Identification of underprivileged areas.. *BMJ* 1983;286(6379):1705-1709.

Jolly SS, Prasad S, Sharma R, Rai B. Human Fluoride Intoxication in Punjab. *Flouride* 1971;4(2):64-79.

Jones CM, Worthington H. The relationship between water fluoridation and socioeconomic deprivation on tooth decay in 5-year-old children. *Br Dent J* 1999;186(8):397-400.

Jones C, Taylor G, Woods K, Whittle G, Evans D, Young P. Jarman underprivileged area scores, tooth decay and the effect of water fluoridation. *Comm Dent Health* 1997;14(3):156-60.

Jones C, Worthington H. Water fluoridation, poverty and tooth decay in 12-year-old children. Unpublished, submitted by author 2000.

Jooste P, Weight M, Kriek J, Louw A. Endemic goitre in the absense of iodine deficiency in schoolchildren of the Northern Cape Province of South Africa. *Eur J Clin Nutr* 1999;53(1):8-12.

Kalsbeek H, Kwant GW, Groeneveld A, Dirks OB, Vaneck A, Theuns HM. Caries Experience of 15-Year-Old Children in the Netherlands After Discontinuation of Water Fluoridation. *Caries Res* 1993;27(3):201-205.

Karagas M, Baron J, Barrett J, Jacobsen S. Patterns of fracture among the United States elderly: geographic and fluoride effects. *Ann Epidemiol* 1996;6:209-16.

Karjalainen S, Karja J, Harma R, Juola E. Effect Of Drinking Water Fluoridation On Stapedial Otosclerosis In A Low Fluoride Area. *Acta Otolaryngologica* 1982;94(1-2):111-119.

Karthikeyan G, Pius A, Apparao BV. Contribution of fluoride in water and food to the prevalence of fluorosis in areas of Tamil Nadu in South India*.. Fluoride*. 1996;29(3):151-155.

Kelly M, Steele J, Nuttall N, al e. *Adult dental health survey, oral health in the United Kingdom 1998:* Office for National Statistics; 2000.

Kelsey J, Keggi K. An epidemiological study of the effect of fluorides in drinking water on the frequency of slipped capital femoral epiphysis. *J Biol Med* 1971;44(3):274-85.

Kendall M, Buckland W. *A dictionary of statistical terms*. London: Longman; 1982.

Kinlen L. Cancer incidence in relation to fluoride level in water supplies. *Br Dent J* 1975;138:221-4.

Kinlen L, Doll R. Fluoridation of Water Supplies and Cancer Mortality 3. a Reexamination of Mortality in Cities in the Usa. *J Epidemiol Community Health* 1981;35(4):239-244.

Klein H. Dental caries (DMF) experience in relocated children exposed to water containing fluorine II. *J Am Dent Assoc* 1946;33:1136-1141.

Klein H, Palmer C, Knutson JW. Studies on dental caries 1. Dental status and dental needs of elementary school children. *Public Health Report* (Washington) 1938;53:751-765.

Knijhnikigov V. The effect of water with a high fluorine content on the health of the adult population. *Gig I San* 1958;8:18-23.

Korns R. Relationship of water fluoridation to bone density in two NY towns. *Pub Health Rep* 1969;84(9):815-25.

Kroger H. The effect of fluoridated drinking water on axial bone mineral density-a population based study. *J Bone and Mineral Res* 1994;27(1):33-41.

Kumar JV, Green EL, Wallace W, Carnahan T. Trends in dental fluorosis and dental caries prevalences in Newburgh and Kingston, NY. *Am J Pub Health* 1989;79(5):565-9.

Kumar JV, Swango PA, Lininger LL, Leske GS, Green EL, Haley VB. Changes in dental fluorosis and dental caries in Newburgh and Kingston, New York. *Am J Pub Health* 1998;88(12):1866-1870.

Kumar JV, Swango PA. Fluoride exposure and dental fluorosis in Newburgh and Kingston, New York: policy implications. *Community Dent Oral Epidemiol* 1999;27(3):171-180.

Kunzel W. Water fluoridation in Karl Marx Stadt. IX. Caries after twelve years of control Trinkwasserfluoridierung Karl Marx Stadt. Ix. Kariesstatistische Ergebnisse Nach Zwolfjahriger. *Stomat.Ddr* 1974;24(4):290-297.

Kunzel W, Padron F. Caries and dental fluorosis in Cuban children. *Caries Res* 1976;10(2):104-112.

Kunzel W. Effect of an interruption in water fluoridation on the caries prevalence of the primary and secondary dentition. *Caries Res* 1980;14(5):304-310.

Kunzel W, Fischer T. Rise and fall of caries prevalence in German towns with different F concentrations in drinking water. *Caries Res* 1997;31(3):166-73.

Kurttio P, Gustavsson N, Vartiainen T, Pekkanen J. Exposure to natural fluoride in well water and hip fracture: A cohort analysis in Finland. *Am J Epidemiol* 1999;150(8):817-824.

Kwant G. Artificial fluoridation of drinking water in the Netherlands. *Netherlands Dental Journal* 1973;80(Supplement 9):6-27.

Kwant G, Howink B, Backer Dirks O, Pot T. Artificial fluoridation of drinking water in the Netherlands; results of the Tiel-Culemborg experiment after 16 1/2 years. *Netherlands Dental Journal* 1973;80(9):6-27.

Larsen MJ, Kirkegaard E, Poulsen S. Patterns of Dental Fluorosis in a European-Country in Relation to the Fluoride Concentration of Drinking-Water. *J Dent Res* 1987;66(1):10-12.

Last J, editor. *A dictionary of epidemiology*. Second edition ed. Oxford: Oxford University Press; 1988.

Latham M, Grech P. The effects of excessive fluoride intake. *Amer J Pub Health* 1967;57/4:651-660.

Lehmann R, Wapniarz M, Hofmann B, Pieper B, Haubitz I, Allolio B. Drinking water fluoridation: Bone mineral density and hip fracture incidence. *Bone* 1998;22(3):273-278.

Leverett D. Prevalence of dental fluorosis in fluoridated and nonfluoridated communities--a preliminary investigation. *J Pub Health Dent* 1986;46(4):184-7.

Levine R, Beal J, Flemming C. A photographically recorded assesment of enamel hypoplasia in fluoridated and non fluoridated areas. *Br Dent J* 1989;166:249-252.

Li Y, Liang C, Slemenda C, Ji R, Sun S, Gao J, et al. Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. 1999. Unpublished report, submitted by author.

Lin F-F, Zhao H-X, Lin J, Jian J-Y. The relationship of a low-iodine an high-fluoride environment to subclinical cretinism in Xinjiang. 1991 Xinjiang Institute for Endemic Disease Control and Research, Office of Leading Group for Endemic Disease Control of Hetian Prefectural Committee of the Communist Party of China and County Health and Endemic Prevention Station, Yutian, Xinjiang. Unpublished report submitted through NHS CRD web site.

Loh T. Thirty-eight years of water fluoridation--the Singapore scenario. *Comm Dent Health* 1996;13 Suppl 2:47-50.

Lynch C. Fluoride in drinking water and state of Iowa cancer incidence. PhD Thesis: The University of Iowa; 1985.

Madans J, Kleinman JC, Cornoni-Huntley J. The relationship between hip fracture and water fluoridation: An analysis of national data. *Am J Pub Health* 1983;73(3):296-298.

Mahoney MC, Nasca PC, Burnett WS, Melius JM. Bone Cancer Incidence Rates in New York State: Time Trends and Fluoridated Drinking Water. *Am J Pub Health* 1991;81(4):475-479.

Mansfield P. The distribution of urinary fluoride concentration in the UK. *Fluoride* 1999;32(1):27-32.

Masztalerz A, Masztalerzowa Z, Szymanska M, Tomelka J. [Fluorine and the dentition]. *Fortschr Kieferorthop* 1990;51(4):234-7.

Maupome G, Clark D, Levy S, Berkpwitz J. Patterns of dental caries following the cessation of water fluoridation. *Community Dent Oral Epidemiol* 2000;in press.

Mazzotti L, Gonzalez Rivera M. Dental fluorosis in Mexico. *Rev d Inst salub y enferm trop* 1939;1:105-121.

McCLure. FLuoride domestic waters and systemic effects 1. Relation to bone fracture experience height and weight of high school boys and young selectees of the armed forces of the united states. *Public Health Reports* 1944;59:1543-1558.

McGuire S, Vanable E, McGuire M, JA B, CW D. Is there a link between fluoridated water and osteosarcoma? *IJ Am Dent* 1991;122:38-45.

McInnes PM, Richardson BD, Cleaton Jones PE. Comparison of dental fluorosis and caries in primary teeth of preschool-children living in arid high and low fluoride villages. *Community Dent Oral Epidemiol* 1982;10(4):182-6.

Mella S, Atalah E, Aranda W, Montagna R. Prevalence of Dental Fluorosis in Chile - a Pilot-Study. *Revista Medica De Chile* 1992;120(8):866-871.

Mella S, Molina X, Atalah E. Prevalence of Dental Fluorosis and Its Relation With Fluoride Content of Communal Drinking-Water. *Revista Medica De Chile* 1994;122(11):1263-1270.

Mella S, Molina M X, Atalah Samur E. Prevalencia de fluorosis dental end,mica en relacion al contenido de fluoruros en las aguas de abasto publico Prevalence of dental endemic fluorosis in relation to fluoride content of comunal drinking water. *Revista Medica De Chile*; 1994;122(11 (nov)):1263-70.

Milsom K, Mitropoulos C. Enamel defects in 8 year old children in fluoridated and non-fluoridated parts of Cheshire. *Caries Res* 1990;1990(24):286-289.

Mitchell E, Thompson J, Borman B. No association between fluoridation of water supplies and sudden infant death syndrome. *NZ Med J* 1991;104:500-501.

Morgan L, Allred E, Tavares M, Bellinger D, Needleman H. Investigation of the possible associations vetween fluorosis, fluoride exposure and childhood behaviour problems. *Paediatric Dentistry* 1998;20(4):244-252.

Moss M, Kanarek M, Anderson H, Hanrahan L, Remington P. Osteosarcoma, seasonality, and environmental factors in Wisconsin, 1979-1989. *Arch Environ Health* 1995;50(235-41).
Murray J, Gordon P, Carmichael C, French A, Furness JA. Dental caries and enamel opacities in 10-year old children in Newcastle. *Br Dent J* 1984;156:255-258.

Murray J, Rugg-Gunn A, Jenkins G. *Fluorides in caries prevention*. 3rd Edition. Reed Educational & Professional Publishing, Oxford 1991.

Murray J, Breckon J, Reynolds P, Nunn J. The effect of residence and social class on dental caries experience in 15-16 year old children living in three towns (natural fluoride, adjusted fluoride and low fluoride). 1991.

Nanda RS, Zipkin I, Doyle J, Horowitz HS. Factors affecting the prevalence of dental fluorosis in Lucknow, India. *Archives of Oral Biology* 1974;19(9):781-792.

NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness.* 1996 CRD Report Number 4

Needleman HL, Pueschel SM, Rothman KJ. Fluoridation and the occurrence of Down's syndrome. *N Engl J Med* 1974;291:821-823.

Nixon J, Carpented R. Mortality in areas containing natural fluoride in their water supplies, takin account of socio-environmental factors and water hardness. *The Lancet* 1974;2:1068-71.

Nunn JH, Murray JJ, Reynolds P, Tabari D, Breckon J. The prevalence of developmental defects of enamel in 15-16-year-old children residing in three districts (natural fluoride, adjusted fluoride, low fluoride) in the north east of England. *Comm Dent Health* 1992;9(3):235-47.

Nunn JH, Ekanayake L, Rugg Gunn AJ, Saparamadu KD. Distribution of developmental defects of enamel on ten tooth surfaces in children aged 12 years living in areas receiving different water fluoride levels in Sri Lanka and England. *Comm Dent Health* 1993;10(3):259-68.

Nunn JH, Ekanayake L, Rugg Gunn AJ, Saparamadu KD. Assessment of enamel opacities in children in Sri Lanka and England using a photographic method. *Comm Dent Health* 1993;10(2):175-88.

Nunn J, Rugg-Gunn A, Ekanayake L, Saparamandu K. Prevalence of developmental defects of enamel with different fluoride and socio-economic groups. *International Dental Journal* 1994;44:165-173.

Ockerse. Fluorosis in Kenhardt and Gordonia districts Cape Province, South Africa. *J Am Dent Assoc*.1941;28:936-941.

Oldham P, Newell D. Fluoridation of water supplies and cancer: a possible association. *Appl Stat* 1977;26:125-35.

Opinya GN, Valderhaug J, Birkeland JM, Lokken P. Fluorosis of Deciduous Teeth and 1st Permanent Molars in a Rural Kenyan Community. *Acta Odontologica Scandinavica* 1991;49(4):197-202.

Overton D, Chase H. Newburgh-Kingston caries fluorine study; pediatric aspects - current status. *New York J. Med.* 1954;54(Sept 1 (pt.1)):2452-2457.

Packington I. Untitled. Unpublished, submitted by author 1999.

Penman AD, Brackin BT, Embrey R. Outbreak of acute fluoride poisoning caused by a fluoride overfeed, Mississippi, 1993. *Public Health Reports* 1997;112(5):403-409.

Phipps KR, Community water fluoridation, bone mineral density and fractures.Unpublished report, submitted by author. 1999.

Pitts NB. Inequalities in children's caries experience: the nature and size of the UK problem. *Comm Dent Health* 1998;1:296-300.

Pot T, Purdell Lewis DJ, Groeneveld A. The influence of 17 years of water fluoridation upon the dentition of adults De Invloed Van 17 Jaren Drinkwater Van Volwassenen. Ned.T.Tandheelk. 1974;81(1):5-12.

Provart S, Carmichael C. The relationship between caries, fluoridation and material deprivation in five-year-old children in Country Durham. *Comm Dent Health*1995;12:200-203.

Raman S, Becking G, Grimard M, Hickman J, McCullough R, Tate R. *Fluoridation and cancer: an analysis of Canadian drinking water fluoridation and cancer mortality data*. Ottawa, Canada: Environmental Health Directorate, Health Protection Branch: Authority of the Minister of National Health and Welfare; 1977.

Rapaport I. Contribution a l'etude du mongolisme,; role pathogenique du fluor. *Bull Acad nat med* (*Par*is) 1957;140(28-29):529-531.

Rapaport. New research on mongolism: concerning the pathogenic role of fluoride. *Bull Acad Natl Med (Paris)* 1959;143:367-370.

Rapaport I. Oligophrnic mongolienne et caries dentairs. *Rev Stomatol Chir Maxillofac* 1963;46:207-18.

Ray SK, Ghosh S, Tiwari IC, Nagchaudhuri J, Kaur P, Reddy DC. Prevalence of dental fluorosis in relation to fluoride in drinking water in two villages of Varanasi (U.P.). *Indian J Public Health* 1982;26(3):173-8.

Richards G, Ford J. cancer mortality in selected New South Wales localities with fluoridated and non-fluoridated water supplies. *Med J Aust* 1979;2:521-3.

Riley J, Lennon M, Ellwood R. The effect of water fluoridation and social inequalities on dental caries in 5-year-old children. *Intl J Epidemiol* 1999;28:300-305.

Riordan PJ, Banks JA. Dental fluorosis and fluoride exposure in Western Australia. *J Dent Res* 1991;70(7):1022-1028.

Rogot E, Sharrett AR, Feinleib M, Fabsitz RF. Trends in urban mortality in relation to fluoridation status. *Am J Epidemiol* 1978;107(2):104-112.

Rozier RG, Dudney GG. Dental fluorosis in children exposed to multiple sources of fluoride: implications for school fluoridation programs. *Public Health Reports* 1981;96(6):542-546.

Rugg-Gunn A, Carmichael C, French A, Furness JA. Fluoridation in Newcastle and Northumberland: a clinical study of five year old children. *Br Dent J* 1977;142:395-402.

Rugg-Gunn A, Nicholas K, Potts A, Cranage J, Carmichael C, French A. Caries experience of 5-year old children living in four communities in North East England receiving differing water fluoride levels. *Brit Dent J* 1981;150:9-12.

Rugg-Gunn A, Carmichael C, Ferrell R. Effect of fluoridation and secular trend in caries in 5-year old children living in Newcastle and Northumberland. *Br Dent J* 1988;165:359-364.

Rugg-Gunn A, Carmicheal C, Ferrell R. Relation between fluoridation social class and caries in 5-year-old children. 67th General Session Of The International Association For Dental Research (IADR), 6th meeting of the IADR Irish division, 72nd annual meeting of the Scandinavian association for dental research and the 26th annual meeting of the continental European division of the IADR, Dublin, Ireland, June 28-july 1, 1989. 1989;68(spec. issue june):941.

Rugg-Gunn AJ, Al Mohammadi SM, Butler TJ. Effects of fluoride level in drinking water, nutritional status, and socio-economic status on the prevalence of developmental defects of dental enamel in permanent teeth in Saudi 14-year-old boys. *Caries Res* 1997;31(4):259-267.

Russell A, Elvove E. Domestic water and dental caries; study of fluoride-dental caries relationship in adult population; 1951.*Pub Health Rep*; 66: 1389-140

Rwenyonyi MC, Birkeland JM, Bjorvatn K, Haugejorden O. Dental fluorosis in Ugandans related to fluoride in drinking water and altitude. *J Dent Res* 1998;77:1299.

Rwenyonyi CM, Bjorvatn K, Birkeland JM, Haugejordan O. Altitude as a risk indicator of dental fluorosis in children residing in areas with 0.5 and 2.5 mg fluoride per litre in drinking water. *Caries Res* 1999;33(4):267-274.

Sack A. Caries incidence in children of Zittau and Karl Marx Stadt. *Dtsch Stomat* 1969;19(3):212-216.

Schatz A. Increased Death Rates in Chile with Artificial Fluoridation of Drinking Water, wtih Implications for other Countries. *Journal of Arts Humanities and Science* 1976:1-17.

Scheinin A, Kalijaervi E, Harjola O, Heikkinen K. Prevalence of Dental Caries and Dental Health in Relation to Variable Concentration of Fluorides in Drinking Water; a Clinical Study On Finnish School-Children. *Acta Odontol Scand* 1964;22:229-54.

Schlesinger E, Overton D, Chase H. Newburgh-Kingdton caries fluorine study. V. Pediatric aspects - continuation report. *Am J Pub Health* 1953;43(8):1011-1015.

Schlesinger E, Overton D, Chase H. Newburgh-Kingston caries fluorine study: pediatric study - preliminary report. *Am J Pub Health* 1950;40:725-727.

Schlesinger E. Newburgh-Kingston caries-fluoride study. *J Am Dent Assoc*.1956;52:290-325.

Segreto VA, Collins EM, Camann D, Smith CT. A current study of mottled enamel in Texas. *J Am Dent Assoc* 1984;108(1):56-9.

Sellman S, Syrrist A, Gustafson G. Fluorine and dental health in Southern Sweden. *Odont T* 1957;65:61-93.

Selwitz RH, Nowjack Raymer RE, Kingman A, Driscoll WS. Prevalence of dental caries and dental fluorosis in areas with optimal and above-optimal water fluoride concentrations: a 10-year follow-up survey. *J Pub Health Dent* 1995;55(2):85-93.

Selwitz RH, Nowjack Raymer RE, Kingman A, Driscoll WS. Dental caries and dental fluorosis among schoolchildren who were lifelong residents of communities having either low or optimal levels of fluoride in drinking water. *J Pub Health Dent* 1998;58(1):28-35.

Seppa L, Karkkainen S, Hausen H. Caries frequency in permanent teeth before and after discontinuation of water fluoridation in Kuopio, Finland. *Community Dent Oral Epidemiol* 1998;26:256-62.

Shaw L, Murray JJ. Inter-examiner and intra-examiner reproducibility in clinical and radiographic diagnosis. *Int Dent J* 1975;25(4):280-8.

Simonen O, Laitinen O. Does fluoridation of drinking water prevent bone fragility in osteoporosis? *The Lancet* 1985;2:432-434.

Skotowski MC, Hunt RJ, Levy SM. Risk-Factors For Dental Fluorosis in Pediatric Dental Patients. *J Pub Health Dent* 1995;55(3):154-159.

Smith A. An examination of the relationship between fluoridation of water and cancer mortality in 20 large US cities. *NZ Med J* 1980;91:413-16.

Sowers M, Wallis R, Lemke J. The relationship of bone mass and fracture history to fluoride and calcium intake: a study of three communities. *Am J Clin Nutrition* 1986;44:889-98.

Sowers M, Clark M, Jannausch M, Wallace R. A prospective study of bone mineral content and fracture in communities with differential fluoride exposure. *Am J Epidemiol* 1991;133:649-660.

Spadaro O, Pagano V. Fluorosis and dental caries in the community of Barcellona Pozzo di Gotto. *Igiene Sanit. Pubbl*. 1955;11(7-8):403-410.

Spittle B. Allergy and hypersensitivity to fluoride. *Fluoride* 1993;26(4):267-273.

Stephen K. *A blind dental caries and fluorosis prevalence study of school children in naturally fluoridated and non-fluoridated townships of Moray*. Glasgow: University of Glasgow Dental School; 1999.

Still CN, Kelley P. On the incidence of primary degenerative dementia vs. water fluoride content in South Carolina. *Neurotoxicology*. 1980;1(4):125-131.

Suarez-Almazor M, Flowerdew G, Saunders L, Soskolne C, Russel A. The fluoridation of drinking water and hip fracture hospitalization rates in two Canadian connunities. *Am J Pub Health* 1993;83:689-693.

Sutton AJ, Abrams KR, Jones DR, et al Systematic reviews of trials and other studies. *Health Technol Assess* 1998; 2 (19).

Swanberg H. Fluoridation of Water and its relation tocancer. *Miss Valley Med J* 1953;75:125-8.

Swinscow T. *Statistics at square on*. London: BMJ Publishing Group; 1996.

Szpunar S, Burt B. Dental caries, fluorosis, and fluoride exposure in Michigan school children. *J Dent Res* 1988;67:802-806.

Teng GX, Zhao XH, Shi YX, Yu GQ, Wang LH, Shen YF, et al. A study of water-borne endemic fluorosis in China. *Fluoride*. 1996;29(4):202-206.

Townsend P, Philmore P, Beattie A. *Health and Deprivation: inequality in the North*. London: Routeledge; 1988.

Venkateswarlu P, Narayanu Rao D, Ranganatha Rao K. Endemic fluorosis: Visakhaptnam and suburban areas; fluorine, mottled enamel and dental caries. *Indian J M Res* 1952;40(October):535-548.

Vignarajah S. Dental caries experience and enamel opacities in children residing in urban and rural areas of Antigua with different levels of natural fluoride in drinking water. *Comm Dent Health* 1993;10(2):159-66.

Villa AE, Guerrero S, Villalobos J. Estimation of optimal concentration of fluoride in drinking water under conditions prevailing in Chile. *Community Dent Oral Epidemiol* 1998;26(4):249-55.

Wang J, Yang C, Xu X. An investigation into the fluoride levels of drinking water and the condition of fluorosis in some areas of south Xinjiang. *Endemic Diseases Bulletin* 1993;8(3):57-60.

Wang XC, Kawahara K, Guo XJ. Fluoride contamination of groundwater and its impacts on human health in Inner Mongolia area. *Journal of Water Services Research and Technology-Aqua* 1999;48(4):146-153.

Warnakulasuriya K, Balasuriya S, Perera PAJ, Peiris LCL. Determining Optimal Levels of Fluoride in Drinking-Water For Hot, Dry Climates - a Case-Study in Sri-Lanka. *Community Dentistry and Oral Epidemiology* 1992;20(6):364-367.

Weaver R. Fluorine and dental caries: further investigations in Tyneside and in Sunderland. *Brit Dental Journal* 1944;77:185-193.

Wenzel A, Thylstrup A, Melsen B. Skeletal development and dental fluorosis in 12--14-year-old Danish girls from a fluoride and a non-fluoride community. *Scand J Dent Res* 1982;90(2):83-8.

Wenzel A, Thylstrup A. Dental fluorosis and localized enamel opacities in fluoride and nonfluoride Danish communities. *Caries Res* 1982;16(4):340-8.

Whelton H, O'Mullane D, Moran A, O'Hickey S. Changes in frequency distribution of caries in children aged 12 and 15 years between 1961-65 and 1984. *J Dent Res* 1986;65(4):569.

Wragg K. Dental Caries Experience of 5 year olds in South Derbyshire. (unpublished) 1992.

Yiamouyiannis J, Burk D. Fluoridation and caner: Age-dependence of cancer mortality related to artificial fluoridation. *Fluoride* 1977;10:102-125.

Yiamouyiannis JA. Fluoridation and cancer: The biology and epidemiology of bone and oral cancer related to fluoridation. *Fluoride* 1993;26(2):83-96.

Zhao L, Liang G, Zhang D, Wu X. Effect of a high fluoride water supply on children's intelligence. *Fluoride* 1996;29:190-192.

Zheng C, et al. A Survey of Dental Caries in Guangzhou China After 18 Years of Community Water Fluoridation. *Chin J Prev Med* 1986;20(2):79-82.

Zimmermann. Fluoride and nonfluoride enamel opacities involving fluorosis. *Pub Health Rep*. 1954;69:1115-1120.

Zipkin I. Interrelation of fluoride with other components of calcified tissue. *Biblioteca Nutritio at Dicta.* 1970;15:62-78.

APPENDIX A
Glossary

Specialised terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases usage differs from that found in the literature, but the term has a constant meaning throughout the report. Some glossary entries adapted from the Glossary in The Cochrane Library, Issue 4, 1998. Oxford: Update Software. Updated quarterly.

Abstracts
A very brief summary or digest of the study and its results. The abstract describes the study purpose, methods, results and conclusions. Abstracts are often included in database records located by searching bibliographic databases.

Adverse effect
Any undesirable or unwanted consequence of a preventive, diagnostic or therapeutic procedure (Last, 1988)

AGRICOLA (AGRICultural OnLine Access)
An extensive bibliographic database which provides selective worldwide coverage of primary information sources in agriculture and related fields. AGRICOLA consists of records for literature citations of journal articles, monographs, theses, patents, translations, microforms, audiovisuals, software, and technical reports. Coverage: 1970 to date. AGRICOLA is produced by the National Agricultural Library (NAL) of the U.S. Department of Agriculture (USDA).

Al-Alousi's Index
One of the indices used to measure dental fluorosis, please refer to Appendix I.

AMED (Allied and Complementary Medicine Database)
AMED is a bibliographic database produced which covers a selection of journals in complementary medicine, palliative care, and several professions allied to medicine. Coverage: 1985 to date. Produced by the Health Care Information Service of the British Library, UK.

Anterior teeth
Refers to the front teeth, either incisor or canine.

Apatite
An inorganic mineral substance, a calcium phosphate found in teeth and bone (Harty, 1994).

Approximal surface
Term describing the adjoining surfaces of the teeth.

Artificially fluoridated water
Water supplies to which soluble fluoride has been added to adjust the level to a defined ‘optimum’ level.

Baseline examination
The initial measurement done at the beginning of the study to establish the starting point.

Before-and-after studies
Such studies compare the prevalence of a disease at two points in time in one or more study areas. The aim of these studies is to provide an estimate of how much an outcome has changed over a period of time. Often the baseline survey is conducted before a change in a risk factor for the outcome, and then the final survey is conducted after the change in the risk factor is expected to have had an effect on the occurrence of the outcome. The baseline and final surveys are usually conducted in different subjects; for example the baseline survey may examine all 8 year olds in the study areas and then the final survey several years later will also look at 8 year olds. Such studies have an advantage over cross sectional studies in that the baseline values for the prevalence of the outcome

are known. If the only factor to have changed between the baseline and final surveys is the risk factor under investigation then it is likely that this risk factor is responsible for the observed change in the outcome.

Bias
Bias is a deviation of a measurement from the 'true' value. Bias can originate from many different sources, such as allocation of patients, diagnosis, analysis, interpretation, publication and review of data. In the worst circumstances it may lead to the wrong conclusions being drawn.

BIOSIS Previews
BIOSIS Previews is the major English-language service providing comprehensive worldwide coverage of research in the biological and biomedical sciences. The database contains citations from Biological Abstracts, Biological Abstracts/Reports, Reviews, and Meetings (formerly BioResearch Index). BIOSIS includes journal citations, meeting abstracts, reviews, books, book chapters, notes, letters, U.S. patents, selected institutional and government reports, and research communications. Coverage: 1969 to date. Produced by BIOSIS, Philadelphia, PA, USA.

Biting surface
That surface of the teeth on which food is chewed also the occlusal surface.

Blinding (Synonym: masking)
Keeping confidential group assignment (e.g. to intervention or control) from the study participants or investigators. Blinding is used to protect against the possibility that knowledge of assignment may affect participant response to intervention, provider behaviours (performance bias) or outcome assessment (detection bias).

Buccal surface
Term denoting the tooth surface adjacent to the cheeks

CAB Health
CAB Health is a bibliographic database of information relating to human health and communicable diseases, including non-English-language journals, developing country information, books, research reports, patents and standards, dissertations, conference proceedings, annual reports, and other difficult to obtain material. CAB Health combines the resources of two international databases - the human health and diseases-related information extracted from CAB Abstracts and the complete file from the Public Health and Tropical Medicine Database (previously produced by the Bureau of Hygiene and Tropical Diseases). Coverage: 1973 to date. substantially deeper subject coverage. Produced by CAB INTERNATIONAL, Oxfordshire, UK.

Calibration exercises
Exercises used to standardise the diagnostic criteria and to assess any variation between examiners.

Canine tooth
A single pointed tooth intended for tearing and cutting food. Canines are situated towards the front of the dental arch, and appear in both the deciduous and permanent dentition.

Carcinogenicity studies
Studies which investigate the possible relationship between potential causal factors and cancers.

Caries
Disease resulting in the demineralisation, cavitation and breakdown of calcified dental tissue by microbial activity.

% Caries-free children
The percentage of children in a group who show no evidence of dental caries.

Cases
Person in the population or study group identified as having the particular disease under investigation

Case control study
A population with the outcome of interest (cases) is selected and compared with another group in which the outcome is absent (controls), differences in exposures between the groups are assumed to be responsible for the occurrence of the disease. One of the advantages of this design is that multiple exposures can be examined for one particular outcome. This type of study design has many methodological weaknesses and is particularly susceptible to bias. The most important methodological issues relate to the way in which the cases and controls are selected and the comparability of the exposure data obtained; controls should be a representative sample of the population from which the cases were drawn. As data is collected retrospectively it is difficult to demonstrate whether or not an observed correlation is causal.

Categorical variable
Refers to a particular type of variable, which may be nominal (unordered) e.g. male / female, or ordinal (ordered) e.g. grade of fluorosis (Swinscow, 1996).

Causal agents
Those factors which are supposed to cause a disease or condition.

Causal relationship
Observed changes (the 'effect') in one variable are owing to earlier changes in another (Bowling, 1997).

Cavitation
Process in which the hard tissues of a tooth crown are undermined by caries, causing them to cave in and form a cavity (Harty, 1994).

Chemical Abstracts
This database includes citations to worldwide literature of chemistry and its applications. The Chemical Abstracts database corresponds to the bibliographic information and complete indexing found in the print Chemical Abstracts. Coverage: 1967 to date. Produced by Chemical Abstracts Service, Columbus, OH, USA.

Cohort study (Synonyms: follow-up study)
Individuals are recruited into the study and are allocated to one of two or more study groups depending on whether they have or have not been exposed to the agent under investigation. The selected study groups are followed-up for a period of time that may extend to many years in order to measure the frequency of occurrence of the outcome of interest in those exposed compared to those not exposed. The group that is not subjected to the exposure of interest must be drawn from a population that is similar to the exposed group in all respects other than the exposure under investigation. Cohort studies have the advantage that the exposure and confounding factors are measured before the outcome of interest has developed and so are unbiased in terms of disease development, time-order relationships are known as subjects are classified by risk factors before the outcome becomes manifest, and multiple outcomes can be examined for one exposure. Potential weaknesses of this type of design include loss to follow-up, changes in subject characteristics, and surveillance bias where one population is observed in more detail than the other is.

Community Fluorosis Index (CFI)
The CFI enables a community based score to be calculated for fluorosed teeth, (see Appendix I).

Conference Papers Index
This database covers the life sciences, chemistry, physical sciences, geosciences, and engineering. Conference Papers Index consists of reports of current research and development from papers presented at conferences and meetings; providing titles of the papers and contact details of authors. The database also includes announcements of publications issued from the meetings, in addition to available preprints, reprints, abstract booklets, and proceedings volumes, including dates of availability, costs and ordering information. Coverage: 1973 to date. Produced by Cambridge Scientific Abstracts, Bethesda, MD, USA.

Confidence interval (CI)
The range within which the 'true' value (e.g. size of effect of an intervention) is expected to lie with a given degree of certainty (e.g. 95%). This is the interval that includes the true value in 95% of cases. Note: Confidence intervals represent the probability of random errors, but not systematic errors (bias).

Confounding factors
Another factor or effect that confuses the picture. A confounder distorts the ability to attribute the cause of something to the treatment, because something else could be influencing the result.

Controlled trial
Refers to a study that compares one or more intervention groups to one or more comparison (control) groups.

Controls
The people in the 'control' group or 'arm' in a controlled trial or a case-control study (also called the comparison group). In a trial, people who are the 'controls' represent the status quo, against which the effectiveness of a treatment is tested. These could receive no treatment, a placebo treatment, or the standard or conventional treatment. The people in the other arm of a trial are the 'experimental' group. In a case-control study, the controls are the people who don't have the condition being studied: the 'cases' are the people who have the condition.

Correlation
The degree to which variables change together (Last, 1988).

Cost-effectiveness
The cost-effectiveness of a particular form of health care depends upon the ratio of the costs of health care to its health outcomes.

Cross-sectional studies
These are used to investigate the prevalence of a defined condition. Data is collected in a planned way from a defined population. The aim of such studies is to describe individuals in the population at a particular point in time in terms of their personal attributes and their history of exposure to suspected causal agents. These data are then investigated in relation to the presence or absence of the disease under investigation or its severity with a view to developing or testing hypotheses. These studies are relatively simple to conduct, take only a short time and are relatively cheap. However, these studies are often difficult to interpret, as it is not possible to assess whether the outcome followed the exposure or the exposure resulted from the outcome.

Current Contents Search (Social Science Citation Index and Science Citation Index)
This database reproduces the tables of contents from current issues of leading journals in the sciences and social sciences. Current Contents search also includes complete bibliographic records for articles, reviews, letters, notes, and editorials. Coverage: 1990 to date. Produced by Institute for Scientific Information, Philadelphia, PA, USA.

Crystal lattice
A homogeneous and angular solid, having a definite form characterized by geometric plane surfaces and a symmetrical internal structure, whereby atoms, ions or molecules are arranged in a definite pattern known as the space lattice (Jablonski, 1982).

Dean's Index
One of the principal indices used to measure dental fluorosis (see Appendix I).

Deciduous dentition (Synonym: Primary dentition)
Primary dentition which starts to erupt about the age of 6 months and is complete at about 2½ years, when complete it consists of 20 teeth. Deciduous teeth are gradually replaced by the permanent dentition (Harty, 1994).

deft index
A method of measuring caries experience in the deciduous dentition

Demarcated defect
An area of well-circumscribed enamel of altered colour or appearance.

Demineralisation
Reduction of the mineral content of a tissue.

Dental caries (Synonym: Tooth decay)
Disease resulting in the demineralisation, cavitation and breakdown of calcified dental tissue by microbial activity.

Dental decay (Synonym: Dental caries)
Disease resulting in the demineralisation, cavitation and breakdown of calcified dental tissue by microbial activity.

Dental fluorosis
Enamel hypoplasia (defective development of tissue) caused by the ingestion of water containing excess fluoride during the time of enamel formation.

Dentine
Sensitive calcified tissue forming the bulk of a tooth and surrounding the pulp (Harty, 1994).

Developmental Defects of Enamel Index (DDE Index)
One of the principal indices used to measure defects of enamel development (see Appendix I).

Diffuse defect
An indefinitely defined area of enamel altered in colour or appearance.

dmfs index
A method of measuring carious tooth surfaces in the deciduous dentition

DMFS index
A method of measuring carious tooth surfaces in the permanent dentition

dmft index
A method of measuring caries experience in the deciduous dentition.

DMFT index
A method of measuring caries experience in the permanent dentition.

Dose-response relationship
A change in dose is associated with a correlated change in effect. An example is when an increase in dose of a pain-relieving drug leads to an increased effect (reduction of pain). In the context of observational studies, a change in the 'dose' of exposure is associated with a change (increase or a decrease) in risk of a specified outcome (Last, 1988).

Ecological studies
Such studies provide a relatively simple and inexpensive method of looking at disease occurrence, especially with regard to an environmental exposure determined by geography. The average exposure of the population is plotted against the rate of the outcome for that population to investigate any possible association between the two. These studies are considered to provide weak evidence because of concern about compatibility of information from different areas, data is often unavailable on many risk factors and because of uncertainties in extrapolating results of analyses at population level to the individual.

Effectiveness
Extent to which an intervention does people more good than harm. An effective treatment or intervention is effective in real life circumstances, not just an ideal situation. It answers the question *does it work?*

Efficacy
The extent to which an intervention improves the outcome for people under ideal circumstances. Testing efficacy means finding out whether something is capable of causing an effect at all. It answers the question *can it work?*

EI Compendex
This database is the electronic version of the print Engineering Index. EI Compendex covers worldwide civil, energy, environmental, geological, and biological engineering; electrical, electronics, and control engineering; chemical, mining, metals, and fuel engineering; mechanical, automotive, nuclear, and aerospace engineering; and computers, robotics, and industrial robots literature. The database includes abstracted citations from journals, selected government reports, books and published proceedings of engineering and technical conferences. Coverage: 1970 to date. Produced by Engineering Information, Inc., Hoboken, NJ, USA.

EMBASE
This is a major bibliographic database which covers worldwide biomedical journals, with emphasis in the areas of drugs and toxicology. Inclusion of European material is particularly strong. Coverage: 1974 to date. Produced by Elsevier Science B.V., Amsterdam, The Netherlands.

EMTREE
EMTREE is a highly developed classification system and controlled vocabulary, used to index articles on EMBASE.

Enamel
The hard outer covering of the anatomical crown of a tooth (Harty, 1994).

Enviroline
This database corresponds to the print Environment Abstracts. Enviroline provides indexing and abstracting coverage of worldwide environmental related information, including such fields as management, technology, planning, law, political science, economics, geology, biology, and chemistry as they relate to environmental issues. Coverage: 1975 to date. Produced by Congressional Information Service, Inc., Bethesda, MD, USA.

Epidemiologic studies
Studies of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems (Last, 1988).

Exposed group
A group whose members have been subject to possess, or possess a characteristic that is a determinant of the health outcome of interest.

Exposure
The amount of a factor to which a group or individual was exposed; sometimes contrasted with dose, the amount that enters or interacts with the organism (Last, 1988).

Fermentable carbohydrates
Sugars or starch which can be broken down by micro-organisms.

Final survey
The end survey or data collection on subjects in a particular study.

Fissure
A small grove or trough in the enamel of the tooth

Fluorapatite
The compound formed when fluoride is incorporated into hydroxyapatite.

Fluoride
Naturally occurring inorganic ion of fluorine, a non-metallic gaseous element (Harty, 1994).

Fluoridation
In this review, indicates water fluoridation.

Fluorosed
Teeth or other hard tissue affected by fluorosis.

FSTA (Food Science and Technology Abstracts)
This database corresponds to the printed publication Food Science and Technology Abstracts. FSTA provides comprehensive coverage of research and new development literature in the areas related to food science and technology, and includes evaluated abstracts, patents, reviews, poster presentations, abstracts of theses, technical sessions, reports, symposia, books, conference proceedings, legislation, standards, lectures, yearbooks, and special workshops. Coverage: 1969 to date. Produced by IFIS Publishing, Reading, UK.

Forest plot
A graphical representation of a number of studies showing the mean result with associated confidence intervals.

Free smooth surfaces
Tooth surfaces adjacent to the tongue, palate, cheek, or lips.

Funnel plots
A graphical display of sample size plotted against measure of effect for the studies included in a systematic review, which can be used to investigate publication bias.

Generalisability (Synonyms: applicability, external validity, relevance, transferability)
Generalisability is the degree to which the results of a study or systematic review can be extrapolated to other circumstances, in particular to routine health care situations.

Grey Literature
Grey literature refers to research findings and results which may have been published in reports, booklets, conference proceedings, technical reports, unpublished theses, discussion papers or other formats which are not indexed on the main databases.

Handsearching
Handsearching involves systematically looking through journals by hand, to identify any appropriate articles which may have been overlooked, or which might have been missed by an electronic literature search due to inaccurate or incomplete indexing of the record. Handsearching is also a vital way of identifying very recent publications which have yet to be cited or entered and indexed on the electronic databases.

HealthStar (Health Services Technology, Administration, and Research)
This bibliographic database contains citations to journal articles, monographs, technical reports, meeting abstracts and papers, book chapters, government documents, and newspaper articles. HealthStar incorporates all records from the former Health Planning and Administration database, the HSTAR database, and the printed index Hospital and Health Administration Index. Coverage: 1975 to date. Produced co-operatively by the U.S. National Library of Medicine and the American Hospital Association, USA.

Heterogeneity
In systematic reviews, heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between "statistical heterogeneity" (differences in the reported effects), "methodological heterogeneity" (differences in study design) and "clinical heterogeneity" (differences between studies in key characteristics of the participants, interventions or outcome measures). Statistical tests of heterogeneity are used to assess whether the observed variability in study results (measures of effect) is greater than that expected to occur by chance.

Histological changes
Changes seen in tissues at a microscopic level.

Homogeneity
Homogeneity refers to 'similarity'. Studies are said to be homogeneous if their results vary no more than might be expected due to chance. The opposite of homogeneity is heterogeneity.

HSRProj (Health Services Research Projects in Progress)
HSRProj is a database of descriptions of ongoing research projects, in the field of health services research including health technology assessment and the development and use of clinical practice guidelines. HSRProj includes monographs, journal articles, publications from symposia and congresses. Coverage: not known. Produced by the National Information Center on Health Services Research and Health Care Technology (NICHSR), Bethesda, MD, USA. Accessible free via the internet: http://igm.nlm.nih.gov/

Hydroxyapatite crystal
Mineral compound of the general form hydroxyapatite: $Ca_{10}(PO_4)_6(OH)_2$, which is the principal inorganic component of bone, teeth and dental calculus (Zipkin, 1970).

Hypersensitivity
An excess response to a stimulus. Often used to denote an allergic response.

Hypoplasia
A defect of enamel structure arising from disturbance of matrix formation.

Hypomaturation
A defect of enamel structure resulting from disturbance of mineralisation during tooth formation.

Hypothesis (Plural: hypotheses)
A theory or suggestion to be tested.

ICD-9
International Classification of Diseases 9th Edition. The classification of specific conditions and groups of conditions determined by an internationally representative group of experts who advise the World Health Organization (publishers of the ICD) which is revised periodically.

Incisor
Single-rooted tooth with a cutting or shearing edge. Incisor teeth occur in both the primary and secondary dentition, and are situated at the front of the dental arch.

Inclusion criteria
The criteria used by authors of a review to decide whether to include studies.

Increment
A change in value of a variable. In this review, denotes the amount of new disease occurring between two defined points in time.

Index Medicus
A printed index of journal articles, reports, books and theses, relating to biomedicine. This cumulative publication was published as Index Medicus (19879-1915), Quarterly Cumulative Index to Current Medical Literature (1916-1926), Quarterly Cumulative Index Medicus (1927-1959), and Cumulated Index Medicus (1960-present). From 1966, the contents of Index Medicus can be searched electronically via the **MEDLINE** database. Records from 1960-1965 can be searched electronically via the **OLDMEDLINE** database. Each record in Index Medicus is indexed using NLM's controlled vocabulary, MeSH (Medical Subject Heading). Coverage: 1879 to date. Produced by the National Library of Medicine (NLM), Bethesda, MD, USA.

Intervention
Anything meant to change the course of events for someone: surgery, a drug, a test, a treatment, change in environment, counselling, giving someone a pamphlet - all of these are interventions.

JICST-EPlus (Japanese Science and Technology)
This is a comprehensive bibliographic database covering literature published in Japan from all fields of science, technology, and medicine. JICST-E contains bibliographic data, abstracts (when available), and indexing from 1985 to the present. Coverage: 1985 to date. Produced by Japan Science and Technology Corporation (JST), Tokyo, Japan.

Labial surface
Term denoting the tooth surface adjacent to the lip.

LILACS (Latin American and Caribbean Literature on the Health Sciences)
This is a bibliographic database, which contains literature related to the health sciences published in Latin America and the Caribbean. Publication types indexed by LILACS include journal articles, theses, chapters of theses, books, chapters of books, congress and conference annals, technical and scientific reports and governmental publications. Coverage: 1982 to date. Produced by BIREME (Biblioteca Regional de Medicina), Sao Paulo, Brazil. Accessible free via the internet: http://www.bireme.br/iah2/homepagei.htm

Lingual surface
Term describing the tooth surface adjacent to the tongue.

Logistic regression (See also regression)
Logistic regression is used to investigate the relationship between an event rate or proportion and a set of independent variables. In systematic reviews it can be used to explore the relationship between key characteristics of included studies and the results (observed effects) for each study.

Longitudinal designs
A method of epidemiologic study in which subsets of a population are followed up over time, retrospectively or prospectively, to observe changes occurring over time.

Median
Is the value on the scale that divides the distribution into two equal parts. Half of the observations have a value less than or equal to the median, and half have a value greater than or equal to the median.

MEDLINE
This database corresponds to three print indexes: **Index Medicus**, Index to Dental Literature, and International Nursing Index. Additional materials not published in Index Medicus are included on MEDLINE in the areas of communication disorders, and population and reproductive biology. Medline is the NLM's premier bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, and the preclinical sciences. Each record is indexed using NLM's controlled vocabulary, MeSH (Medical Subject Heading). Coverage: 1966 to date. Produced by the National Library of Medicine (NLM), Bethesda, MD, USA.

MeSH (Medical Subject Heading)
MeSH is a highly developed classification system and controlled vocabulary produced by the National Library of Medicine (NLM), used to index articles on Medline. Records are also indexed using MeSH on other NLM databases, such as AIDSLINE, AIDSTRIALS, AVLINE, BIOETHICSLINE, CATLINE, DIRLINE, **HealthStar** and POPLINE.

Meta-analysis
A statistical technique which summarises the results of several studies into a single estimate of their combined result.

Meta-regression
Meta-regression is a form of meta-analysis which investigates the importance and nature of relationships between study results and study characteristics, and can be used to explore reasons for heterogeneity.

Methodological Filter Search Strategy
An electronic **search strategy** which has been designed to identify records of studies with specific methodologies, e.g. systematic reviews or meta-analyses.

Methodological quality
The extent to which the design and methodology of a trial are likely to have prevented systematic errors (bias). Variation in quality can explain variation in results of trials included in systematic reviews. More rigorously designed (better 'quality') trials are more likely to yield results that are closer to the 'truth'.

Methodological weakness
Inherent flaws in a particular study design.

Methodology
The methods and principles used in a study. For example authors of a systematic review will explain its methodology in terms of their search strategy, criteria for including trials, statistical methods used, etc.

Micro-organisms
Very small unicellular organism such as bacteria, fungi, viruses or spores.

Mixed dentition
Dentition consisting of deciduous and permanent teeth during the period when the deciduous teeth are being shed.

Modified Developmental Defects of Enamel
Modification of DDE index (see Appendix I).

Mottled teeth (synonym Dental Fluorosis)
Enamel hypoplasia (defective development of tissue) caused by the ingestion of water containing excess fluoride during the time of enamel formation.

Mottled enamel (synonym Dental Fluorosis)
Enamel hypoplasia (defective development of tissue) caused by the ingestion of water containing excess fluoride during the time of enamel formation.

Multiple regression
Multiple regression is used to investigate the joint influences of several variables, taking account of possible correlations among them.

Multivariate analysis
Measuring the impact of more than one variable at a time while analysing a set of data, e.g. looking at the impact of age, gender, and occupation on a particular outcome.

Naturally fluoridated water
Water supplies that have fluoride occurring naturally in the water source.

Negative effects
Undesired impacts upon an individual's or population's health resulting from exposure to a factor.

NNH
Number Needed to Harm. NNH is the number of patient who need to be treated to cause one bad outcome (e.g. side effect). In a trial where side effects are one of the outcomes, if NNH = 10, for every 10 people treated one extra person will suffer the side effect.

Non-milk extrinsic sugars
Sugars arising outside the cellular matrix of food, not of milk origin.

NTIS (National Technical Information Service)
The database consists of summaries of U.S. government-sponsored research, development, and engineering, plus analyses prepared by federal agencies, their contractors, or grantees. NTIS enables the sale of unclassified, publicly available, unlimited distribution reports from agencies such as NASA, DOD, DOE, HUD, DOT, Department of Commerce, and some 240 other agencies. Coverage: 1964 to date. Produced by National Technical Information Service (Office of Product Management), U.S. Department of Commerce, Springfield, VA, USA.

Occlusal surface
Term describing the surfaces of the teeth that make contact with those of the opposing jaw.

Odds ratio (OR)
The ratio of the odds of an event in the experimental (intervention) group to the odds of an event in the control group.

OLDMEDLINE
OLDMEDLINE contains citations published in the 1960 through 1965 Cumulated **Index Medicus** and covers the fields of medicine, preclinical sciences, and allied health sciences. Coverage: 1960 to 1965. Produced by the National Library of Medicine (NLM), Bethesda, MD, USA.
Accessible free via the internet: http://igm.nlm.nih.gov/

Outcome
Result of an intervention.

Outliers
Observations differing so widely from the rest of the data as to lead one to suspect that a gross error may have been committed, or suggesting that these values come from a different population.

P-value
The probability (ranging from zero to one) that the observed results in a study could have occurred by chance.

PAIS
This database covers the full range of the social sciences, with emphasis on contemporary public issues and the making and evaluating of public policy. The database is the online version of the print publications PAIS Bulletin (1976-1990), PAIS Foreign Language Index (1972-1990), and PAIS International in Print (1991-present). Coverage: 1972 to date. Produced by Public Affairs Information Service, Inc. (PAIS), New York, USA.

Parts per million (ppm)
A measurement of the concentration of a solid dissolved into a liquid. In the context of fluoridation of water, it is the concentration of fluoride in water supplies, and is equivalent to milligrams per litre (mg/L).

Pascal
This bibliographic database contains references to scientific and technical literature. PASCAL corresponds to the print publication Bibliographie internationale (previously Bulletin signaletique). Coverage: 1973 to date. Produced by INIST, the Scientific and Technical Information Institute of the Centre National de la Recherche Scientifique (CNRS), Vandoeuvre-les-Nancy CEDEX, France.

Permanent dentition (Synonym: Secondary dentition)
The 32 teeth present in an adult mouth.

Pit
A small depression in the enamel of a tooth

Plaque
A highly variable and tenacious film composed of 70% micro-organisms and 30%.

Pooled effect estimate
Grouping together of statistical estimates.

Population
This describes the people that are being investigated.

Posterior teeth
Teeth situated at the back of the mouth including molars and premolars.

Positive effects
Beneficial or desired impact on an individual's or a population's health resulting from exposure to an intervention or agent.

Prevalence
The number of cases of the disease (or other outcome of interest) in a defined population at a specified point in time, taken as a proportion of the total numbers of people in that population during that time.

Primary dentition (Synonym: Deciduous dentition)
Primary dentition which starts to erupt about the age of 6 months and is complete at about 2½ years, when complete it consists of 20 teeth. Deciduous teeth are gradually replaced by the permanent dentition.

Primary studies
A study of other studies is called a review, or secondary study. A primary study is one of the individual studies within that review.

Proportion caries-free
The proportion, or percentage, of individuals who have experienced no caries.

Prospective study design / retrospective study design
In a retrospective study, the outcomes are examined in hindsight, using existing records. In a prospective study, the study is designed ahead of time, and people are then recruited and studied according to the study's criteria.

Protocol
The methods and procedures to be followed in the conduct of a study.

Proximal surfaces
Adjacent surfaces of teeth in the same dental arch.

PsycLit
This database provides access to the international literature in psychology and related behavioral and social sciences, including psychiatry, sociology, anthropology, education, pharmacology, and linguistics. PsycLit contains all records from the printed Psychological Abstracts, plus material from Dissertation Abstracts International and other sources. Publication types indexed include journal articles, dissertations, reports, books and book chapters. Coverage:1887 to date. Produced by American Psychological Association, Washington, DC, USA.

Q Statistic
Statistic used to measure heterogeneity.

Random Effects
A method of meta-analysis (and general statistical modelling) which estimates the effect of an intervention, assuming that variation in the meta-analysis is a combination of random sampling error within studies and variation between studies. Random effects models are more conservative than fixed effects models, giving estimates with wider confidence intervals.

Randomised Controlled Trial (RCT) (Synonym: randomised clinical trial)
These are designed to measure the efficacy and safety of particular types of health care interventions, by randomly assigning people to one of two or more treatment groups and, where possible, blinding them and the investigators to the treatment that they are receiving. The outcome of interest is then compared between the treatment groups. Such studies are designed to minimise the possibility of an association due to confounding and remove many sources of bias present in other study designs. However, such studies are not infallible and there are areas of methodological concern: selection bias (bias in the way subjects are assigned to experimental groups), issues relating to reproducibility of results, bias introduced by co-interventions and bias in assessing the outcomes.

Range
The difference between the largest and smallest values in a distribution.

Regression (Synonym: Regression analysis)
A statistical modelling technique. Regression analysis is used to estimate or predict the relative influence of more than one variable on something e.g., the effect of age, gender, and educational level on the prevalence of a disease. There are different types of these models, including 'linear' and 'logistic' regression.

Regression models
Examples include the Linear regression model. A statistical model in which the value of the parameter for a given value of a factor, x, is assumed to be equal to $a + bx$, where a and b are constants (Last, 1988).

Relative Risk (RR) (Synonym: risk ratio)
Risk of an adverse effect with exposure to a treatment relative to risks for those who do not receive the treatment. A ratio of 1.0 indicates no increased risk over receiving no treatment. A ratio greater than 1.0 indicates the risk is higher in the group that did receive the treatment. A ratio less than 1.0 indicates the risk of the adverse effect is higher in the group that did not receive treatment.

Relevance criteria
Pre-determined yardsticks by which the papers were assessed for inclusion in the primary stage of the review.

Remineralisation
Restoration of mineral salts to a tissue, such as calcium salts to enamel or bone.

Representative sample
The sample resembles the population, particularly on key variables (e.g. age, gender, ethnic origin)

Retrospective study design
A study looking back in time.

Risk
Risk is used to describe the chances of something happening. Researchers often use the work risk to state the proportion of people in a group in whom an event is observed.

Risk Difference
The absolute difference in the event rate between two comparison groups. A risk difference of zero indicates no difference between the comparison groups.

Risk factor
An aspect of a person's condition, lifestyle or environment that increase the probability of occurrence of a disease. For example, cigarette smoking is a risk factor for lung cancer.

Sampling
The process of selecting participants for research.

Search strategy
A combination of queries or commands designed to retrieve relevant records on a specific topic from an electronic database.

Secondary dentition (Synonym: Permanent dentition)
The 32 teeth present in an adult mouth.

Selection bias
Selection bias occurs when individual subjects are assigned to experimental groups in a biased or non-randomised way.

SIGLE (System for Information on Grey Literature in Europe)
This is a bibliographic database covering European non-conventional (so-called grey) literature in the fields of pure and applied natural sciences and technology, economics, social sciences, and humanities. SIGLE also includes the FTN database for German grey literature, published in the printed abstract journal Forschungsberichte aus Naturwissenschaft und Technik/Reports in the Fields of Science and Technology.
Coverage:1976 to date. Produced by EAGLE (European Association for Grey Literature Exploitation).

Skeletal fluorosis
Characterised by an increase in the X-ray density of trabecular bone in the lumbar spine, pelvis and elsewhere, and an increase in the thickness of long bone cortices due to endosteal and periosteal apposition. In more advanced cases, calcification of ligaments occurs, especially in the spine (Murray, 1991).

Standard Deviation (SD) / Standard Error (SE)
The standard deviation measures the amount of scatter in results. Approximately two-thirds of values will fall within one standard deviation of the mean and 95% will fall within two standard deviations of the mean.

Statistical significance
An estimate (usually expressed as a p-value or 95% confidence interval) of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance. At the 95% certainty level, a p-value < 0.05 is statistically significant. When considering the 95% CI of a ratio (e.g. relative risk) the estimate of effect is statistically significant if the 95% CI does NOT include 1.0. When considering risk difference, the estimate of effect is statistically significant when the 95% CI does NOT include zero.

Surveillance bias
Surveillance bias is said to exist where one of the groups being studied is observed in greater detail than the other groups in the study.

Systematic review
A review of studies in which evidence has been systematically searched for, studied, assessed and summarised according to pre-determined criteria.

Systemic
Acting throughout the whole body (generally after being absorbed into the system).

Thylstrup and Fejerskov Index [TFI]
One of the principal indices used to measure dental fluorosis (see Appendix I).

Tooth pulp
Soft tissue lying within the dentine of a tooth, containing fibres, cells and structures such as blood vessels, sensory nerves and lymphatic system (Harty, 1994).

Tooth Surface Index of Fluorosis [TSIF]
One of the principal indices used to measure dental fluorosis (see Appendix I).

Topical
Pertaining to the surface. In the context of fluoride, topical refers to the application of a substance containing fluoride to the surface of the teeth.

TOXLINE
This bibliographic database covers the toxicological, pharmacological, biochemical, and physiological effects of drugs and other chemicals. Coverage: c. 1940 to date. Produced by National Library of Medicine, Bethesda, MD, USA. Accessible free of charge from: http://toxnet.nlm.nih.gov

Validity
The degree to which a result is likely to be 'true' and free of bias.

Variance
A measure of the variation shown by a set of observations defined by the sum of the squares of deviations from the mean, divided by the degrees of freedom in the set of observations.

WATERNET
This bibliographic database provides a comprehensive index of the publications of the American Water Works Association and the AWWA Research Foundation. Included are books and proceedings, journals, technical reports, newsletters, standards, manuals, handbooks, and water quality standard test methods. The database is the online counterpart to the index to the Journal AWWA from 1971 to the present, and all AWWA and AWWARF publications from 1973 to the present, with non-AWWA materials included on a selective basis. Coverage: 1971 to date. Produced by American Water Works Association, Denver, CO, USA.

Water Resources Abstracts
This database offers a comprehensive range of water-related topics in the life and physical sciences, as well as the engineering and legal aspects of the conservation, control, use, and management of water. Coverage: 1968 to date. Produced by Cambridge Scientific Abstracts, Bethesda, MD, USA.

Weighted mean difference
The mean difference between experimental groups, adjusted for the variance of the observations in the groups sampled, such that those with less variance are given more weight.

Weighting
The importance of a measure in relation to a set of measures to which it belongs; a numerical coefficient attached to an observation, frequently by multiplication, in order that it shall assume a desired degree of importance in a function of all the observations of the set (Kendall, 1982).

ABBREVIATIONS

BMI	Body Mass Index
CFI	Community Fluorosis Index
CI	Confidence interval
IP	Internet Protocol Address
Fl	Fluoride
MMWR	Morbidity and Mortality Weekly Review
NNH	Numbers Needed to Harm
Non-Fl	non-fluoridated
NTIS	National Technical Information Service
OR	Odds ratio
PAIS	Public Airs Information Service
QOL	Quality of life
OPCS	Office for Population Census and Statistics (now called ONS = Office of National Statistics)
RCT	Randomised controlled trial
RR	Relative risk or risk ratio
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology and End Results
SIDS	Sudden Infant Death Syndrome

SIGLE	System for Information in Grey Literature in Europe
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
TCP	Transmission Control Protocol
TFI	Thylstrup and Fejerskov Index
TSIF	Tooth Surface Index of Fluorosis
WHO	World Health Organization

APPENDIX B
Search Strategy

Initial WWW browse. This was not intended to be a systematic examination of web-based information resources on the topic, but the main dental websites were visited. As a result of the preliminary web search 41 reports and journal references were identified and obtained.

A rapid appraisal of the literature was carried out in order to identify the scope and scale of existing review literature surrounding this topic. The rapid appraisal search process involves searching a checklist of the following resources in order to gauge the amount of literature surrounding this topic. Scoping searches were also carried out on the DataStar and Dialog services in order to identify other databases for inclusion for future searching.

The next level of searching involved an initial literature search of the Medline database. The date period covered was 1966 – 03/1999, and foreign language papers were not excluded. This level of searching focussed on retrieval of systematic reviews and meta-analyses only; therefore the literature search used a quality filter component to identify such material. The filter strategy was included to identify systematic reviews, overviews and meta-analysis literature, and to exclude editorials, case studies and other irrelevant publication types. The final stage of searching involved the retrieval of primary studies looking at fluoridation. Medline and Embase were both searched using a strategy designed to retrieve primary studies including cohort studies, clinical trials, RCTs, longitudinal studies, prospective studies etc. The Medline search covered the date range 1966 - 05/1999 and found 295 studies. The Embase search covered the date range 1980 – 05/1999 (07/1999-12/1999 was excluded due to technical reasons) and found 107 studies. Overall a total of 394 studies were found (402 including duplicates).

WWW Resources searched

- American Dietetic Association
http://www.eatright.org/fluoride.html
- British Dental Association
http://www.dba-dentistry.org.uk
- British Fluoridation Society
http://www.derweb.ac.uk/bfs/
- International Society for Fluoride Research
http://www.fluoride-journal.com/
- OMNI (Organising Medical Networked Information)
http://www.omni.ac.uk
- National Institute of Dental and Craniofacial Research
http://www.nidr.nih.gov/news/index.htm
- World Health Organization
http://www.who.org
- Fluoride Issues
http://www.sonic.net/~kryptox/fluoride.htm)
- Dangers of fluoridated water
http://www.nofluoride.com/
- Preventive Dental Health Association
http://emporium.turnpike.net/P/PDHA/health.htm

Rapid appraisal checklist and results

Completed and ongoing reviews	
Cochrane Library: Cochrane Database of Systematic Reviews	1 protocol
Cochrane Library: DARE	6
National Research Register	0
SHPIC Reports	0
SIGN Guidelines	0
Agency for Health Care Policy and Research (AHCPR)	Not available
Guide to Clinical Preventive Guidelines	Not available
Development and Evaluation (DEC) Reports	0
INAHTA Published Reports	0
INAHTA Ongoing Reviews	0
National Co-ordinating Centre for Health Technology Assessment	0
Indexes to clinical effectiveness sources including reviews, appraisal of reviews, and evidence-based guidelines	
TRiP (Turning Research into Practice)	2
ScHARR-Lock's Guide to the Evidence	0
IDEA Topic List	0

Preliminary Search strategy to retrieve systematic reviews & meta-analyses

MEDLINE SEARCH STRATEGY (using Silverplatter software)

No.	Records	Request
The searches below are from: A:\FLUOR_1.HIS.		
1	5535	"meta" in ab
2	180395	"synthesis" in ab
3	116144	"literature" in ab
4	12311	"randomized" in mesh
5	47782	"published" in ab
6	3678	"meta-analysis" in PT
7	42067	"extraction" in ab
8	72637	"trials" in mesh
9	17655	"controlled" in mesh
10	3337	"medline" in ab
11	57034	"selection" in ab
12	42176	"sources" in ab
13	56714	"trials" in ab
14	119760	"review" in ab
15	659244	"review" in pt
16	7117	"articles" in ab
17	109815	"reviewed" in ab
18	8280	"english" in ab
19	14415	"language" in ab
20	132637	"comment" in pt
21	370229	"letter" in pt
22	100035	"editorial" in pt
23	2847541	"ANIMAL" in TG
24	6061664	"human" in TG
25	2272460	#23 not (#23 and #24)
26	3887	explode "Fluoridation"/ all subheadings
27	17134	explode "Fluorides"/ all subheadings
28	4031	explode "Fluorine"/ all subheadings
29	18170	fluorid* in ti,ab
30	4298	fluorin* in ti,ab
31	17	flurid* in ti,ab
32	2	flurin* in ti,ab
33	31788	#27 or #28 or #29 or #30 or #31 or #32
34	137426	water in ti,ab
35	65384	supplement* in ti,ab
36	23350	additive* in ti,ab

37	777	"Dietary-Supplements"/ all subheadings
38	13057	explode "Water-Supply"/ all subheadings
39	227228	#34 or #35 or #36 or #37 or #38
40	2809	#39 near #33
41	5345	#40 or #26
42	1277	"Dental-Caries-Susceptibility"/ all subheadings
43	67933	explode "Treatment-Outcome"/ all subheadings
44	325575	effective* in ti,ab
45	100210	prevention in ti,ab
46	1022	preventative in ti,ab
47	26562	preventive in ti,ab
48	56103	explode "Primary-Prevention"/ all subheadings
49	434716	#42 or #43 or #44 or #48
50	123098	#45 or #46 or #47
51	22964	tooth in ti,ab
52	31024	teeth in ti,ab
53	76919	dental in ti,ab
54	14451	(dentition or enamel) in ti,ab
55	120884	#51 or #52 or #53 or #54
56	18169	decay* in ti,ab
57	1227	erode* in ti,ab
58	5008	erosion in ti,ab
59	14473	caries in ti,ab
60	1015	mottle* in ti,ab
61	1785	discolor* in ti,ab
62	320	discolour* in ti,ab
63	115	"cosmetic effect*"
64	84158	appearance in ti,ab
65	124383	#56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64
66	10504	#55 near #65
67	21536	explode "Dental-Caries"/ all subheadings
68	24423	#66 or #67
69	1186	"Fluorosis,-Dental"/ all subheadings
70	1480	"Tooth-Discoloration"/ all subheadings
71	1052	(fluorosis or flurosis) in ti,ab
72	1219	#50 near (#66 or #71)
73	4171	#69 or #70 or #71 or #72
74	1449	"Hazardous-Substances"/ all subheadings
75	82967	toxicity in ti,ab
76	60781	toxic in ti,ab
77	49132	safety in ti,ab
78	54217	allerg* in ti,ab
79	218589	#74 or #75 or 76 or #77 or #78
80	58638	adverse in ti,ab
81	140713	side in ti,ab
82	4282	undesirable
83	1636	unpleasant
84	152	unattractive
85	197975	#80 or #81 or #82 or #83 or #84
86	925121	effect in ti,ab
87	778145	effects in ti,ab
88	302666	reaction* in ti,ab
89	231877	result in ti,ab
90	1370502	results in ti,ab
91	2715219	#86 or #87 or #88 or #89 or #90
92	115635	#85 near #91
93	315672	#79 or #92
94	718822	#49 or #68 or #73 or #93 or #72
95	2907	#41 and #94
96	2654	#95 not (#20 or #21 or #22 or #25)
97	1260749	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

		or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
98	403	#96 and #97

Preliminary search strategy to retrieve clinical trials and primary studies

MEDLINE SEARCH STRATEGY (using Silverplatter software)

No.	Records	Request
1	12637	explode "Randomized-Controlled-Trials"/ all subheadings
2	114299	randomized controlled trial in pt
3	38507	explode "Random-Allocation"/ all subheadings
4	55024	explode "Double-Blind-Method"/ all subheadings
5	4228	explode "Single-Blind-Method"/ all subheadings
6	250395	clinical trial in pt
7	76287	explode "Clinical-Trials"/ all subheadings
8	942	explode "Controlled-Clinical-Trials"/ all subheadings
9	18935	explode "Placebos"/ all subheadings
10	115141	explode "Research-Design"/ all subheadings
11	274521	explode "Evaluation-Studies"/ all subheadings
12	205276	explode "Follow-Up-Studies"/ all subheadings
13	105337	explode "Prospective-Studies"/ all subheadings
14	840525	tg = "comparative-study"
15	192487	random*
16	65866	placebo*
17	315081	explode "Longitudinal-Studies"/ all subheadings
18	329552	explode "Cohort-Studies"/ all subheadings
19	2108820	control* or clinical or cohort or longitudinal or follow-up or prospective
20	496408	single or double or treble or triple
21	2925329	project or projects or stud* or trial* or evaluation* or blind or mask*
22	101885	comparative* or evaluative*
23	2567541	#15 or #16 or #20 or #19 or #22
24	669325	#23 near #21
25	299862	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
26	1357038	#9 or #10 or #11 or #12 or #13 or #14 or #17 or #18
Searches and records above from: Selected Databases		
27	1438620	#26 or #25 or #26
28	101529	editorial in pt
29	133486	c omment in pt
30	374004	letter in pt
31	2867966	tg = "animal"
32	6114154	tg = "human"
33	2285948	#31 not (#31 and #32)
34	1139912	#27 not (#33 or #28 or #29 or #30)
35	3894	explode "Fluoridation"/ all subheadings
36	17189	explode "Fluorides"/ all subheadings
37	4036	explode "Fluorine"/ all subheadings
38	18253	fluorid* in ti,ab
39	4338	fluorin* in ti,ab
40	2	flurin* in ti,ab
41	17	flurid* in ti,ab
42	32668	#35 or #36 or #37 or #38 or #39 or #40 or #41
43	138770	water in ti,ab
44	66214	supplement* in ti,ab
45	23650	additive* in ti,ab
46	920	"Dietary-Supplements"/ all subheadings
47	13117	explode "Water-Supply"/ all subheadings
48	229711	#43 or #44 or #45 or #46 or #47
49	6600	#48 and #42
50	6600	#49 or #35
51	1281	"Dental-Caries-Susceptibility"/ all subheadings
52	70979	explode "Treatment-Outcome"/ all subheadings
53	329913	effective* in ti,ab

54	101505	prevention in ti,ab
55	26870	preventive in ti,ab
56	1054	preventative in ti,ab
57	56473	explode "Primary-Prevention"/ all subheadings
58	441840	#51 or #52 or #53 or #57
59	124652	#54 or #55 or #56
60	23141	tooth in ti,ab
61	31231	teeth in ti,ab
62	77316	dental in ti,ab
63	14542	(dentition or enamel) in ti,ab
64	121517	#60 or #61 or #62 or #63
65	18405	decay* in ti,ab
66	1242	erode* in ti,ab
67	5081	erosion in ti,ab
68	14545	caries in ti,ab
69	1025	mottle* in ti,ab
70	1807	discolor* in ti,ab
71	325	discolour* in ti,ab
72	116	"cosmetic effect*"
73	84903	appearance in ti,ab
74	125544	#65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73
75	10573	#64 near #74
76	21605	explode "Dental-Caries"/ all subheadings
77	6144	#66 or #67
78	1191	"Fluorosis-Dental"/ all subheadings
79	1495	"Tooth-Discoloration"/ all subheadings
80	1056	(fluorosis or flurosis) in ti,ab
81	266	#58 near (#75 or #80)
82	2862	#78 or #79 or #81
83	1465	"Hazardous-Substances"/ all subheadings
84	83953	toxicity in ti,ab
85	61403	toxic in ti,ab
86	49996	safety in ti,ab
87	54758	allerg* in ti,ab
88	119495	efficacy in ti,ab
89	326494	#83 or #84 or #85 or #86 or #87 or #88
90	59590	adverse in ti,ab
91	142299	side in ti,ab
92	4327	undesirable in ti,ab
93	1658	unpleasant in ti,ab
94	153	unattractive in ti,ab
95	200476	#90 or #91 or #92 or #93 or #94
96	933688	effect in ti,ab
97	786532	effects in ti,ab
98	305761	reaction* in ti,ab
99	234934	result in ti,ab
100	1392082	results in ti,ab
101	1934282	#95 or #96 or #97 or #98 or #99
102	200476	#95 near #101
103	487693	#89 or #102
104	599171	#59 or #82 or #103 or #81
105	1666	#50 and #104
106	295	#105 and #34

EMBASE SEARCH STRATEGY (using Silverplatter software)
(due to technical difficulties, the 07/1999 – 12/1999 section of Embase was omitted from the search).

No.	Records	Request
1	868857	explode "controlled-study"/ all subheadings
2	2292	"randomization"/ all subheadings

3	45185	"placebo"/ all subheadings
4	152104	random*
5	32071	randomized in de
6	28778	"double-blind-procedure"/ all subheadings
7	2058	"single-blind-procedure"/ all subheadings
8	12840	"prospective-study"/ all subheadings
9	3261	"longitudinal-study"/ all subheadings
10	4834	explode "cohort-analysis"/ all subheadings
11	142005	explode "clinical-trial"/ all subheadings
12	595822	"major-clinical-study"/ all subheadings
13	178244	explode "evaluation-and-follow-up"/ all subheadings
14	101949	explode "comparative-study"/ all subheadings
15	2613277	control* or clinical or cohort or longitudinal or follow-up or prospective
16	394966	double or single or treble or triple
17	2884209	project or projects or stud* or trial* or evaluation* or blind or mask*
18	73483	placebo*
19	174154	comparative* or evaluative* or prospective*
20	2846796	#4 or #15 or #16 or #18 or #19
21	1618601	#20 near #17
22	359896	"methodology"/ all subheadings
23	32249	"technique"/ all subheadings
24	1895396	#1 or #2 or #3 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #22 or #23
25	2068278	#21 or #24
26	86262	note in dt
27	148047	letter in dt
28	49547	editorial in dt
29	283856	#26 or #27 or #28
30	2027112	#25 not #29
31	25561	explode "animal"/ all subheadings
32	820374	explode "animal-experiment"/ all subheadings
33	3078551	explode "human"/ all subheadings
34	150414	explode "human-experiment"/ all subheadings
35	833298	#31 or #32
36	3079302	#33 or #34
37	792668	#35 not (#35 and #36)
38	1737155	#30 not #37
39	292	explode "fluoridation"/ all subheadings
40	9708	fluoride* in su
41	938	explode "fluorine"/ all subheadings
42	9580	fluorid* in ti,ab
43	23	flurid* in ti,ab
44	3911	fluorin* in ti,ab
45	2	flurin* in ti,ab
46	17603	#39 or #40 or #41 or #42 or #43 or #44 or #45
47	131482	water in ti,ab
48	50358	supplement* in ti,ab
49	20622	additive* in ti,ab
50	6954	explode "diet-supplementation"/ all subheadings
51	3535	explode "water-supply"/ all subheadings
52	202158	#47 or #48 or #49 or #50 or #51
53	982	#52 near #46
54	1133	#39 or #53
55	109459	efficacy in ti,ab
56	43884	explode "treatment-outcome"/ all subheadings
57	274533	effective* in ti,ab
58	66108	prevention in ti,ab
59	1005	preventative in ti,ab
60	15464	preventive in ti,ab
61	190	explode "caries-prevention"/ all subheadings
62	1299	"primary-prevention"/ all subheadings

63	25249	preventing in ti,ab
64	100867	#58 or #59 or #60 or #61 or #62 or #63
65	387181	#55 or #56 or #57
66	4868	tooth in ti,ab
67	5202	teeth in ti,ab
68	11287	dental in ti,ab
69	2708	(dentition or enamel) in ti,ab
70	18924	#66 or #67 or #68 or #69
71	15623	decay* in ti,ab
72	1059	erode* in ti,ab
73	1915	caries in ti,ab
74	624	mottle* in ti,ab
75	1060	discolor* in ti,ab
76	187	discolour* in ti,ab
77	61	"cosmetic effect" in ti,ab
78	62708	appearance in ti,ab
79	82632	#71 or #72 or #73 or #74 or #75 or #76 or #77 or #78
80	1539	#70 near #79
81	2584	"dental-caries"/ all subheadings
82	3149	#80 or #81
83	579	"fluorosis"/ all subheadings
84	126	"tooth-color"/ all subheadings
85	441	(fluorosis or flurosis) in ti,ab
86	168	#64 near (#82 or #85)
87	855	#83 or #84 or #86
88	159054	explode "toxicity"/ all subheadings
89	77140	toxicity in ti,ab
90	130018	toxic* in ti,ab
91	45650	safety in ti,ab
92	39748	allerg* in ti,ab
93	2718	"allergic-reaction"/ all subheadings
94	319196	#88 or #87 or #89 or #90 or #91 or #92 or #93
95	55714	adverse in ti,ab
96	119820	side in ti,ab
97	3697	undesirable in ti,ab
98	1434	unpleasant in ti,ab
99	122	unattractive in ti,ab
100	173610	#95 or #96 or #97 or #98 or #99
101	697848	effect in ti,ab
102	651423	effects in ti,ab
103	239105	reaction* in ti,ab
104	192271	result in ti,ab
105	1134822	results in ti,ab
106	2138019	#101 or #102 or #103 or #104 or #105
107	105832	#100 near #106
108	35863	explode "side-effect"/ all subheadings
109	133114	#107 or #108
110	412994	#94 or #109
111	718906	#65 or #87 or #110 or #86
112	383	#54 and #111
113	109	#112 and #38
114	558131	"rat-" in DE

APPENDIX C
Included Studies Data Tables

Table C1 = Caries studies: baseline data
Table C2 = Caries studies: Individual study results

Table C3 = Social Class studies: baseline data
Table C4 = Social Class studies: Individual study results

Table C5 = Fluorosis studies: baseline data
Table C6 = Fluorosis studies: Individual study results

Table C7 = Bone studies: baseline data
Table C8 = Bone studies: Individual study results

Table C9 = Cancer studies: baseline data
Table C10 = Cancer studies: Individual study results

Table C11 = Other adverse effects studies: baseline data
Table C12 = Other adverse effects studies: Individual study results

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) Adriasola (1959) **Country of study** Chile **Geographic location** San Fernando (non-F), Curico (F) **Year study started** 1953 **Year study ended** 1956 **Year of change in fluoridation status** 1953	**Inclusion criteria** Children aged 3-15 Children from 2 primary schools in the study areas **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** None stated **Outcome(s):** % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* Low (Natural) *Control:* Low (Natural) **Age:** 5, 8, and 12	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* Low (Natural) **Age:** 5, 8, and 12
Author (year) Alvarez-Ubilla (1959)) **Country of study** Chile **Geographic location** San Fernando (low-F), Curico (F) **Year study started** 1953 **Year study ended** 1956 **Year of change in fluoridation status** 1953	**Inclusion criteria** Children aged 3 to 15 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** None stated **Outcome(s):** Dmft score **%** caries free subjects«Outcome2»	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural)) *Control:* low (Natural) **Age:** 5	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* low (Natural) **Age:** 5
Author (year) Arnold (1956) **Country of study** USA **Geographic location** Grand Rapids (F), Muskegon (non-F) **Year study started** 1944 **Year study ended** 1951 **Year of change in fluoridation status** 1945	**Inclusion criteria** Children aged 4-16 years Used city water supplies since birth **Exclusion criteria** Children who lived outside study areas for more than 3 months of any one year	**Other sources of fluoride:** Author states that there were no concerted efforts to commence special caries control programmes e.g. topical fluoride programmes, in either of the cities since the study began **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** deft score DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* <0.2 (Natural) **Age:** 5, 8, 12 and 15	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* <0.2 (Natural) **Age:** 5, 8, 12 and 15

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) Ast (1951) **Country of study** USA **Geographic location** Newburgh (F), Kingston (non-F) **Year study started** 1945 **Year study ended** 1952 **Year of change in fluoridation status** 1945	**Inclusion criteria** All 5-12 year old children present at school on days of examination Continuous residents of study areas **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** DMFT rate per 100 erupted permanent teeth % caries free subjects (primary teeth) Number of erupted permanent teeth per child	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* <0.1 (Natural) *Control:* <0.1 (Natural) **Age:** 5, 8 and 12	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1-1.2 (Artificial) *Control:* <0.1 (Natural) **Age:** 5, 8 and 12
Author (year) Attwood (1988) **Country of study** Scotland **Geographic location** Annan (non-F), Stranraer (F) **Year study started** 1980 **Year study ended** 1986 **Year of change in fluoridation status** 1983	**Inclusion criteria** Children aged 10 years attending non-denominational primary schools Lifetime residents of study areas **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Areas similar small towns in south-west Scotland with approximately equal dentist/population ratios and clinical care provided by general and community dental services **Outcome(s):** DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* high (Artificial) *Control:* low (Natural) **Age:** 10	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* low (Natural) **Age:** 10
Author (year) Backer Dirks (1961) **Country of study** Holland **Geographic location** Tiel (F), Culemborg (non-F) **Year study started** 1952 **Year study ended** 1959 **Year of change in fluoridation status** 1953	**Inclusion criteria** Children aged 11-15 Lifelong residents of the study areas Used the piped water supply 100 children of each age examined **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Areas similar in social class structure and proportional numbers of subjects selected from each school type **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** Average number of all aproximal lesions Average number of approximal dental lesions	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* 0.1 (Natural) **Age:** 11-15	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.1 (Artificial) *Control:* 0.1 (Natural) **Age:** 11-15

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) Beal (1981) **Country of study** England **Geographic location** Corby (non-F) and Scunthorpe (F) **Year study started** 1969 **Year study ended** 1975 **Year of change in fluoridation status** 1968	**Inclusion criteria** Continuous residents in study areas Children aged 5, 8, and 12 **Exclusion criteria** Teeth extracted for orthodontic purposes	**Other sources of fluoride:** Not stated **Social class:** Both areas have iron/steel as main industry - socio-economic composition of 2 areas similar **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** dmft score DMFT score % caries free subjects (permanent teeth) % caries free subjects (primary teeth)	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* 0.35 (Natural) **Age:** 5, 8 and 12	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.9 (Artificial) *Control:* 0.35 (Natural) **Age:** 5, 8 and 12
Author (year) Beal (1971) **Country of study** England **Geographic location** Balsall Heath and Northfield, Birmingham (F) and Dudley (non-F) **Year study started** 1967 **Year study ended** 1970 **Year of change in fluoridation status** 1965	**Inclusion criteria** Children aged 5 attending schools that participated in each year of the study **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Balsall heath is poor area of city with high prop of immigrants, Northfield and Dudley are both industrial areas with comparable pops., but more immigrants in Dudley **Ethnicity:** All areas have some proportion of immigrants **Other confounding factors:** Not stated **Outcome(s):** deft score % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Group 2:* low (Natural) *Control:* <0.1 (Natural) **Age:** 5	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Group 2:* 1 (Artificial) *Control:* <0.1 (Natural) **Age:** 5
Author (year) Blayney (1960) **Country of study** USA **Geographic location** Evanston (F), Oak Park (non-F), Illinois **Year study started** 1946 **Year study ended** 1956 **Year of change in fluoridation status** 1946	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Detailed questionnaire completed by parents before baseline examination, collected: length of residency, water supply, mother's pregnancy, diet, school behaviour - no results provided **Outcome(s):** DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* low (Natural) **Age:** 8 and 12	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* high (Artificial) *Control:* low (Natural) **Age:** 8 and 12

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) Brown (1965) **Country of study** Canada **Geographic location** Brantford (F), Stratford (Natural F), Sarnia (non-F), Ontario **Year study started** 1948 **Year study ended** 1959 **Year of change in fluoridation status** 1945	**Inclusion criteria** Children aged 9-14 Continuous residents (absence of <6 weeks since birth) All primary and secondary schools in study areas **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** % caries free subjects (permanent teeth) DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Group 3:* high (Natural) *Control:* low (Natural) **Age:** 9-11 and 12-14	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* high (Artificial) *Group 3:* high (Natural) *Control:* low (Natural) **Age:** 9-11 and 12-14
Author (year) DHSS (1969) **Country of study** England **Geographic location** Watford (F), Sutton (non-F) **Year study started** 1956 **Year study ended** 1967 **Year of change in fluoridation status** 1956	**Inclusion criteria** Continuous residents of study areas Consumed piped water at home and at school **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated (social class data available only for 1967 survey - see objective 3) **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** % caries free subjects dmft score DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* Low (Natural) *Control:* Low (Natural) **Age:** 5, 8, 12 and 14	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.89-0.99 (Artificial) *Control:* Low (Natural) **Age:** 5, 8, 12 and 14
Author (year) DHSS (1969) **Country of study** Wales **Geographic location** Holyhead (mainly F -gets most of water from Gwalchmai, but occasionally also receives water from Bodafon) and Gwalchmai zone (F) and Bodafon zone (Non-F), Anglesey **Year study started** 1956 **Year study ended** 1965 **Year of change in fluoridation status** 1955	**Inclusion criteria** Continuous residents of study areas Consumed piped water at home and at school **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated (social class data available only for 1967 survey - see objective 3) **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Group 2:* low (Natural) *Control:* low (Natural) **Age:** 5, 8, 12 and 14	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.8-0.9 (Artificial) *Group 2:* 0.8-0.9 (Artificial) *Control:* low (Natural) **Age:** 5, 8, 12 and 14

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) DHSS (1969) **Country of study** Scotland **Geographic location** Ayr (non-F), Kilmarnock (F) **Year study started** 1956 **Year study ended** 1968 **Year of change in fluoridation status** 1956	**Inclusion criteria** Continuous residents of study areas Consumed piped water at home and at school **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated (social class data available only for 1967 survey - see objective 3) **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** % caries free subjects dmft score DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* low (Natural) **Age:** 5, 9, 12 and 14	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* low (Natural) **Age:** 5, 9, 12 and 14
Author (year) DHSS (1969) **Country of study** Scotland **Geographic location** Ayr (non-F), Kilmarnock (F) **Year study started** 1961 **Year study ended** 1968 **Year of change in fluoridation status** «YearFluor»2	**Inclusion criteria** Continuous residents of study areas Consumed piped water at home and at school **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated (social class data available only for 1967 survey – see Objective 3) **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** Dmft score % caries free subjects (primary teeth)	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* low (Natural) **Age:** 5	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control*: low (Natural) **Age:** 5
Author (year) Gray (2000) **Country of study** England **Geographic location** Dudley, Sedgeley & Cosely, Halesowen, Brierly Hill & Kingswinford (F), Stourbridge (non-F) **Year study started** 1988 **Year study ended** 1997 **Year of change in fluoridation status** 1987	**Inclusion criteria** Children living in study area since 1988 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** % caries free subjects (primary teeth)	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Group 2:* low (Natural) *Group 3:* low (Natural) *Group 4:* low (Natural) *Control:* low (Natural) **Age:** 5	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Group 2:* 1 (Artificial) *Group 3:* 1 (Artificial) *Group 4:* 1 (Artificial) *Control:* low (Natural) **Age:** 5

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) Guo (1984) **Country of study** Taiwan **Geographic location** Chung-Hsing New Village (F), Tsao-Tun (non-F) **Year study started** 1971 **Year study ended** 1984 **Year of change in fluoridation status** **1971**	**Inclusion criteria** Continuous residents of study areas **Exclusion criteria** Children who migrated from other areas during study period	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Similar climate - mean daily air temp = 24°C **Outcome(s):** % caries free subjects dmft score DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.07 (Natural) *Control:* 0.08 (Natural) **Age:** 5, 8, 12, and 15	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.6 (Artificial) *Control:* 0.08 (Natural) **Age:** 5, 8, 12, and 15
Author (year) Hardwick (1982) **Country of study** England **Geographic location** Alsager, Middlewich, Nantwich (F), Northwich (not F) **Year study started** 1974 **Year study ended** 1978 **Year of change in fluoridation status** 1975	**Inclusion criteria** 12 year old children living in study area Consent from relevant country authorities and teachers at schools included in the study **Exclusion criteria** None stated	**Other sources of fluoride:** 152 fluoride group: 142(94%) used only fluoride dentrifices & 125 (83%) used at least once a day. 194 control group, 185 (95%) used only fluoride dentrifices, 147 (76%) used at least once per day. Two children in fluoride group and 4 children in control had ever used fluoride tablets. **Social class:** Control and experimental groups matched on urban and rural characteristics **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** DMFS score DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* <0.1 (Natural) *Control:* <0.1 (Natural) **Age:** 12	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.0 (Artificial) *Control:* <0.1 (Natural) **Age:** 16
Author (year) Hobbs (1994) **Country of study** Wales **Geographic location** Powys (non-F) and Llandrindod (F) **Year study started** 1989 **Year study ended** 1993 **Year of change in fluoridation status** 1989	**Inclusion criteria** Children aged 5 years **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** dmft score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* <0.2 (Natural) **Age:** 5	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* <0.2 (Natural) *Control:* <0.2 (Natural) **Age:** 5

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) Kalsbeek (1993) **Country of study** Holland **Geographic location** Tiel (F), Culemborg (non-F) **Year study started** 1968 **Year study ended** 1987 **Year of change in fluoridation status** 1973	**Inclusion criteria** 15 year old children born and still resident in study areas **Exclusion criteria** None stated	**Other sources of fluoride:** No difference between 2 study areas in fluoride tablet use, use of fluoridated toothpaste, frequency of toothbrushing and % of children that visited dentist more than twice a year, fluoride applied more frequently by dentists in Culemborg than in Tiel **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** DMFT score DMFS score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1ppm (Artificial) *Control:* Low (Natural) **Age:** 15	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* Low (Natural) *Control:* Low (Natural) **Age:** 15
Author (year) Kunzel (1997) **Country of study** Germany **Geographic location** Chemnitz(F), Plauen (non-F) **Year study started** 1959 **Year study ended** 1971 **Year of change in fluoridation status** 1959	**Inclusion criteria** Children born in study areas **Exclusion criteria** Children who had moved into the 2 study areas Disabled children	**Other sources of fluoride:** Number of topical applications of fluoride toothpastes, solutions and gel was low - water fluoridation was the only preventive measure **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Increasing annual sugar consumption in both areas **Outcome(s):** dmft score DMFT score % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.2 (Natural) *Control:* 0.2 (Natural) **Age:** 5, 8, 12 and 15	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* 0.2 (Natural) **Age:** 5, 8, 12 and 15
Author (year) Kunzel (1997) **Country of study** Germany **Geographic location** Chemnitz(F), Plauen (non-F) **Year study started** 1991 **Year study ended** 1995 **Year of change in fluoridation status** 1990	**Inclusion criteria** Children born in Chemnitz or Plauen **Exclusion criteria** Children who had moved into the 2 study areas Disabled children	**Other sources of fluoride:** In 1992 F-enriched domestic salt became available - reached market share of 10-15% in 1995. Quota of fluoride toothpaste increased from 15-88% after 1992. **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Sugar consumption decreased in 1993 from high level of past decade to level of 1967. Complete restructuring of dental care system occurred between 1987 & 1995 **Outcome(s):** DMFT score % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Natural) *Control:* 0.2 (Natural) **Age:** 8, 12 and 15	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.2 (Artificial) *Control:* 0.2 (Natural) **Age:** 8, 12 and 15

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) Loh (1996) **Country of study** Singapore and West Malaysia **Geographic location** Malacca (non-F), Singapore (F) **Year study started** 1957 **Year study ended** 1966 **Year of change in fluoridation status** 1958	**Inclusion criteria** Chinese and Malay children aged 7-9 years **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Chinese and Malay children - results presented separately **Other confounding factors:** Hot & humid climate - mean daily temp 26.°C **Outcome(s):** DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* low (Natural) **Age:** 7-9	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.7 (Artificial) *Control:* low (Natural) **Age:** 7-9
Author (year) Pot (1974) **Country of study** Holland **Geographic location** Tiel (F), Culemborg (non-F) **Year study started** 1950 **Year study ended** 1970 **Year of change in fluoridation status** 1953	**Inclusion criteria** Residents of study areas born between 1896 and 1945 Lifelong residents of study areas **Exclusion criteria** Subjects who left the study areas for more than 3 months after fluoridation was introduced	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Age - results for final survey presented in 5 year age groups - shows that higher proportion of younger subjects have prosthetic teeth in Culemborg compared to Tiel **Outcome(s):** % with false teeth	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* 0.1 (Natural) **Age:** 5-55	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.1 (Artificial) *Control:* 0.1 (Natural) **Age:** 25-75
Author (year) Seppa (1998) **Country of study** Finland **Geographic location** Kuopio (F), Jyvaskyla (non-F) **Year study started** 1992 **Year study ended** 1995 **Year of change in fluoridation status** 1992	**Inclusion criteria** Return of signed parental consent form Children aged 3-15 **Exclusion criteria** Did not show up for examination	**Other sources of fluoride:** Use of F toothpaste & F tablets, consumption of xylitol chewing gum - info obtained from questionnaire. Info on sealants & fluoride varnish use obtained from dental records **Social class:** Similar distribution of demographic and socio-economic characteristics **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** DMFS score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* 0.1 (Natural) **Age:** 6, 9, 12 and 15	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Control:* low (Natural) **Age:** 6, 9, 12 and 15

C1: Caries Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Survey Characteristics	Final Survey Characteristics
Author (year) Wragg (1999) **Country of study** England **Geographic location** Swadlincote (non-F), Ilkeston and Alfreton (F) **Year study started** 1985 **Year study ended** 1995 **Year of change in fluoridation status** 1984	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** dmft score % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Group 2:* 1 (Artificial) *Control:* 0.2 (Natural) **Age:** 5	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* low (Natural) *Group 2:* low (Natural) *Control:* 0.2 (Natural) **Age:** 5

C2: Caries studies: Individual study results

Study Details	Group	Fluoride level		Outcome 1				Outcome 2				Outcome 3				Outcome 4			
				Baseline		Final		Baseline		Final		Baseline		Final		Baseline		Final	
		Base	Final	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.
Adriasola (1959)				**Outcome:** % caries free subjects **Age:** 5				**Outcome :** % caries free subjects **Age:** 8				**Outcome :** % caries free subjects **Age:** 12							
	Group 1	Low	1	2.2	186	13.3	340	4.2	493	2.4	458	2.3	293	0.2	419				
	Control	Low	Low	4.0	174	10.0	140	7.6	234	0.8	226	1.5	197	4.3	211				
Alvarez-Ubilla (1959)				**Outcome:** dmft score **Age:** 5				**Outcome :** % caries free subjects **Age:** 5											
	Group 1	low	1	8.9	186	6.4	340	2.2	186	13.3	340								
	Control	low	low	8.1	174	7.8	140	4	174	10	140								
Arnold (1956)				**Outcome:** deft score **Age:** 5				**Outcome :** DMFT score **Age:** 12				**Outcome :** DMFT score **Age:** 15							
	Group 1	Low	1	5.4	1633	2.3	853	8.1	1685	5.9	176	12.5	1511	8.9	53				
	Control	<0.2	<0.2	6.8	402	5.3	351	8.7	328	7.7	48	12.9	292	12.4	21				
				Outcome: deft score **Age:** 8				**Outcome :** DMFT score **Age:** 8											
	Group 1	Low	1	5.8	1647	4.1	470	3.0	1647	1.6	470								
	Control	<0.2	<0.2	6.1	376	5.3	275	2.8	376	2.6	275								
Ast (1951)				**Outcome:** DMFT rate per 100 erupted permanent teeth **Age:** 8				**Outcome :** DMFT rate per 100 erupted permanent teeth **Age:** 12				**Outcome :** % caries free subjects (primary teeth) **Age:** 5							
	Group 1	<0.1	1-1.2	17.1	355	9.9	356	25.4	412	16.5	206	23.0	274	49.9	217				
	Control	<0.1	<0.1	17.3	393	17.2	400	25.4	357	27.0	178	28.2	259	33.0	324				
				Outcome: Number of erupted permanent teeth per child **Age:** 8				**Outcome :** Number of erupted permanent teeth per child **Age:** 12											
	Group 1	<0.1	1-1.2	11.4	355	11.7	356	25.1	412	25.2	363								
	Control	<0.1	<0.1	11.7	393	11.7	400	24.9	357	25.1	316								
Attwood (1988)				**Outcome:** DMFT score **Age:** 10															
	Group 1	high	low	1.7	147	1.7	127												
	Control	low	low	3.4	141	2.8	105												
Backer Dirks (1961)				**Outcome:** Average number of all aproximal lesions **Age:** 11-15				**Outcome :** Average number of approximal dental lesions **Age:** 11-15											
	Group 1	low	1.1	13.1		10.8		3.8		3.1									
	Control	0.1	0.1	13.4		13.8		4.1		4.8									
Beal (1981)				**Outcome:** dmft score **Age:** 8				**Outcome :** DMFT score **Age:** 8				**Outcome :** % caries free subjects (permanent teeth) **Age:** 8				**Outcome :** % caries free subjects (primary teeth) **Age:** 8			
	Group 1	low	0.9	5.0	189	3.4	167	1.5	189	0.7	167	41	189	69	167	10	189	19	167
	Control	0.35	0.35	5.4	163	5.0	186	1.6	163	1.3	186	35	163	44	186	7	163	10	186
				Outcome: dmft score **Age:** 5				**Outcome :** % caries free subjects **Age:** 5				**Outcome :** DMFT score **Age:** 12				**Outcome :** % caries free subjects **Age:** 12			
	Group 1	low	0.9	4.3	196	1.8	170	21	196	46	170	3.5	192	2.7	189	27	192	22	189
	Control	0.35	0.35	4.3	205	3.5	180	21	205	30	180	4.3	188	4.1	197	7	188	7	197
Beal (1971)				**Outcome:** deft score **Age:** 5				**Outcome :** % caries free subjects **Age:** 5											
	Group 1	low	1	5.2	115	1.9	132	9	115	48	132								
	Group 2	low	1	4.9	182	2.5	182	29	182	41	182								
	Control	<0.1	<0.1	5.0	217	5.1	229	16	217	24	229								
Blayney (1960)				**Outcome:** DMFT score **Age:** 8				**Outcome :** DMFT score **Age:** 12											
	Group 1	low	high	2.5		0.9		7.6		3.6									
	Control	low	low	2.2		2.4		7.7		7.1									

C2: Caries studies: Individual study results

Study Details	Group	Fluoride level		Outcome 1				Outcome 2				Outcome 3				Outcome 4			
				Baseline		Final		Baseline		Final		Baseline		Final		Baseline		Final	
		Base	Final	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.
Brown (1965)				**Outcome:** % caries free subjects (permanent teeth) **Age:** 9-11				**Outcome :** DMFT score **Age:** 9-11				**Outcome :** % caries free subjects (permanent teeth) **Age:** 12-14				**Outcome :** DMFT score **Age:** 12-14			
	Group 1	low	high	5.7	595	43.8	502	4.1	595	1.5	502	1.2	593	18.7	503	7.7	593	3.2	503
	Group 2	high	high	52.1	432	49.9	527	1.1	432	1.2	527	27.2	371	28.1	480	2.6	371	2.3	480
	Control	low	low	6.1	571	8.1	521	4.2	571	3.7	521	0.6	486	2.3	485	7.9	486	7.5	485
DHSS (1969) England				**Outcome:** % caries free subjects **Age:** 5				**Outcome :** % caries free subjects (permanent teeth) **Age:** 8				**Outcome :** % caries free subjects (permanent teeth) **Age:** 12				**Outcome :** % caries free subjects (permanent teeth) **Age:** 14			
	Group 1	Low	0.9-1.0	8	148	46	111	20	199	53	95	3	111	15	134	0	70	4	90
	Control	Low	Low	14	110	35	119	22	148	37	79	0	51	4	99	6	36	5	108
				Outcome: dmft score **Age:** 5				**Outcome :** DMFT score **Age:** 8				**Outcome :** DMFT score **Age:** 12				**Outcome :** DMFT score **Age:** 14			
	Group 1	low	0.9-1.0	5.43	148	1.61	111	2.4	199	1.08	95	5.6	111	3.52	134	8.4	70	5.77	90
	Control	low	low	4.97	110	2.79	119	2.4	148	1.85	79	6.1	51	4.99	99	7.9	36	6.74	108
DHSS (1969) Wales				**Outcome:** % caries free subjects (permanent teeth) **Age:** 5				**Outcome :** % caries free subjects% caries free subjects **Age:** 8				**Outcome :** % caries free subjects **Age:** 12				**Outcome :** % caries free subjects (permanent teeth) **Age:** 14			
	Group 1	low	0.8-0.9	10	367	31	170	23	320	32	156	8	186	9	108	5	158	3	93
	Group 2	low	0.8-0.9	10	249	32	114	24	287	49	127			2					
	Control	low	low	7	256	14	138	25	351	21	125	10	265		108	6	243	1	96
				Outcome: dmft score **Age:** 5				**Outcome :** DMFT score **Age:** 8				**Outcome :** DMFT score **Age:** 12				**Outcome :** DMFT score **Age:** 14			
	Group 1	low	0.8-0.9	5.56	367	2.85	170	2.05	320	1.51	156	4.65	186	4.38	108	6.95	158	6.73	93
	Group 2	low	0.8-0.9	5.39	249	2.85	114	1.95	287	1.06	127								
	Control	low	low	5.49	256	4.83	138	1.95	351	2.16	125	3.95	265	6.16	108	5.60	243	7.64	96
DHSS (1969) Scotland				**Outcome:** % caries free subjects **Age:** 5				**Outcome :** % caries free subjects (permanent teeth) **Age:** 9				**Outcome :** % caries free subjects (permanent teeth) **Age:** 12				**Outcome :** % caries free subjects (permanent teeth) **Age:** 14			
	Group 1	low	1	6		7		4		4		2		0		0		0	
	Control	low	low	4		7		7		2		5		0		0		0	
				Outcome: dmft score **Age:** 5				**Outcome :** DMFT score **Age:** 9				**Outcome :** DMFT score **Age:** 12				**Outcome :** DMFT score **Age:** 14			
	Group 1	low	1	6.44		5.81		3.4		3.7		7.4		6.6		9.0		9.6	
	Control	low	low	6.52		5.98		3.7		4.2		7.3		9.1		8.7		12.4	
DHSS (1969)				**Outcome:** dmft score **Age:** 5				**Outcome :** % caries free subjects (primary teeth) **Age:** 5											
	Group 1	1	low	4.0		5.8		20		7									
	Control	low	low	6.9		6.0		4		7									
Gray (2000)				**Outcome:** % caries free subjects (primary teeth) **Age: 5**															
	Group 1	low	1	49	552	70.5	594												
	Group 2	low	1	57	537	79.8	475												
	Group 3	low	1	69	547	80.0	564												
	Group 4	low	1	62	826	74.1	891												
	Control	low	low	74	466	64.2	419												

C2: Caries studies: Individual study results

Study Details	Group	Fluoride level		Outcome 1				Outcome 2				Outcome 3				Outcome 4			
				Baseline		Final		Baseline		Final		Baseline		Final		Baseline		Final	
		Base	Final	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.
Guo (1984)				**Outcome:** % caries free subjects (primary teeth) **Age:** 5				**Outcome :** % caries free subjects (permanent teeth) **Age:** 12				**Outcome :** % caries free subjects (permanent teeth) **Age:** 15							
	Group 1	0.07	0.6	10.4	589	0.4	226	51.3	468	40.1	329	47.6	164	35.7	129				
	Control	0.08	0.08	8.3	218	0.3	319	56.5	841	16.8	458	54.5	121	8.2	207				
				Outcome: dmft score **Age:** 8				**Outcome :** DMFT score **Age:** 8				**Outcome :** % caries free subjects (primary teeth) **Age:** 8				**Outcome :** % caries free subjects (permanent teeth) **Age:** 8			
	Group 1	0.07	0.6	4.2	392	2.5	319	0.5	392	0.2	319	13.5	392	0.6	319	70.9	392	85.3	319
	Control	0.08	0.08	3.5	343	6.2	374	0.4	343	1.7	374	14.6	343	1.3	374	79.6	343	29.9	374
				Outcome: dmft score **Age:** 5				**Outcome :** DMFT score **Age:** 12				**Outcome :** DMFT score **Age:** 15							
	Group 1	0.07	0.6	6.5	589	5.1	226	1.1	468	1.9	329	1.7	164	2.6	129				
	Control	0.08	0.08	6.4	218	8.6	319	0.9	841	4.3	458	1.2	121	5.9	207				
Hardwick (1982)				**Outcome:** Caries increment (DMFT) **Age:** 12				**Outcome :** Caries increment (DMFS) **Age:** 12											
	Group 1	<0.1	1.0			3.76	144			6.73	144								
	Control	<0.1	<0.1			4.85	199			9.19	199								
Hobbs (1994)				**Outcome:** dmft score **Age:** 5															
	Group 1	1	<0.2	0.74	47	1.94	69												
	Control	<0.2	<0.2	2.32	421	2.33	708												
Kalsbeek (1993)				**Outcome:** DMFT score **Age:** 15				**Outcome :** DMFS score **Age:** 15											
	Group 1	1	Low	7.4	285	5.5	297	10.8	285	9.6	297								
	Control	Low	Low	14.1	261	4.8	241	27.7	261	7.7	241								
Kunzel (1997)				**Outcome:** DMFT score **Age:** 8				**Outcome :** DMFT score **Age:** 12				**Outcome :** DMFT score **Age:** 15							
	Group 1	0.2	1	1.3	2419	0.5	3016	3.6	1626	2.0	2426	5.7	1995	4.0	1897				
	Control	0.2	0.2	1.3	777	1.8	1076	3.5	563	4.8	925	5.4	744	7.4	756				
				Outcome: % caries free subjects (permanent teeth) **Age:** 8				**Outcome :** % caries free subjects (permanent teeth) **Age:** 12				**Outcome :** % caries free subjects (permanent teeth) **Age:** 15							
	Group 1	0.2	1	42.2	2419	71.2	3016	8.2	1626	32.0	2426	5.9	1995	12.1	1897				
	Control	0.2	0.2	43.0	777	30.9	1076	6.6	563	5.2	925	5.8	744	2.5	756				
				Outcome: % caries free subjects (primary teeth) **Age:** 5				**Outcome :** % caries free subjects (primary teeth) **Age:** 8				**Outcome :** dmft score **Age:** 5				**Outcome :** dmft score **Age:** 8			
	Group 1	0.2	1	33.6	688	52.5	1306	4.8	2438	24.7	3020	2.4	688	1.4	1306	4.9	2438	2.8	3020
	Control	0.2	0.2	22.7	172	32.2	597	5.2	777	5.7	1078	3.3	172	2.9	597	4.9	777	4.9	1078
Kunzel (1997)				**Outcome:** DMFT score **Age:** 8				**Outcome :** DMFT score **Age:** 12				**Outcome :** DMFT score **Age:** 15							
	Group 1	1	0.2	0.6		0.3		2.5		1.9		4.4		3.8					
	Control	0.2	0.2	0.6		0.6		2.5		2.0		4.5		3.5					
				Outcome: % caries free subjects **Age:** 8				**Outcome :** % caries free subjects **Age:** 12				**Outcome :** % caries free subjects **Age:** 15							
	Group 1	1	0.2	67.8		81.6		25.2		38.0		13.4		16.0					
	Control	0.2	0.2	75.6		70.4		16.7		34.8		15.0		20.1					
Loh (1996)				**Outcome:** DMFT score **Age:** 7-9															
Chinese	Group 1	low	0.7	4.4		2.1													
	Control	low	low	3.7		4.5													
				Outcome: DMFT score **Age:** 7-9															
Malay	Group 1	low	0.7	2.9		2.0													
	Control	low	low	1.9		3.1													

C2: Caries studies: Individual study results

Study Details	Group	Fluoride level		Outcome 1				Outcome 2				Outcome 3				Outcome 4			
				Baseline		Final		Baseline		Final		Baseline		Final		Baseline		Final	
		Base	Final	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.	Results	No.
Pot (1974)				**Outcome:** % with false teeth **Age:** 5-55															
	Group 1	low	1.1	14.4	521	50.5	521												
	Control	0.1	0.1	16.2	507	63.5	507												
Seppa (1998)				**Outcome:** DMFS score **Age:** 6				**Outcome :** DMFS score **Age:** 9				**Outcome :** DMFS score **Age:** 12				**Outcome :** DMFS score **Age:** 15			
	Group 1	1	low	0.1	68	0.1	152	0.9	8	0.7	159	1.9	66	1.6	158	4.0	64	3.2	148
	Control	0.1	low	0.0	66	0.1	148	0.7	69	0.7	149	3.0	77	1.6	151	5.6	6	3.9	133
Wragg (1999)				**Outcome:** dmft score **Age:** 5				**Outcome :** % caries free subjects **Age:** 5											
	Group 1	1	low	1.1	88	1.9	84	59.1	88	51.2	84								
	Group 2	1	low	1.2	107	1.9	191	60.7	107	46.6	191								
	Control	0.2	0.2	1.7(2.8)	112	1.0	123	56.3	112	65.9	123								

C3: Social Class Studies: Baseline Data

1. Before-After Studies

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Survey Characteristics
Author (year) Beal (1971) **Country of study** England **Geographic location** Balsall Heath and Northfield, Birmingham (F) and Dudley (non-F) **Year study started** 1967 **Year study ended** 1970 **Year of change in fluoridation status** 1965	**Inclusion criteria** Children aged 5 attending schools that participated in each year of the study **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Balsall Heath is poor area of city with high prop of immigrants, Northfield and Dudley are both industrial areas with comparable pops., but more immigrants in Dudley **Ethnicity:** All areas have some proportion of immigrants **Other confounding factors:** Not stated **Outcome(s):** deft score % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Group 2:* 1 (Artificial) *Control:* <0.1 (Natural) **Age:** 5
Author (year) Gray (2000) **Country of study** England **Geographic location** South East Staffordshire, Sandwell, Walsall, Dudley and North Birmingham (F), North Staffordshire, Herefordshire, Shropshire and Kidderminster (non-F) **Year study started** 1987-1997 **Year fluoridation started** 1969	**Inclusion criteria:** Not stated **Exclusion criteria:** Not stated	**Other sources of fluoride:** Not stated **Social class:** Jarman scores presented **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcomes**: % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** Group 1: 1 (Artificial) Control: Low (Natural) **Age:** 5
Author (year) Holdcroft (1999) **Country of study** England **Geographic location** North Birmingham and Sandwell (F), North Staffordshire, Herefordshire and Shropshire (Non-F) **Year study started** 1985/6 **Year fluoridation started** Not stated	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Measured using Jarman scores **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** dmft	**Fluoride level (artificially or naturally fluoridated):** Not stated **Age:** Not stated

C3: Social Class Studies: Baseline Data

2. Cross Sectional Studies

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Survey Characteristics
Author (year) Bradnock (1984) **Country of study** England **Geographic location** 4 West Midlands conurbations **Year study started** 1981 **Year fluoridation started** 1964	**Inclusion criteria:** Indigenous children resident in West Midlands. Children aged 5 Wards of mainly caucasian residents **Exclusion criteria:** Not stated	**Other sources of fluoride:** None stated **Social class:** Reg Gen: I & II [High Seg], and IV & V [Low Seg] **Ethnicity:** Mainly caucasian **Other confounding factors:** Not stated **Outcomes:** dmft score and % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** Group 1: High (Artificial) Control: Low (Natural) **Age:** 5
Author (year) Carmichael (1980) **Country of study** England **Geographic location** Newcastle (F) and Northumberland (non-F) **Year study started** 1975 **Year fluoridation started** 1969	**Inclusion criteria:** Children aged 5 Lifelong residents Completed parental questionnaire **Exclusion criteria:** None stated	**Other sources of fluoride:** Not stated **Social class:** Registrar General: I & II, III, IV & V & 'other' **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcomes:** % caries free subjects & deft score	**Fluoride level (artificially or naturally fluoridated):** Group 1: 1 (Artificial) Control: <0.1 (Natural) **Age:** 5
Author (year) Carmichael (1984) **Country of study** England **Geographic location** Newcastle (F) and Northumberland (non-F) **Year study started** 1987 **Year fluoridation started** 1969	**Inclusion criteria:** Children aged 5 Lifelong residents **Exclusion criteria:** None stated	**Other sources of fluoride:** Not stated **Social class:** I-V and unclassified [unemployed] using Registrar General classification **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcomes:** dmft score, % Caries free and dmfs score	**Fluoride level (artificially or naturally fluoridated):** Group 1: 1 (Artificial) Control: <0.1 (Natural) **Age:** 5

C3: Social Class Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Survey Characteristics
Author (year) Carmichael (1989) **Country of study** England **Geographic location** Newcastle (F) and Northumberland (non-F) **Year study started** 1987 **Year fluoridation started** 1969	**Inclusion criteria:** Children aged 5 Lifelong residents **Exclusion criteria:** None stated	**Other sources of fluoride:** Fluoride toothpaste **Social class:** I-V and unclassified [unemployed] using Registrar General classification **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcomes:** dmft score, dmfs score and % caries free subjects	**Fluoride level (artificially or naturally fluoridated** Group 1: 1 (Artificial) Control: <0.1 (Natural) **Age:** 5
Author (year) DHSS (1969) **Country of study** England **Geographic location** Watford (F), Sutton (non-F) **Year study ended** 1967 **Year fluoridation started** 1956	**Inclusion criteria** Lifelong residents Consumed piped water at home and at school **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Registrar General: I & II, III, IV & V, stratified by number of children under 15 in family **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** % caries free subjects dmft score DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.89-0.99 (Artificial) *Control:* Low (Natural) **Age:** 5, 8, 12 and 14
Author (year) DHSS (1969) **Country of study** Wales **Geographic location** Gwalchmai zone (F) and Bodafon zone (Non-F), Anglesey **Year study started** 1965 **Year fluoridation starteds** 1955	**Inclusion criteria** Lifelong residents Consumed piped water at home and at school **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Registrar General: I & II, III, IV & V , stratified by number of children under 15 in family **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.83-0.89 (Artificial) *Control:* low (Natural) **Age:** 5, 8, 12 and 14
Author (year) Evans (1996) **Country of study** England **Geographic location** Newcastle (F) and SE Northumberland (non-F) **Year study started** 1994 **Year fluoridation started** 1969	**Inclusion criteria:** Children aged 5 Parental consent Completed parental questionnaire Agreement from school **Exclusion criteria:** Non-white children Non-co-operative children during examination	**Other sources of fluoride:** None stated **Social class:** Registrar General: I & II, III, IV & V & 'other' **Ethnicity:** Non-white children excluded **Other confounding factors:** Not stated **Outcomes**: dmft score and % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** Group 1: 1 (Artificial) Control: <0.1 (Natural) **Age:** 5

C3: Social Class Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Survey Characteristics
Author (year) Jones (1997) **Country of study** England **Geographic location** Salford and Trafford and Liverpool (non-F), Newcastle and North Tyneside (F) **Year study started** 1991/2, 1992/3 and 1993/94 **Year fluoridation started** **Not stated**	**Inclusion criteria** Children aged 5 and 12 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Jarman score **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** dmft and DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (artificial *Control:* lowatural) **Age:** 5 and 12
Author (year) Jones (2000) **Country of study** England **Geographic location** Salford and Trafford and Liverpool (non-F), Newcastle and North Tyneside (F) **Year study started** 1991/2, 1992/3 and 1993/94 **Year fluoridation started** **Not stated**	**Inclusion criteria** Children aged 12 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Townsend score **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** dmft and DMFT score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (artificial *Control:* lowatural) **Age:** 12
Author (year) Murray (1984) **Country of study** England **Geographic location** Newcastle (F) and Ashington, Blyth & Morpeth (non-F) **Year study started** 1981 **Year fluoridation started** 1969	**Inclusion criteria:** 10 year old children Continuous residence in their schools' locality Parental consent **Exclusion criteria:** Child's race not recorded Child's date of birth not recorded Non-caucasian children	**Other sources of fluoride:** Newcastle: 1969-77 F 0.8-1.1 Suboptimal supply 1977-1981 F 0.6. **Social class:** I & II, III & IIIm, IV & V **Ethnicity:** Caucasian **Other confounding factors:** Not stated **Outcomes:** DMFT score and % caries free subjects	**Fluoride level (artificially or naturally fluoridated)** Group 1: 1 (Artificial) Control: <0.1 (Natural) **Age:** 10
Author (year) Murray (1991) **Country of study** England **Geographic location** Newcastle (F), Middlesborough (non F) and Hartlepool (Natural F) **Year study started** 1989-1990 **Year fluoridation started** 1969	**Inclusion criteria:** Children aged 15-16 Parental consent **Exclusion criteria:** Non-Anglo-Saxon children	**Other sources of fluoride:** Not stated **Social class:** I + II; III; IV + V; Unclassified **Ethnicity:** Anglo-Saxon **Other confounding factors:** Not stated **Outcomes:** DMFT score and % caries free subjects	**Fluoride level (artificially or naturally fluoridated):** Group 1: 1 (Artificial) Group 2: 1-1.3 (Natural) Control: 0.2 (Natural) **Age:** 15-16

C3: Social Class Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Survey Characteristics
Author (year) Provart (1995) **Country of study** England **Geographic location** County Durham **Year study started** 1991-92 **Year fluoridation started** 1969	**Inclusion criteria:** Children aged 5 Children resident in electoral wards in the upper & lower quartiles of material deprivation **Exclusion criteria:** None stated	**Other sources of fluoride:** Not stated **Social class:** Children resident in high 7.85 and low material deprivation -6.69 wards studied [Townsend material deprivation scores] **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcomes:** dmft score	**Fluoride level (artificially or naturally fluoridated):** Group 1: 1 (Artificial) Control: 0.1-0.4 (Natural) **Age:** 5
Author (year) Riley (1999) **Country of study** England **Geographic location** 7 fluoridated and 7 non-fluoridated areas **Year study started** 1993-94 **Year fluoridation started** Not stated	**Inclusion criteria** District included if carried out full population survey of 5 year old children Fluoridated districts had at least 90% of pop. receiving fluoridated water, F level >=0.7ppm and supply had been fluoridated continuously for last 5 years. Non-fluoridated areas had <0.3ppm continuously for last 5 years **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Townsend score **Ethnicity:** Not stated **Other confounding factors:** Not stated **Outcome(s):** dmft score	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >=0.7 (not stated) *Control:* <0.3 (Natural) **Age:** 5
Author (year) Rugg-Gunn (1977) **Country of study** England **Geographic location** Newcastle, Prudhoe, Ovingham, & Corbridge (F) and Alnwick, Amble & Rothbury Ashington (non-F) **Year study started** 1975 **Year fluoridation started** 1968	**Inclusion criteria:** 5 Year old children Lifelong residents Parental consent Completion of questionnaire Consenting schools with ordinary, social priority & rural status **Exclusion criteria:** Non-caucasian children	**Other sources of fluoride:** Use of fluoride toothpaste: 80% in F areas & 85% in non-F areas **Social class:** Urban industrial areas & rural areas included in study. Social class similar in rural communities except for 1 non-F school where records were not available **Ethnicity:** Caucasian **Other confounding factors:** Tea drinking: F 72% regular tea drinkers, NF 73% regular tea drinkers. Differential dental attendance patterns **Outcomes:** % caries free subjects and deft score	**Fluoride level (artificially or naturally fluoridated):** Newcastle: 1.0ppm.(artificial) Ashington: <0.1ppm. Prudhoe, Ovingham, & Corbridge: 1.0ppm. Alnwick, Amble & Rothbury: <0.1ppm. **Age:** 5

C4: Social Class Studies: Individual Study Results

1. Studies which present results by Registrar General's social class groupings

Study Details	Outcome	Age	Group	Fluoride level	Social class I & 11		Social class III		Social class IV and V		Unclassified	
					Results (SD)	Number	Results (SD)	Number	Results (SD)	Number	Results (SD)	Number
Bradnock (1984)	dmft	5	Group 1	High	0.47 (0.14)	76			1.56(0.24)	98		
			Control	Low	0.9 (0.2)	81			2.74 (0.34)	98		
	% Caries free		Group 1		81.6				57.1			
			Control		71.6				35.7			
Carmichael (1980)	deft	5	Group 1	High	2.5 (3.33)	62	2.4 (2.71)	282	2.0 (2.42)	111		
			Control	Low	3.4 (3.85)	18	6.0 (4.03)	110	7.0 (2.66)	61		
	% Caries free		Group 1		35		33		37			
			Control		17		15		3			
Carmichael (1984)	dmft	5	Group 1	High	0.98	119	1.54	295	1.54	70		
			Control	Low	2.15	93	3.55	253	3.91	137		
	% caries free		Group 1		67.2		52.2		51.4			
			Control		48.4		30.8		20.4			
Carmichael (1989)	dmft		Group 1	High	1.2 (2.08)	117	1.7 (2.53)	170	2.4 (2.87)	52	2.4 (2.7)	118
			Control	Low	2.2 (2.66)	56	3.7 (4.05)	146	5.0 (4.56)	64	4.5 (4.64)	104
	dmfs		Group 1		1.6		2.5 (4.2)		4.4			
			Control		3.4		6.2 (8.2)		9.8			
	% Caries free		Group 1		65		54		33			
			Control		41		33		23			
DHSS (1969) **England**	dmft	5	Group 1	High	0.4	5	1.36	14	1.75	4		
			Control	Low	2.2	27	2.09	23	4.67	3		
1 or 2 children under 15	DMFT	8	Group 1		0.5	2	0.88	16	2.13	8		
			Control		1.8	20	1.89	18	2.38	8		
	DMFT	12	Group 1		3.42	12	3.61	33	4.00	11		
			Control		5.11	9	6.69	16	4.86	7		
	DMFT	14	Group 1		6.67	6	6.10	10	5.00	5		
			Control		7.18	11	7.24	21	6.50	6		
3 or more children under 15	dmft	5	Group 1		1.6	5	1.74	23	2.20	10		
			Control		1.31	13	2.71	17	4.25	4		
	DMFT	8	Group 1		0.6	5	1.06	17	0.86	7		
			Control		1.5	4	0.85	13	1.00	1		
	DMFT	12	Group 1		4.33	3	3.21	14	2.67	6		
			Control		5.67	6	4.09	11	5.67	3		
	DMFT	14	Group 1		2.00	2	4.57	7	5.00	3		
			Control		5.00	2	9.13	8	6.50	2		
DHSS (1969) **Wales**	dmft	5	Group 1	High	2.08	25	3.53	36	4.00	8		
			Control	Low	4.45	22	4.96	25	7.00	13		
1 or 2 children under 15	DMFT	8	Group 1		1.19	21	1.54	28	1.56	16		
			Control		0.75	13	2.48	23	2.17	12		
3 or more children under 15	dmft	5	Group 1		3.04	23	3.52	42	2.05	19		
			Control		3.64	14	4.48	29	4.04	25		
	DMFT	8	Group 1		0.91	11	1.49	37	1.81	16		
			Control		0.75	12	2.29	34	2.19	16		

C4: Social Class Studies: Individual Study Results

Study Details	Outcome	Age	Group	Fluoride level	Social class I & 11		Social class III		Social class IV and V		Unclassified	
					Results (SD)	Number	Results (SD)	Number	Results (SD)	Number	Results (SD)	Number
Evans (1996)	dmft	5	Group 1 Control	High Low	0.59 (1.37) 1.46 (2.61)	92 79	1.21 (2.36) 2.04 (3.42)	103 143	1.17 (2.73) 2.74 (3.05)	36 34		
	% Caries free		Group 1 Control		77 62		61 53		69 38			
Murray (1984)	DMFT	10	Group 1 Control	High Low	1.45 1.82	67 80	1.71 2.04	249 225	1.62 2.02	99 163		
	% Caries free		Group 1 Control		43 26		29 26		30 23			
Murray (1991)	DMFT	15-16	Group 1 Group 2 Control	High (n) High (a) Low	1.9 2.2 2.9	68 94 80	1.8 2.7 3.4	164 135 140	2.0 3.3 3.9	68 35 57	1.3 3.0 3.7	91 86 98
	% Caries free		Group 1 Group 2 Control		32 31 23		36 27 20		38 23 25			

2. Studies which present results by other social class groupings

Study Details	Outcome	Age	Group	Fluoride level	Social grouping 1	Social grouping 1		Social grouping 2	Social grouping 2	
						Results	Number		Results	Number
Provart (1995)	dmft	5	Group 1 Control	High Low	Low deprivation	0.8 (1.8) 1.2 (2.3)	325 820	High deprivation	1.2 (2.1) 2.1 (2.9)	389 1217
	% Caries free		Group 1 Control			70 66			60 45	
Rugg-Gunn (1977)	deft	5	Group 1 Control	High Low	Urban ordinary	2.4 (2.73) 6.1 (4.03)	323 132	Social priority	2.0 (2.47) 6.1 (4.3)	93 108
	% Caries free		Group 1 Control			36.3 10.6			34.4 12	

C4: Social Class Studies: Individual Study Results

3. Studies which use a regression analysis to investigate the association of decay with social class stratified by water fluoride level

Study Details	Outcome	Age	Group	Fluoride level	Number of subjects per ward (SD)	Mean outcome score (sd)	Social class measure	Mean social class score	Slope of regression line (β) (SE)	Intercept of line (α) (SE)	r^2 (p-value)
Riley (1999)	dmft	5	Solihull	>0.7	118.5 (36.3)	0.7 (0.4)	Townsend score	-0.9 (4.3)	0.08 (0.01)	0.77 (0.03)	0.91 (<0.001)
			Bromsgrove & Redditch		64.8 (26.2)	0.6 (0.2)		-1.1 (3.2)	0.05 (0.01)	0.65 (0.04)	0.33 (0.001)
			West Birmingham		362.9 (82.3)	1.3 (0.2)		6.2 (4.2)	0.04 (0.02)	1.02 (0.12)	0.50 (<0.05)
			North Birmingham		293.5 (77.6)	0.8 (0.3)		2.6 (3.7)	0.05 (0.03)	0.60 (0.10)	0.49 (0.12)
			North Warwickshire		66.2 (34.6)	0.9 (0.3)		-0.2 (2.6)	0.05 (0.02)	0.90 (0.05)	0.24 (<0.01)
			Sandwell		142.0 (22.6)	1.1 (0.3)		4.5 (2.5)	0.08 (0.02)	0.68 (0.10)	0.45 (<0.001)
			East Birmingham		383.1 (157.0)	1.3 (0.4)		5.0 (2.3)	0.17 (0.05)	0.44 (0.29)	0.71 (0.02)
			Combined						0.08 (0.006)	0.77 (0.03)	0.61 (<0.001)
			Shropshire	<0.3	30.1 (25.7)	1.1 (0.7)		-0.7 (2.3)	0.09 (0.02)	1.20 (0.04)	0.18 (<0.001)
			Chester		62.7 (26.6)	1.8 (0.8)		0.7 (4.3)	0.12 (0.02)	1.72 (0.10)	0.48 (<0.001)
			Liverpool		155.5 (76.1)	2.5 (0.8)		6.5 (3.9)	0.14 (0.02)	1.71 (0.16)	0.55 (<0.001)
			Trafford		105 (19.5)	2.0 (0.8)		0.0 (3.4)	0.19 (0.02)	1.99 (0.08)	0.76 (<0.001)
			Warrington		88.3 (44.3)	1.7 (0.7)		-0.5 (3.9)	0.13 (0.03)	1.74 (0.10)	0.53 (<0.001)
			Sheffield		188.7 (57.9)	2.3 (0.8)		3.4 (4.0)	0.17 (0.02)	1.69 (0.09)	0.76 (<0.001)
			St Helens and Knowsley		108.3 (50.4)	3.3 (1.0)		4.3 (4.3)	0.18 (0.02)	2.53 (0.14)	0.58 (<0.001)
			Combined						0.17 (0.08)	1.7 (0.04)	0.56 (<0.001)

4. Studies which used a multiple-regression analysis to investigate the association of decay, social class and water fluoride levels

Study Details	Outcome	Age	Multiple regression Co-efficients					
			Water fluoridation		**Social deprivation (measured by Jarman score)**		**Interaction**	
			Slope of regression line (β)	**F statistic (p)**	**Slope of regression line (β)**	**F statistic (p)**	**Slope of regression line (β)**	**F statistic (p)**
Jones (1997)	dmft	5	-0.46	42.26 (<0.001)	0.89	146.9 (<0.001)	-0.49	28.71 (<0.001)
	DMFT	12	-1.21	29.47 <0.001	0.27	15.45 (<0.001)	0.50	(<0.05)
			Water fluoridation		**Social deprivation (measured by Townsend score)**		**Interaction**	
			Slope of regression line (β)	**p-value**	**Slope of regression line (β)**	**p-vakue**	**Slope of regression line (β)**	**p-value**
Jones (2000)	DMFT	12	-0.45	<0.001	0.11	<0.001	-0.09	<0.001

C4: Social Class Studies: Individual Study Results

5. Before-After Studies

Study Details	Age	Group	Measure of social class	Social class	Baseline				Final			
					Fluoride level (%F)	Number of subjects	% Caries Free	deft (SE) (Beal) dmft (SD) (Gray)	Fluoride level (%F)	Number of subjects	% Caries Free	deft (SE) (Beal) dmft (SD) (Gray)
Beal (1971)	5	Balsall health	Descriptive	Poor area	Low	115	9	5.16 (0.44)	1	132	48	1.94 (0.22)
		Northfield		Industrial area	Low	182	29	4.91 (0.36)	1	182	41	2.45 (0.24)
		Dudley		Industrial area	<0.1	217	16	4.97 (0.28)	<0.1	229	24	5.09 (0.32)
Grey (2000)	5	SE staffs	Jarman score	-23.09	Low	3435	66	1.21 (0.59)	1 (100)	3120	75	0.64 (1.46)
		Sandwell		18.10	Low	3950	51	1.93 (2.88)	1 (100)	3598	69	0.83 (1.68)
		Walsall		1.67	Low	3120	54	1.85 (2.31)	1 (85)	363	67	0.94 (1.77)
		Dudley		-13.68	Low	3657	58	1.6 (2.54)	1 (75)	3474	73	0.78 (1.75)
		N. Birmingham		21.57	Low	1965	72	0.88 (1.97)	1 (100)	1904	74	0.71 (1.65)
		N. Staffs		-3.59	Low	464	47	2.24 (3.04)	Low	1947	59	1.49 (2.46)
		Herefordshire		-13.01	Low	406	57	1.61 (2.55)	Low	305	50	1.79 (2.68)
		Shropshire		-12.34	Low	366	61	1.29 (2.22)	Low	311	60	1.33 (2.33)
		Kidderminster		-13.13	Low	904	58	1.74 (2.81)	Low	1053	61	1.4 (2.52)
Holdcroft (1999)	Not stated	N Birmingham	Jarman score	-7.85	Not stated	Not stated		2.18	High	Not stated		0.68
		Sandwell		15.03	Not stated	Not stated		2.55	High	Not stated		1.13
		N Staffordshire		-4.07	Not stated	Not stated		2.24	Not stated	Not stated		1.48
		Shropshire		-11.73	Not stated	Not stated		1.76	Not stated	Not stated		1.29
		Herefordshire		-11.97	Not stated	Not stated		2.56	Not stated	Not stated		1.53

C5: Fluorosis Studies: Baseline Data

1. Before-After Studies

Study Details	Inclusion/ Exclusion Criteria	Confounding Factors	Baseline Group Characteristics	Final Group Characteristics
Author (year) Chen (1993) **Country of study** China **Geographic location** Anquan (low F) and Hubei (high F) villages, Fenshun county, Guangdong Provinces **Year study started** 1984 **Year study ended:** 1991	**Inclusion criteria** Children aged 8-12 for dental fluorosis **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Author states that economic and living habits are similar in all study areas **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:* 3 (Natural) *Control:* 6 (Natural) **No of subjects:** *Group 1:* 211 *Control:* 101 **Age:** 8-12	**Fluoride level (ppm):** *Group 1:* 3.1(Natural) *Control:* 0.4(Natural) **No of subjects:** *Group 1:* 153 *Control:* 135 **Age:** 8-12
Author (year) Heifetz (1988) **Country of study** USA **Geographic location** 7 rural towns within 75 miles of each other in Illinois **Year study started** 1980 **Year study ended:** 1985	**Inclusion criteria** Children aged 8-10 and 13-15 Continuous residence in study community **Exclusion criteria** None stated	**Other sources of fluoride:** Food and drinks produced in fluoride areas **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:* 3.8-4.1(Natural) *Group 2:* 2.8-3.8(Natural) *Group 3: 2.1*(Natural) *Control:* 1.1(Natural) **No of subjects:** *Group 1:* 34 *Group 2:* 50 *Group 3:* 39 *Control:* 111 **Age:** 13-15	**Fluoride level (ppm):** *Group 1:* 3.8-4.1(Natural) *Group 2:* 2.8-3.8(Natural) *Group 3: 2.1*(Natural) *Control:* 1.1(Natural) **No of subjects:** *Group 1:* 29 *Group 2:* 47 *Group 3:* 23 *Control:* 94 **Age:** 13-15
Author (year) Kumar (1999) **Country of study** USA **Geographic location** Newburgh City (F), Newburgh Town (F 1984), New Windsor (non-F), Kingston (non-F) **Year study started** 1986 **Year study ended:** 1995	**Inclusion criteria** Children aged 7-14 Lifetime residents of study areas **Exclusion criteria** Not stated	**Other sources of fluoride:** Fluoridation + early brushing or tablet use, fluoride tablet + early brushing, early brushing, fluoride tablet all associated with increased risk of fluorosis scored very mild to severe compared to children exposed to none of these additional sources **Social class:** Not stated **Ethnicity:** No difference in odds of fluorosis in African-Americans compared to white and other races **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:* 1 (Artificial) *Group 2:* Low(Natural) *Group 3:* Low (Natural) *Control:* Low (Natural) **No of subjects:** *Group 1:* 459 *Group 2:* 289 *Group 3:* 134 *Control:* 425 **Age:** 7-14	**Fluoride level (ppm):** *Group 1:* 1(Artificial) *Group 2:* 1(Artificial) *Group 3: low*(Natural) *Control:* low(Natural) **No of subjects:** *Group 1:* 847 *Group 2:* 289 *Group 3:* 237 *Control:* 646 **Age:** 7-14

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/ Exclusion Criteria	Confounding Factors	Baseline Group Characteristics	Final Group Characteristics
Author (year) Selwitz (1995) **Country of study** USA **Geographic location** Kewanee (optimal), Monmouth (2x optimal), Abingdon, Elmwood (3x optimal), Bushneell, Ipava, Table Grove (4x optimal), Illinois **Year study started** 1980 **Year study ended:** 1990	**Inclusion criteria** Children aged 8-10 & 14-16 years Written parental consent Lifetime residents of study areas Continuous use of community water supply **Exclusion criteria** None stated	**Other sources of fluoride:** F-mouthrinses, topical applications **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:* 4 (Natural) *Group 2:* 3 (Natural) *Group 3:* 2 (Natural) *Control:* 1 (Natural) **Age:** 8-10 and 13-15 **No of subjects:** *Group 1:* 93 *Group 2:* 132 *Group 3:* 100 *Control:* 224	**Fluoride level (ppm):** *Group 1:* 4 (Natural) *Group 2:* 3 (Natural) *Group 3:* 2 (Natural) *Control:* 1 (Natural) **Age:** 8-10 and 13-15 **No of subjects:** *Group 1:* 77 *Group 2:* 117 *Group 3:* 105 *Control:* 258

2. Case-Control Studies

Study Details	Case and control selection	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data	
Author (year) Skotowski (1995) **Country of study** USA **Geographic location** Iowa **Year study started** 1991 **Year study ended**	**Case-Definition:** Dental fluorosis considered present if subject received TSIF score of 1 or more on any surface of criteria teeth - all permanent incisors and first molars. Emphasis placed on selecting cases with the most dental fluorosis to enhance contrast **Method of control selection:** Subjects undergoing same clinical examination as cases who did not meet the case definition - subjects exhibiting no dental fluorosis (TSIF = 0) on criteria teeth **Matching:** Sex and age within 2 years **Ratios of cases to controls:** 1:1	**Inclusion criteria** Children aged 8-17 Patients attending Iowa College of Dentistry's Paediatric clinic All permanent incisors and first molars present and erupted Parent who could provide consent and details of fluoride exposure accompanied child **Exclusion criteria** Children with fixed orthodontic appliances All permanent incisors and first molars present and erupted	**Other sources of fluoride:** Dietary fluoride supplement use, age began brushing with toothpaste, toothpaste usage in 8 years, mouthrinse usage, professional fluoride treatments **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Number of subjects** *Cases:* 54 *Controls 1:* 54 **Age:** *Cases:* 8-17 *Controls1 :* 8-17	**Exposure :** Fluoride exp. from drinking water in first 8 years of life, total ppm

C5: Fluorosis Studies: Baseline Data

3. Cross–sectional studies

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Adair (1999) **Country of study** USA **Geographic location** Warren County, Georgia **Year study started** Not stated	**Inclusion criteria** Children attending sole elementary and middle schools in study area **Exclusion criteria** Children whose homes were served with well water	**Other sources of fluoride:** Parents completed questionnaire regarding dentrifice use, home water source and current use of systemic fluoride supplements. All subjects received school water fluoridated at 0.5ppm **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.5-1.2 (Both) *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 82 *Control:* 113	**Age:** 8-10 and 11-13
Author (year) Al-Alousi (1975) **Country of study** England **Geographic location** Leeds (non-F) and Anglesey (F) **Year study started** 1973	**Inclusion criteria** Lifetime residents of study areas Children aged 12-16 **Exclusion criteria** Missing, fractured or crowned teeth Refusal to participate (1 school in Leeds)	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.9 (Artificial) *Control:* <0.01 (Natural) **No of subjects:** *Group 1:* 171 *Control:* 178	**Age:** 12-16
Author (year) Angelillo (1999) **Country of study** Italy **Geographic location** Area around Naples (F), area around Catanzaro (non-F) **Year study started** 1997	**Inclusion criteria** Lifetime residents of study areas (children only) Children aged 12 Used community water supply as main sources of drinking water **Exclusion criteria** Partially erupted teeth Orthodontic banding	**Other sources of fluoride:** Tooth brushing habits (frequency of tooth brushing), fluoride tablets, fluoride dentrifices **Social class:** Parents employment status **Ethnicity:** Not stated **Other confounding factors:** Sweet consumption, climate	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >=2.5 (Natural) *Control:* <=0.3 (Natural) **No of subjects:** *Group 1:* 553 *Control:* 461	**Age:** 12
Author (year) Azcurra (1995) **Country of study** Argentina **Geographic location** Sampacho (F) and Portena (non-F) in the Cordoba province **Year study started** 1993	**Inclusion criteria** Children aged 6,7 ,12 and 13 years at primary school **Exclusion criteria** None stated	**Other sources of fluoride:** Frequency of tooth brushing, **Social class:** Classified as high, medium, and low social class **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 9.05 (Natural) *Group 2:* 0.19 (Natural) **No of subjects:** *Group 1:* 100 *Group 2:* 100	**Age:** 6-7 and 12-13

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Booth (1991) **Country of study** England **Geographic location** Huddersfield (F), Dewsbury (non-F) **Year study started** 1989	**Inclusion criteria** All 3 year old white children Lifetime residents of study areas Positive informed consent **Exclusion criteria** Children who had moved out of the area Children who were ill or had died Children taking fluoride tablets	**Other sources of fluoride:** Children taking fluoride tablets excluded from study **Social class:** Areas matched using socio-economic data from the 1981 census and recent unemplyment data. Parents asked about occupation of head of household during interview **Ethnicity:** White children only **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* <0.3 (Natural) **No of subjects:** *Group 1:* 121 *Control:* 107	**Age:** 3
Author (year) Brothwell (1999) **Country of study** Canada **Geographic location** Wellington-Dufferin-Guelph Health Unit, Ontario **Year study started** 1997	**Inclusion criteria** Children resident in Wellington-Dufferin-Guelph Health Unit area Parental consent Children aged 7-8 years **Exclusion criteria** Children with non-erupted or insufficiently erupted central incisors Children absent on day of examination	**Other sources of fluoride:** Amount of toothpaste usually used, fluoride supplements, age started brushing, use of mouthwash, breast/bottle fed, whether toothpaste used when brushing **Social class:** Household income, highest level of education received **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >=0.7 (Natural) *Control:* <0.7 (Natural) **No of subjects:** *Group 1:* 72 *Control:* 646	**Age:** 7-8
Author (year) Butler (1985) **Country of study** USA **Geographic location** 16 Texas communities **Year study started** 1980	**Inclusion criteria** Lifetime residents of study areas, enrolled in grades 2-6 and 9-12 **Exclusion criteria** None stated	**Other sources of fluoride:** Fluoride toothpaste, fluoride drops, number of fluoride treatments **Social class:** Mother's education **Ethnicity:** White/Spanish/Black **Other confounding factors:** Home air conditioning, no of months breastfed, children in the family, mother's age at child's birth, Total dissolved solids in drinking water and zinc in drinking water, age	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.2-3.3 **No of subjects (min-max):** 23-359 **Sex** Approximately 1:1 ratio overall	**Age** 7-19
Author (year) Chen (1989) **Country of study** Taiwan **Geographic location** Shenkang Hsiang, Changwa **Year study started** 1987	**Inclusion criteria** Children aged 6-16 Lifetime residents of study areas Always used water wells as primary source of drinking water **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Author states that project communities have approximately the same location, climate, diet, food habits and customs, mean average daily temp = 25°C, range = 13-37°C	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 4.2-4.9 (Natural) *Group 2:* 2.1-2.8 (Natural) *Group 3:* 1.4-2.1 (Natural) *Group 4:* 0.7-1.4 (Natural) *Group 5:* 0.4-0.7 (Natural) *Control:* <0.4 (Natural) **No of subjects:** *Group 1:* 380 *Group 2:* 912 *Group 3:* 420 *Group 4:* 849 *Group 5:* 1660 *Control:* 851	**Age:** 6-16

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Clark (1993) **Country of study** Canada **Geographic location** Kelowna (F) and Vernon (non F) **Year study started** Not stated	**Inclusion criteria** Children in selected schools **Exclusion criteria** Children with fixed orthodontic appliances Missing anterior teeth	**Other sources of fluoride:** Not stated **Social class:** Two communities selected because of regional and socio-economic similarities. In each city list of primary school compiled in which schools were divided into high, medium, and low socioeconomic status. Schools were randomly selected from resulting strata **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.2 *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 621 *Control:* 510	**Age:** School aged
Author (year) Clarkson (1989) **Country of study** Ireland and England **Geographic location** Cork (low and high F - 2 separate areas) and Manchester (low F) **Year study started** Not stated	**Inclusion criteria** Children aged 8 and 15 **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.9-0.95 (Artificial) *Group 3:* low (Natural) *Control:* <0.3 (Natural) **No of subjects:** *Group 1:* 207 *Group 3:* 181 *Control:* 205	**Age:** 8 and 15
Author (year) Clarkson (1992) **Country of study** Ireland **Geographic location** Ireland **Year study started** 1984	**Inclusion criteria** Children aged 8 & 15 **Exclusion criteria** None stated	**Other sources of fluoride:** Increase in use of fluoride containing toothpaste and infant formula made with fluoridated water **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Problems of consistent levels in the fluoridated supply during the 1960s and early 1970s	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* high *Control:* low **No of subjects:** *Group 1:* 688 *Control:* 714	**Age:** 8 and 15
Author (year) Colquhoun (1984) **Country of study** New Zealand **Geographic location** New Zealand **Year study started** 1983	**Inclusion criteria** School children aged 7-12 years **Exclusion criteria** Children with mottling who were known to have grown up in areas different in fluoridation status from where they were examined	**Other sources of fluoride:** Fluoride toothpaste use accounted for 76% of toothpaste sales in New Zealand in 1980 **Social class:** Results stratified on social class - incidence of advanced dental fluorosis inversely related to social class but prevalence of dental fluorosis slightly higher in lower social class **Ethnicity:** Ethnic composition of study areas was similar except for higher proportion of Maori and Pacific Island people in the lower socio-economic areas **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* Low (Natural) **No of subjects:** *Group 1:* 1955 *Control:* 732	**Age:** 7-12

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Correia Sampaio (1999) **Country of study** Brazil **Geographic location** Rural areas of Paraiba **Year study started** 1997	**Inclusion criteria** Lifetime residents of study areas Children attending public schools (aged 6-11) **Exclusion criteria** Children who refused to be examined Those without permanent teeth Undetermined birth place	**Other sources of fluoride:** No topical or systemic fluoride programme implemented in schools. Children interviewed about oral health habits and use of toothpaste **Social class:** All study areas are of low socio-economic status **Ethnicity:** Not stated **Other confounding factors:** Nutritional status	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >1.0 (Natural) *Group 2:* 0.7-1.0 (Natural) *Control:* <0.7 (Natural) **No of subjects:** *Group 1:* 126 *Group 2:* 360 *Control:* 164	**Age:** 6-11
Author (year) Cutress (1985) **Country of study** New Zealand **Geographic location** Auckland, Frankton & Rodney **Year study started** Not stated	**Inclusion criteria** Children returning parental consent forms and completed questionnaires Lifetime residents of study areas Children aged 9 **Exclusion criteria** None stated	**Other sources of fluoride:** Ingestion of fluoride tablets **Social class:** Not stated **Ethnicity:** European (80% F, 84% non F), Polynesian (16%F, 11% non-F), Asian (2% F, 1% Non-F), Mixed (2% F, 4% non-F) **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.0 *Control:* <0.3 **No of subjects:** *Group 1:* 1078 *Control:* 680	**Age:** 9
Author (year) de Crousaz (1982) **Country of study** Switzerland **Geographic location** Friburg and Neuchatel (non-F), Bale-Ville (F) **Year study started** 1979	**Inclusion criteria** Not stated for control areas, for fluoride area only Lifetime residents included **Exclusion criteria** Children born outside Switzerland	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* Low (Natural) **No of subjects:** *Group 1:* 73 *Control:* 280	**Age:** 6-13
Author (year) Downer (1994) **Country of study** England, Scotland and Ireland **Geographic location** Dublin (F), North London, Edinburgh and Glasgow (non-F) **Year study started** Not stated	**Inclusion criteria** Children aged 12 years Lifetime residents of study areas **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.9ppm (Artificial) *Group 2:* Low (Natural) *Group 3:* Low (Natural) *Control:* Low (Natural) **No of subjects:** *Group 1:* 551 *Group 2:* 599 *Group 3:* 489 *Control:* 939	**Age:** 12
Author (year) Driscoll (1983) **Country of study** USA **Geographic location** 7 rural Illinois communities within 75 miles of each other **Year study started** 1980	**Inclusion criteria** Lifetime residents of study areas Children in grades 3-10 (age 8-16) Consumed public water Parental consent **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** <5% non white **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 3.84-4.07 (Natural) *Group 2:* 2.84-3.77 (Natural) *Group 3:* 2.08 (Natural) *Control:* 1.06 (Natural) **No of subjects:** *Group 1:* 136 *Group 2:* 192 *Group 3:* 143 *Control:* 336	**Age:** 8-16

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Eklund (1987) **Country of study** USA **Geographic location** Lordsburg (high-F), Deming (lower-F), New Mexico **Year study started** Not stated	**Inclusion criteria** Resident in study areas for the first 6 years of life Subjects aged approximately 30-60 years old Consumed city water supplies **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Areas similar on education and income level - number of years of education similar between areas **Ethnicity:** 89.6 % of Lordsburg subjects Hispanic, 74.2% of Deming Hispanic **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 3.5 (Natural) *Control:* 0.7 (Natural) **No of subjects:** *Group 1:* 164 *Control:* 151	**Age:** 27-65
Author (year) Ellwood (1995) **Country of study** Ireland and Wales **Geographic location** Chester (non-F), Bala (non-F), Anglesey (F), Cork (F) **Year study started** 1991	**Inclusion criteria** Lifetime residents of study areas (children only) Agreement to participate **Exclusion criteria** Fixed orthodontic appliances	**Other sources of fluoride:** Tooth brushing behaviour - age started brushing, weekly tooth brushing frequency, **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.7 (Artificial) *Group 2:* 0.9 *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 196 *Group 2:* 455 *Control:* 267	**Age:** 14
Author (year) Ellwood (1996) **Country of study** England and Wales **Geographic location** Chester and Bala (non-F), and Anglesey (F) **Year study started** 1991	**Inclusion criteria** Children in their 3rd year of secondary education Lifelong residents of study areas **Exclusion criteria** Children with fixed orthodontic appliances	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.7 (Artificial) *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 196 *Control:* 267	**Age:** 14
Author (year) Forrest (1956) **Country of study** England **Geographic location** West Mersey, Burnham-on-Crouch, Harwich (F), Saffron Walden and Malden West (non-F) **Year study started** 1954	**Inclusion criteria** Lifetime residents of study areas Children aged 12-14 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 5.8ppm (Natural) *Group 2:* 3.5ppm (Natural) *Group 3:* 2.0ppm (Natural) *Group 4:* 0.9ppm (Natural) *Group 5:* 0.1-0.2ppm (Natural) *Control:* 0.1ppm **No of subjects:** *Group 1:* 51 *Group 2:* 62 *Group 3:* 92 *Group 4:* 119 *Group 5:* 114 *Control:* 145	**Age:** 12-14

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Forrest (1965) **Country of study** Wales **Geographic location** Gwalchmai (F) and Bodafon (non-F), Anglesey **Year study started** 1963	**Inclusion criteria** Children aged 8 from a selection of schools **Exclusion criteria** Schools in Holyhead Schools in Llangefni and Beaumaris as changed supply from fluoridated to non-fluoridated in 1961	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* <=0.2 (Natural) **No of subjects:** *Group 1:* 91 *Control:* 130	**Age:** 8
Author (year) Gaspar (1995) **Country of study** Brazil **Geographic location** Piracicaba (F), Iracemapolis (non-F) **Year study started** Not stated	**Inclusion criteria** Children aged 10-14 years old Lifetime residents of study areas **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.7 *Control:* <0.2 (Natural) **No of subjects:** *Group 1:* 211 *Control:* 200	**Age:** 10-14
Author (year) Goward (1982) **Country of study** England **Geographic location** Two adjacent districts of Leeds with different fluoride levels **Year study started** 1979	**Inclusion criteria** Lifetime residents of study areas (children only) Children aged 5 **Exclusion criteria** Those who had received systemic or topical fluoride supplements	**Other sources of fluoride:** Children using systemic or topical fluoride supplements excluded from the study **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.9 (Artificial) *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 195 *Control:* 205	**Age:** 5
Author (year) Grimaldo (1995) **Country of study** Mexico **Geographic location** San Luis Potasi **Year study started** Not stated	**Inclusion criteria** Lifetime residents at same address Children aged 11-13 in selected schools Parental consent **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Local diet rich in calcium, reduces fluoride absorption	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >2.0 (Natural) *Group 2:* 1.2-2.0 (Natural) *Group 3:* 0.7-1.2 (Natural) *Control:* <0.7 (Natural) **No of subjects:** *Group 1:* 58 *Group 2:* 58 *Group 3:* 67 *Control:* 16	**Age:** 11-13

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Grobler (1986) **Country of study** South Africa **Geographic location** Nourivier (low F), Tweeriviere (high F) in North Western Cape province **Year study started** Not stated	**Inclusion criteria** Lifetime residents of study areas Children aged 12-13 **Exclusion criteria** None stated	**Other sources of fluoride:** Both communities had virtually no dental care or fluoride therapy **Social class:** Similar socio-economic status in two study areas (reported by authors) **Ethnicity:** Similar ethnicity in two study areas (reported by authors) **Other confounding factors:** Areas similar in nutrition and dietary habits (reported by authors) Temperature 27-32 °C	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 3.7 (Natural) *Control:* 0.62 (Natural) **No of subjects:** *Group 1:* 34 *Control:* 33	**Age:** 12-13
Author (year) Haavikko (1974) **Country of study** Finland **Geographic location** Espoo (low F), Elimaki (high F), Hanko (optimal F), Lohja (low F) **Year study started** 1969	**Inclusion criteria** Children who had been resident in study areas for the first 6 years of life Children aged 10-11 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Food sources of fluoride	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.08 (Natural) *Group 2:* 0.41 (Natural) *Group 3:* 0.11 (Natural) *Control:* 0.05 (Natural) **No of subjects:** *Group 1:* 57 *Group 2:* 62 *Group 3:* 34 *Control:* 51	**Age:** 10-11
Author (year) Heintze (1998) **Country of study** Brazil **Geographic location** Garca (F), Itrapolis (non-F), Sao Paulo state **Year study started** 1995	**Inclusion criteria** Subjects aged 5 - 24 years Subjects from all social strata Subjects that used tap water **Exclusion criteria** Not stated Subjects that used tap water	**Other sources of fluoride:** Subjects asked about use of toothpaste or mouthrinses containing fluoride **Social class:** Cities similar in socio-economic and socio-demographic conditions, subjects from all social strata included **Ethnicity:** Not stated **Other confounding factors:** Garca altitude = 526, mean temp = 22°C, pop. = 41351; Itapolis: altitude = 491m, mean temp = 23°C, pop.=30 111	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.9 (Artificial) *Control:* 0.02 (Natural) **No of subjects:** *Group 1:* 430 *Control:* 348	**Age:** 5-24
Author (year) Heller (1997) **Country of study** USA **Geographic location** National survey of oral health of US school children **Year study started** 1986	**Inclusion criteria** Lifetime residents of study areas Aged 7-17 Completion of survey (parents) **Exclusion criteria** None stated	**Other sources of fluoride:** Written questionnaire included question regarding child's use of fluoride drops, fluoride tablets, professional topical fluoride treatments and school fluoride rinses **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Results standardised to age and sex distribution of US schoolchildren who participated in survey	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >1.2 *Group 2:* 0.7-1.2 *Group 3:* 0.3-0.7 *Control:* <0.3 **No of subjects:** *Group 1:* 772 *Group 2:* 6728 *Group 3:* 1793 *Control:* 6239	**Age:** 7-17

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Hong (1990) **Country of study** Taiwan **Geographic location** Chung-hsing New village (F) and Tsao-tun (non-F) **Year study started** Not stated	**Inclusion criteria** Children aged 6-15 Resident in village since initiation of fluoridation **Exclusion criteria** Children who migrated from other areas during study period	**Other sources of fluoride:** Not stated **Social class:** Two communities alike in social and living customs **Ethnicity:** Not stated **Other confounding factors:** Two areas have virtually identical climates, only 3km apart	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.6 (Artificial) *Control:* 0.08 (Natural) **No of subjects:** *Group 1:* 3066 *Control:* 4087	**Age:** 6-15
Author (year) Ibrahim (1995) **Country of study** Sudan **Geographic location** Treit El Biga (low F), Abu Gronn (F) **Year study started** 1992	**Inclusion criteria** At least one erupted permanent maxillary incisor Lifetime residents of study areas Age 7-16 **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Author states that areas have more or less the same socio-economic background **Ethnicity:** Author states that areas have more or less the same ethnic background **Other confounding factors:** Altitude = 300m for both areas and mean temp = 25-35 °C. In low-fluoride area boys had significantly more fluorosis than girls	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.56 (Natural) *Control:* 0.25 (Natural) **No of subjects:** *Group 1:* 58 *Control:* 55	**Age:** 7-16
Author (year) Ismail (1990) **Country of study** Canada **Geographic location** Public and Private schools in Trois Rivieres (F) and Sherbrooke (non-F), Quebec **Year study started** 1987	**Inclusion criteria** Children randomly selected from private and public schools separately Children aged 11-17 Resident in study areas for more than 10 years **Exclusion criteria** None stated	**Other sources of fluoride:** Fluoride tablet use around 10-15% in F areas and 60-70% in non-F area **Social class:** Stratified on school type: private or public (authors state private school likely to be higher social class) **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.0 (Natural) *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 437 *Control:* 499	**Age:** 11-17
Author (year) Jackson (1975) **Country of study** Wales **Geographic location** Anglesey (F), Bangor and Caernarfon (non-F) **Year study started** 1974	**Inclusion criteria** Lifetime residents of study areas Continuous use of public water supply School children aged 15 years Parental consent **Exclusion criteria** Children who had ever received fluoride tablets	**Other sources of fluoride:** Children who had received fluoride tablets excluded **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.9 (Artificial) *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 88 *Control:* 97	**Age:** 15

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Jackson (1999) **Country of study** USA **Geographic location** Connersville (non-F)m Brownsburg (optimal-F), Lowell (high-F), Indiana **Year study started** 1992	**Inclusion criteria** Lifetime residents of study areas Consumed public water from birth or supply with comparable water level Children aged 7-14 Parental and personal consent **Exclusion criteria** Factors in medical history that would contraindicate a dental examination Full mouth fixed orthodontic appliance	**Other sources of fluoride:** In non-F areas 58% use fluoride supplements, in optimal-F area 20 % use F supplements and in high-F area 9% use F supplements. Also fluoride from mouthrinses, gels, other topical applications **Social class:** Not stated **Ethnicity:** Approximately 2% non-white (stated for baseline survey) **Other confounding factors:** Areas all in same climatic zone	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 4.0 (Natural) *Group 2:* 1.0 (Natural) *Control:* 0.2 (Natural) **No of subjects:** *Group 1:* 105 *Group 2:* 122 *Control:* 129	**Age:** 7-10 and 11-14
Author (year) Jolly (1971) **Country of study** India **Geographic location** The Punjab **Year study started** Not stated	**Inclusion criteria** School children **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.7 – 9.4 **No of subjects (min-max):** Not stated	**Age** 5-15
Author (year) Kunzel (1976) **Country of study** Cuba **Geographic location** La Salud (low F), Mir (medium F), San Augustin and Blanqizal (high F) **Year study started** 1973	**Inclusion criteria** Children resident in study areas **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.3-3.6 (Natural) *Group 2:* 1.1-1.6 (Natural) *Group 3:* 0.6-0.8 (Natural) *Control:* 0.1 (Natural) **No of subjects:** *Group 1:* 37 *Group 2:* 26 *Group 3:* 66 *Control:* 145	**Age:** 9-10
Author (year) Leverett (1986) **Country of study** USA **Geographic location** Rochester, NY and surrounding area(F), four towns in western New York state (Non-F) **Year study started** 1981	**Inclusion criteria** Children resident in study areas Children aged 12-17 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Did not have to be Lifetime residents	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.0 *Control:* <=0.3 **No of subjects:** *Group 1:* 729 *Control:* 564	**Age:** 12-17

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Levine (1989) **Country of study** England **Geographic location** Leeds (non-F), Birmingham (F) **Year study started** 1987	**Inclusion criteria** Lifetime residents of study areas (children only) Schools with catchment areas inside study areas Children aged 9-10 **Exclusion criteria** Asian and West Indian children Non-continuous residents Teeth with fractures, restorations	**Other sources of fluoride:** Children who had received fluoride supplements at any time excluded **Social class:** Schools selected that served similar socio-economic populations (social class groups 3,4,5) **Ethnicity:** Asian and West Indian children excluded **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 483 *Control:* 600	**Age:** 9-10
Author (year) Lin (1991) **Country of study** China **Geographic location** Langan and Jiayi (non-F), Xinyuan (F) **Year study started** Not stated	**Inclusion criteria** School children aged 7 to 14 years **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Low socioeconomic status, mean annual income of about 200 yuan **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.88 (Natural) *Control:* 0.34 (Natural) **No of subjects:** *Group 1:* 250 *Control:* 256	**Age:** 7 to 14
Author (year) Masztalerz (1990) **Country of study** Poland **Geographic location** Militsch (non-F), Breslau (F), Neisse (high-F) **Year study started** Not stated	**Inclusion criteria** Lifetime residents of study areas Children aged 12 years **Exclusion criteria** Children who had not yet changed all their primary dentition	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Fluoride in the air - high in Greifenberg	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 4-7 (Natural) *Group 2:* 0.7-0.9 (Artificial) *Control:* <0.2 (Natural) **No of subjects:** *Group 1:* 101 *Group 2:* 106 *Control:* 112	**Age:** 12
Author (year) Mazzotti (1939) **Country of study** Mexico **Geographic location** All areas in Mexico **Year study started** 1938	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.0-4.0 **No of subjects (min-max):** 20-300	**Age** Not stated
Author (year) McInnes (1982) **Country of study** South Africa **Geographic location** Kenhardt (F), Keimoes (non-F), North western Cape Province **Year study started** Not stated	**Inclusion criteria** Lifetime residents of study area Pre-school children aged 1-5 **Exclusion criteria** None stated	**Other sources of fluoride:** Majority of babies were breastfed - would not be exposed to fluoride from water used in preparation of infant formula. **Social class:** Not stated, but experimental and control groups were similar (parents were land or railway labourers) **Ethnicity:** All children same ethnic origin - European-African-Malay origin **Other confounding factors:** Same climatic conditions in both areas	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.2-4.1 (Natural) *Control:* 0.2 (Natural) **No of subjects:** *Group 1:* 331 *Control:* 177	**Age:** 1-5

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Mella (1992) **Country of study** Chile **Geographic location** Students attending 2 boarding institutions in Santiago, who lived in areas throughout Chile **Year study started** Not stated	**Inclusion criteria** Students at boarding institution, exposure estimated from home fluoride level Lived for first 6 years in home town **Exclusion criteria** Children who could not remember the areas in which they spent the first 6 years of their life	**Other sources of fluoride:** Not stated **Social class:** Distribution of subjects by high, moderate, low social class - no significant differences between fluoride groups **Ethnicity:** Not stated **Other confounding factors:** Years lived in city of birth	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >0.3 (Natural) *Control:* <=0.3 (Natural) **No of subjects:** *Group 1:* 46 *Control:* 72	**Age:** 18-22
Author (year) Mella (1994) **Country of study** Chile **Geographic location** Iquique (F), Santiago (non-F), Valparaiso-Vina (F), Temuco (low-F) **Year study started** 1983	**Inclusion criteria** 4 schools in study areas **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** 2 schools in each area, one from low social class, one from medium/high social class, results presented separately by social class **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.2 (Natural) *Group 2:* 0.0 (Natural) *Group 3:* 1.0 (Artificial) *Control:* 0.3 (Natural) **No of subjects:** *Group 1:* 171 *Group 2:* 203 *Group 3:* 125 *Control:* 194	**Age:** 12
Author (year) Milsom (1990) **Country of study** England **Geographic location** Nantwich (F), Northwich (non-F) **Year study started** 1988	**Inclusion criteria** Children aged 8 years attending state maintained schools Lifetime residents of study areas Parental consent **Exclusion criteria** Parishes not bounded on all sides by parishes with optimally fluoridated water for fluoride areas	**Other sources of fluoride:** Age at which tooth brushing first began **Social class:** Measured by parental occupation - social class makeup of study areas almost identical (data presented in paper) **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Artificial) *Control:* <0.3 (Natural) **No of subjects:** *Group 1:* 91 *Control:* 131	**Age:** 8
Author (year) Nanda (1974) **Country of study** India **Geographic location** Lucknow **Year study started** Not stated	**Inclusion criteria** Lifetime residents of study areas Children from 103 urban & 66 rural schools All permanent teeth (excluding third molars) present Consumed water from one source since birth **Exclusion criteria** None stated	**Other sources of fluoride:** Dietary fluoride intake **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Climate	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >1.21 (Natural) *Group 2:* 0.81-1.2 (Natural) *Group 3:* 0.41-0.8 (Natural) *Control:* 0-0.4 (Natural) **No of subjects:** *Group 1:* 66 *Group 2:* 134 *Group 3:* 499 *Control:* 710	**Age:** 6-17

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Nunn (1992) **Country of study** England **Geographic location** Hartlepool, Newcastle and Middlesborough **Year study started** 1989	**Inclusion criteria** Lifetime residents of study areas Children in selected schools aged 15-16 years **Exclusion criteria** Children with fractured incisor teeth, orthodontic bracket or surface otherwise obscured	**Other sources of fluoride:** Not stated **Social class:** Occupation of head of household recorded **Ethnicity:** Ethnicity recorded but no expansion on variable **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1-1.3 *Group 2:* 1 *Control:* 0.2 **No of subjects:** *Group 1:* 361 *Group 2:* 356 *Control:* 376	**Age:** 15-16
Author (year) Nunn (1994) **Country of study** Sri-Lanka and England **Geographic location** Sri Lanka and North East England **Year study started** 1990	**Inclusion criteria** Lifetime residents of study areas (England only) Children aged 12 Parental consent (England only) **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated, but expected higher use of toothpaste in higher SE groups **Social class:** Children divided into high and low social class **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** <0.1-1.1 **No of subjects (min-max):** 40-175 **Sex** Slightly more females examined than males (1.1:1) but no significant differences in opacities recorded by gender so data combined	**Age** 12
Author (year) Ockerse (1941) **Country of study** South Africa **Geographic location** Upington, Kenhardt and Pofadder **Year study started** 1939	**Inclusion criteria** Children attending schools in study areas Children aged 6-17 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Study areas at same altitude, same climate, similar countryside and vegetation, differences in drinking water composition discussed	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.46 (av) *Group 2:* 6.8 *Control:* 0.38 **No of subjects:** *Group 1:* 183 *Group 2:* 318 *Control:* 767	**Age:** 6-17
Author (year) Ray (1982) **Country of study** India **Geographic location** Rustampur and Ledhupur, 2 adjacent village in Varanasi District **Year study started** Not stated	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Study areas similar in respect to demographic and socio-economic characteristics **Ethnicity:** Not stated **Other confounding factors:** Villages similar in respect to geoclimatic characteristics	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* >2 (Natural) *Group 2:* 1-2 (Natural) *Control:* <1 (Natural) **No of subjects:** *Group 1:* 75 *Group 2:* 471 *Control:* 964	**Age:** Not stated

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Riordan (1991) **Country of study** Australia **Geographic location** Perth (F) and Bunbury (non-F), Western Australia **Year study started** 1989	**Inclusion criteria** Children born in 1978 Children attending government schools in study areas Parental consent **Exclusion criteria** Subjects with amelogenesis imperfecta or orthodontic banding	**Other sources of fluoride:** Questionnaire investigated periods and duration of use of fluoride supplements, use of fluoride toothpaste, included age at which use of toothpaste commenced, whether child swallowed toothpaste **Social class:** Schools assigned socio-economic score - no significant difference in scores between study areas **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.8 (Artificial) *Control:* <0.2 (Natural) **No of subjects:** *Group 1:* 338 *Control:* 321	**Age:** 12
Author (year) Rugg-Gunn (1997) **Country of study** Saudi Arabia **Geographic location** Jeddah (low F), Riyadh (moderate F) and Quassim (high F) adjacent rural areas with similar water supplies to rural area selected **Year study started** 1992	**Inclusion criteria** Lifetime residents of study areas Boys aged 14 Parental consent **Exclusion criteria** Photographs which failed to show whole buccal surface Out of focus photographs	**Other sources of fluoride:** Not stated **Social class:** Schools grouped according to the socio-economic status of residential areas in the urban community. Family income and parental education measured using questionnaire **Ethnicity:** Not stated **Other confounding factors:** Nutritional status	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.7 (Natural) *Group 2:* 0.8 (Natural) *Control:* <0.3 (Natural) **No of subjects:** *Group 1:* 437 *Group 2:* 542 *Control:* 560	**Age:** 14
Author (year) Russell (1951) **Country of study** USA **Geographic location** Colorado Springs (F), Bolder (non-F), Colorado **Year study started** 1950	**Inclusion criteria** White native residents listed in school census record for 1920, 1930 or 1940 and as resident in current city directory Mothers living in study area at time of birth Aged 20-44 Residence and usage of local water unbroken except for periods not exceeding 60 days during calcification and eruption of permanent teeth **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Workers in two communities followed similar occupations and had similar average salaries **Ethnicity:** Native born white 98% of Boulder pop. And 96% of Colorado Springs pop **Other confounding factors:** Colorado Springs 3 times size of Bolder, similar altitude and climate, neither population ageing nor young., both are highly literate, water systems similar	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.5 (Natural) *Control:* <0.1 (Natural) **No of subjects:** *Group 1:* 385 *Control:* 155	**Age:** 20-44
Author (year) Rwenyonyi (1998) **Country of study** Uganda **Geographic location** 4 areas of Uganda located at different altitudes **Year study started** Not stated	**Inclusion criteria** Lifetime residents of study areas **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Mother's interviewed about water intake and food habits of child during early childhood Altitude	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.5 (low alt) (Natural) *Group 2:* 2.5 (high alt) (Natural) *Group 3:* 0.5 (low alt) (Natural) *Control:* 0.5 (high alt) (Natural) **No of subjects:** *Group 1:* 67 *Group 2:* 64 *Group 3:* 81 *Control:* 82	**Age:** 10-14

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Rwenyonyi (1999) **Country of study** Uganda **Geographic location** Kasese (low F), Kisoro (high F) **Year study started** 1996	**Inclusion criteria** Children aged 10-14 Lifetime residents of study areas Consumed drinking water from same source for first 6 years of life Parental consent **Exclusion criteria** None stated	**Other sources of fluoride:** Fluoride exposure from liquid estimated by daily liquid intake - subjects from fluoride area had higher intake of water, consumed more boiled water and consumed less tea than subjects from control area, higher consumption of fluoride from Trona in control group **Social class:** Most families were small scale farmers and all appeared to be of similar social class **Ethnicity:** All children were ethnic Bantu Africans from the Bafumbria and Bakonjo tribes **Other confounding factors:** Vegetarianism (associated with fluorosis), altitude (results presented separately for different altitudes) - no association found between altitude and fluorosis	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.5 (alt= 2800m) (Natural) *Group 2:* 2.5 (alt = 1750 m) (Natural) *Group 3:* 0.5 (alt = 2200m) (Natural) *Control:* 0.5 (alt = 900m) (Natural) **No of subjects:** *Group 1:* 155 *Group 2:* 163 *Group 3:* 82 *Control:* 81	**Age:** 11-14
Author (year) Scheinin (1964) **Country of study** Finland **Geographic location** Artjarvi, Askola, Elimaki, Litti, Myrskyla, Parikkala, Taipalsaari, Valkeala, Vehkalahti **Year study started** Not stated	**Inclusion criteria** Children aged 11 **Exclusion criteria** Children resident in area for < 6 years Fluoride concentration of drinking water unknown	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.0-1.6 **No of subjects (min-max):** 172-211 **Sex** male to female ratios approximately 1:1 for all exposure groups	**Age** 11
Author (year) Segreto (1984) **Country of study** USA **Geographic location** 16 Texas communities **Year study started** Not stated	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** 0.3-4.3 (Natural) **No of subjects:** 23 - 361	**Age:** 7-12 & 14-18
Author (year) Sellman (1957) **Country of study** Sweden **Geographic location** Malmo (low F), Simirshamn, Astorp and Nyvang (High F) **Year study started** 1953	**Inclusion criteria** Children aged 11-14 **Exclusion criteria** Children missed due to illness Children under 11 1/2 and over 14 1/2	**Other sources of fluoride:** All children received yearly systematic treatment by the School Dental Service **Social class:** Socio-economic distribution of Lifetime residents was similar in all study areas, however distribution was different for non-continuous residents as compared to continuous residents **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.0 (Natural) *Group 2:* 1.0-1.3 (Natural) *Group 3:* 1.3 (Natural) *Control:* 0.3-0.5 (Natural) **No of subjects:** *Group 1:* 25 *Group 2:* 55 *Group 3:* 69 *Control:* 145	**Age:** 12-14

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Selwitz (1998) **Country of study** USA **Geographic location** Kewanee (F), Holdrege and Broken Bow (non-F) **Year study started** 1990	**Inclusion criteria** Lifetime residents of study areas Parental consent **Exclusion criteria** None stated	**Other sources of fluoride:** Type of toothpaste currently used and used before age 6, use of dietary fluoride supplements, receipt of professionally applied fluoride treatments **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Private well water use	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 *Group 3:* <0.3 *Control:* <0.3 **No of subjects:** *Group 1:* 260 *Group 3:* 128 *Control:* 107	**Age:** 8-10 and 13-16
Author (year) Spadaro (1955) **Country of study** Italy **Geographic location** Barcelona, Pozzo di Gotto, Sicily **Year study started** 1954	**Inclusion criteria** Children attending schools in study areas **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.4-1.9 **No of subjects (min-max):** 37-727	**Age** Children aged 6-11
Author (year) Stephen (1999) **Country of study** Scotland **Geographic location** Burghead, Findhorn & Kinloss (F), and Buckie & Portessie (Non-F) **Year study started** 1998	**Inclusion criteria** Lifetime or school lifetime fluoridated subjects Parental consent **Exclusion criteria** None stated	**Other sources of fluoride:** Use of fluoride dentifrice, fluoride drops, fluoride tablets, age at which brushing commenced (from parental questionnaire) **Social class:** Socio-economic profiles did not differ between professional, skilled and manual backgrounds between the fluoridated and non-fluoridated study areas **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1 (Natural) *Control:* Low (Natural) **No of subjects:** *Group 1:* 55 *Control:* 136	**Age:** 8-12
Author (year) Szpunar (1988) **Country of study** USA **Geographic location** Cadillac (non-F) , Hudson, Redford, Richmond (F) - Michigan **Year study started** Not stated	**Inclusion criteria** Lifetime residents of study areas Children aged 6-12 **Exclusion criteria** None stated	**Other sources of fluoride:** Use of F supplements, dental attendance, time interval since last dental visit, age began brushing (parent & child), age at start of F rinsing, feeding method in 1st year of life, **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.2 *Group 2:* 1.0 *Group 3:* 0.8 *Control:* 0.0 **No of subjects:** *Group 1:* 43 *Group 2:* 249 *Group 3:* 133 *Control:* 131	**Age:** 6-12

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Venkateswarlu (1952) **Country of study** India, Switzerland **Geographic location** Villages in the Visakhapatnam area (India), 3 villages in Switzerland **Year study started** Not stated	**Inclusion criteria** Children aged 3-14 Areas with <= 2ppm F in water supplies **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.3-1.4 **No of subjects (min-max):** 38-130	**Age** 3-14
Author (year) Vignarajah (1993) **Country of study** Antigua **Geographic location** Urban and rural areas in Antigua **Year study started** Not stated	**Inclusion criteria** Children aged 12-14 Lifetime residents of study areas **Exclusion criteria** Restored or fractured tooth surfaces	**Other sources of fluoride:** Toothpaste swallowing when younger, consumption of mixed sources of water, fluoride mouth rinses **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.6-1 *Control:* 0.1-0.3 **No of subjects:** *Group 1:* 123 *Control:* 154	**Age:** 12-14
Author (year) Villa (1998) **Country of study** Chile **Geographic location** Rancagua (non-F), Santiago (low-F), La Serena (medium F), San Felipe & Iquique (High F) **Year study started** 1996	**Inclusion criteria** Lifetime residents of study areas Children aged 7,12 and 15 in selected schools in study areas **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Children selected from schools graded according to socio-economic status to give similar socio-economic distribution in each study area **Ethnicity:** Not stated **Other confounding factors:** Temperature	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.07 *Group 2:* 0.21 *Group 3:* 0.55 *Group 4:* 0.93 *Group 5*: 1.10 **No of subjects:** *Group 1:* 150 *Group 2:* 203 *Group 3:* 158 *Group 4:* 155 *Group 5:* 132	**Age:** 15
Author (year) Wang (1993) **Country of study** China **Geographic location** Hotan, Kaxgar and Aksu, in south Xinjiang **Year study started** 1991	**Inclusion criteria** Children (age not stated) **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.58 (Natural) *Group 2:* 1.85-2.00 (Natural) *Group 3:* 0.48 (Natural) *Group 4:* 2.55 (Natural) *Group 5:* 0.43 (Natural) *Group 6:* 0.46 (Natural) *Control:* 0.43 (Natural) **No of subjects:** Not stated	**Age:** Not stated

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Wang (1999) **Country of study** China **Geographic location** Xindiliang Village (high F), Shiligetu Village (lower F) **Year study started**	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2-4 (Natural) *Control:* 1.3 (Natural) **No of subjects:** *Group 1:* 12 *Control:* 46	**Age:** 10-19
Author (year) Warnakulasuriya (1992) **Country of study** Sri Lanka **Geographic location** Four geographic areas at same altitude & temp from 4 districts in Sri Lanka (Galewala, Wariyapola, Kekirawa & Rambukkana) **Year study started** 1986	**Inclusion criteria** Lifetime residents of study areas Children aged 14 **Exclusion criteria** Children who lived more than 15 miles from school Children absent on day of examination	**Other sources of fluoride:** Fluoride containing toothpaste or other fluoride therapies had not been used by or on these children during time of development of primary dentition. Tea consumption high. **Social class:** Wide ranges of socio-economic differences not expected **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** <0.39->=1.0 **No of subjects (min-max):** 27-211	**Age** 14
Author (year) Wenzel (1982) **Country of study** Danish **Geographic location** Ry (non-F), Naestved (F), and Greve (F) **Year study started** Not stated	**Inclusion criteria** Lifetime residents of study areas Girls aged 12-15 **Exclusion criteria** Children with orthodontic appliances	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 2.4 *Group 2:* 1.0 *Control:* <0.2 **No of subjects:** *Group 1:* 127 *Group 2:* 50*:* *Control:* 116	**Age:** 12-15
Author (year) Zheng (1986) **Country of study** China **Geographic location** Guangzhou and Fangcun (F), Fushan and Zhaoqing (non-F) **Year study started** Not stated	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 0.6-1.2 (Artificial) *Group 2:* 0.4-1.2 (Artificial) *Group 3:* 0.2 (Natural) *Control:* 0.2 (Natural) **No of subjects:** *Group 1:* 600 *Group 2:* 300 *Group 3:* 450 *Control:* 300	**Age:** 12-17

C5: Fluorosis Studies: Baseline Data

Study Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Characteristics	
Author (year) Zimmermann (1954) **Country of study** USA **Geographic location** Aurora, Illinois (F), Montgomery & Prince Georges counties, Maryland (non-F) **Year study started** 1953	**Inclusion criteria** Lifetime residents of study areas White children aged 12-14 **Exclusion criteria** Children who had left study areas for periods of time other than for holidays	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** White children only **Other confounding factors:** Not stated	**Fluoride level (artificially or naturally fluoridated):** *Group 1:* 1.2 (Natural) *Control:* 0.2 (Natural) **No of subjects:** *Group 1:* 352 *Control:* 220	**Age:** 12-14

C6: Fluorosis Studies: Individual Study Results

1. Before-After Studies

Study Details	Method in which Indices were Applied	Age	Exposure Group	Fluoride Level	Number of Subjects	Fluorosis Score							
						0	1	2	3	4	5	6	7
Chen 1993	Not stated	8-12	**Baseline**										
	Teeth type:		*Group 1:*	3	211								
	Not stated		*Group 4:*	6	101								
	Index:		**Final**										
	% prevalence		*Group 1:*	3.1	153								
			Group 4:	0.4	135								
Heifetz 1988	All permanent tooth surfaces	13-15	**Baseline**										
	Teeth type:		*Group 1:*	3.8-4.1	34	36.9	25.6	16.7	18.6	0.3	1.3	0.1	0.5
	Permanent		*Group 2:*	2.8-3.8	50	54.0	21.6	13.7	9.6	0.2	0.7	0	0.1
	Index:		*Group 3:*	2.1	39	61.7	25.4	7.8	5.0	0	0.1	0	0
	TSIF		*Group 4:*	1.1	111	88.6	9.1	1.5	0.8	0	0	0	0
			Final										
			Group 1:	3.8-4.1	29	22.5	30.8	18.8	22.1	0.5	3.9	0	
			Group 2:	2.8-3.8	47	30.8	34.9	18.2	13.6	0.3	1.2	0.10	
			Group 3:	2.1	23	33.5	32.5	18.6	13.8	0.3	1.3	0	
			Group 4:	1.1	94	70.7	21.6	4.9	2.8	0.1	0		
Kumar 1999	Not stated	7-14	**Baseline**										
	Teeth type:		*Group 1:*	1	459	78.4	13.7	4.8	2.2	0.9	0	0	0
	Not stated		*Group 2:*	Low	289	73.0	13.1	8.7	4.2	1.0	0	0	0
	Index:		*Group 3:*	Low	134	76.1	9.7	8.2	3.7	2.2	0	0	0
	Dean		*Group 4:*	Low	425	81.4	11.3	4.5	2.1	0.7	0	0	0
			Final										
			Group 1:	1	847	62.9	18.5	12.8	5.3	0.4	0.1	0	
			Group 2:	1	289	71.6	13.5	10.0	2.8	1.7	0.3	0	
			Group 3:	low	237	75.5	10.1	8.9	5.1	0.4	0	0	
			Group 4:	low	646	81.4	7.4	7.7	3.1	0.3	0		

C6: Fluorosis Studies: Individual Study Results

Study Details	Method in which Indices were Applied	Age	Exposure Group	Fluoride Level	Number of Subjects	Fluorosis Score							
						0	1	2	3	4	5	6	7
Selwitz 1995	Percent distribution of TSIF scores across subjects & % surfaces fluorosed **Teeth type:** Permanent **Index:** TSIF	14-16	**Baseline**										
			Group 1:	4	34	36.9	25.6	16.7	18.6				2.2
			Group 2:	3	50	54	21.6	13.7	9.6				1.1
			Group 3:	2	39	61.7	25.4	7.8	5				0.1
			Group 4:	1	111	88.6	9.1	1.5	0.8				0.0
			Final										
			Group 1:	4	20	33.3	20.8	18.0	24.8				
			Group 2:	3	48	53.3	21.0	12.4	10.3				
			Group 3:	2	29	52.5	22.9	13.1	11.0				
			Group 4:	1	91	84.7	13.4	1.6	0.2				
	Percent distribution of TSIF scores across subjects & % surfaces fluorosed **Teeth type:** Permanent **Index:** TSIF	8-10	**Baseline**										
			Group 1:	4	59	30.3	28.5	17.1	19.7				4.4
			Group 2:	3	82	48.5	30.6	10.9	8.1				1.9
			Group 3:	2	61	53.0	33.0	6.9	6.7				0.4
			Group 4:	1	113	81.2	14.8	2.3	1.6				0.1
			Final										
			Group 1:	4	57	38.4	24.9	15.3	18.3				
			Group 2:	3	69	45.3	25.1	14.5	12.2				
			Group 3:	2	76	45.0	24.7	14.2	14.7				
			Group 4:	1	167	81.4	14.4	2.9	1.3				

2. Case-Control Studies

Study Details	Outcome	Number of Subjects per Group	Exposures	Level of Exposure in Cases	Level of Exposure in Group 4 1
Skotowski (1995)	Dental fluorosis considered present if subject received TSIF score of 1 or more on any surface of criteria teeth - all permanent incisors and first molars. Emphasis placed on selecting cases with the most dental fluorosis to enhance contrast	54	**Exposure 1:** Fluoride exp. from drinking water in first 8 years of life, total ppm	5.6 (2.4)	3.1 (2.7)

3. Cross–Sectional Studies

a. Al-Alousi Index

Study Details	Method in which Indices were Applied	Age	Exposure Group	Fluoride Level	Number of Subjects	% Fluorosis	Fluorosis Score					
							A	B	C	D	E	F
Goward 1982	Dental fluorosis (% prevalence) **Teeth type:** Permanent	5	*Group 1:* *Group 4*	0.9 <0.1	195 205	9 9	0.61 0.39	0.27 0.26	0.14 0.39	0.34 0.39	0 0	0.48 0.39
Jackson 1975	Dental fluorosis (% prevalence) **Teeth type:** Permanent	15	*Group 1:* *Group 4*	0.9 <0.1	88 97	35 37	3.3 4.0	3.3 2.2	0 0	0.4 0	0.3 0.4	0.6 1.1

C6: Fluorosis Studies: Individual Study Results

b. Developmental Defects of Enamel Index (DDE Index)

Study Details	Method in which Indices were Applied	Age	Exposure Group	Number of Subjects	Fluoride Level	Fluorosis Score							
						0	1	2	3	4	5	6	7
Nunn 1992	Mouth prevalence **Teeth type:** Permanent	15-16	*Group 1:*	361	1-1.3	16.1	41.8	0.6	16.9	35.7	17.7	0.05	2.5
			Group 2:	356	1	21.1	42.0	1.7	17.7	36.6	7.4	0.3	1.4
			Group 4	376	0.2	39.9	48.7	1.9	3.7	18.6	4.8	0.0	2.1

c. Modified Developmental Defects of Enamel Index (modified DDE)

Study Details	Method in which Indices were Applied	Age	Exposure Group	Number of Subjects	Fluoride Level	Fluorosis Score			
						0	1	2	3
Booth 1991	All teeth **Teeth type:** Primary	3	*Group 1:*	121	1	NS	4	1	32
			Group 2:	107	<0.3	NS	2	3	34
			Group 3:						
			Group 4						
Clarkson 1989	% of children with fluorosis presented - The labial surfaces of eight index impermanent teeth and the buccal and lingual surfaces of all erupted permanent teeth **Teeth type:** Permanent	15	*Group 1:*	90	0.9-0.95	37	26	10	2
			Group 2:	84	low	31	27	6	1
			Group 4	80	<0.3	38	35	5	1
		8	*Group 1:*	117	0.9-0.95	33	24	12	1
			Group 2:	97	low	42	41	2	4
			Group 4	125	<0.3	30	24	7	0
Cutress 1985	Mouth prevalence, upper incisors (labial surfaces) only **Teeth type:** Permanent	9	*Group 1:*	1078	1.0	36	19	19	4
			Group 4	680	<0.3	27	18	8	4
Downer 1994	10 index teeth **Teeth type:** Not stated	12	*Group 1:*	551	0.9ppm	61.9	29.2	16.7	2.2
			Group 2:	599	Low	72.6	25.4	6.9	2.2
			Group 3:	489	Low	59.1	32.7	28.6	13.3
			Group 4	939	Low	69.5	26.6	27.7	5.4
Milsom 1990	Buccal surfaces of all upper and lower permanent central and lateral incisors together with the first permanent molars **Teeth type:** Permanent	8	*Group 1:*	91	1	60	28	48	2
			Group 4	131	<0.3	44	31	22	4
Rugg-Gunn 1997	Buccal surface of all teeth **Teeth type:** Permanent	14	*Group 1:*	437	2.7	93	6	93	75
			Group 2:	542	0.8	82	44	77	22
			Group 4	560	<0.3	75	12	71	16

C6: Fluorosis Studies: Individual Study Results

d. Dean's Index

Study Details	Method in which Indices were Applied	Age	Exposure Group	Number of Subjects	Fluoride Level	Normal	Questionable	Very Mild	Mild	Mod	Severe	CFI (SD)
Angelillo 1999	All fully erupted permanent teeth. Two teeth in mouth showing most advanced signs of fluorosis, child assigned score of lesser affected teeth **Teeth type:** Permanent	12	*Group 1:* *Group 4:*	553 461	>=2.5 <=0.3	32.4 82.1	23.0 12.3	27.7 4.8	14.3 0.4	2.4 0.0	0.4 0.4	0.76(0.77) 0.14(0.37)
Butler (1985)	Not stated – only present CFI	7-19	Group1 Group2 Group3 Group4 Group5 Group6 Group7 Group8 Group9 Group10 Group11 Group12 Group13 Group14 Group15 Group16	103 223 125 359 211 187 128 23 108 300 197 169 91 111 67 190	0.2 0.2 0.3 0.7 1 1 1.1 1.8 1.9 1.9 2.1 2.1 2.3 2.3 2.4 3.3							0 0 0 1 0 0.59 0.33 1.41 1.36 1.06 1.37 1.35 1.33 1.2 2.02 1.89
Chen 1989	Not stated **Teeth type:** Not stated	6-16	*Group 1:* *Group 2:* *Group 3:* *Group 4:* *Group 5:* *Group 4:*	380 912 420 849 1660 851	4.2-4.9 2.1-2.8 1.4-2.1 0.7-1.4 0.4-0.7 <0.4	12.1 27.7 43.8 67.7 86.2 89.7	7.6 16.6 17.1 12.2 7.3 4.9	18.2 18.1 18.6 13.3 3.6 4.1	48.2 31.6 16.2 5.6 2.7 1.3	12.6 5.7 4.3 0.8 0.1 0	1.3 0.3 0 0.2 0 0	1.61 1.08 0.72 0.34 0.13 0.09
Clarkson 1992	Not stated **Teeth type:** Permanent	8	*Group 1:* *Group 4:*	459 372	High Low	94 98.1	5 1.9	1 0	0 0	0 0	0 0	- -
		15	*Group 1:* *Group 4:*	229 342	High Low	94.7 99.4	4 0.6	0.9 0	0.4 0	0 0	0 0	- -
Driscoll 1983	Two teeth most affected by fluorosis, if not equally affected take the least affected of the 2. Teeth had to have erupted to line of occlusion **Teeth type:** Permanent	8-16	*Group 1:* *Group 2:* *Group 3:* *Group 4*	136 192 143 336	3.84-4.07 2.84-3.77 2.08 1.06	12.5 22.9 18.2 56.0	15.4 26.0 28.7 29.5	16.9 15.1 23.1 7.4	25.0 19.8 16.8 4.8	7.4 7.8 8.4 1.8	22.8 8.3 4.9 0.6	1.88 1.25 1.16 0.39
Eklund 1987	Most severe form of dental fluorosis scored for 2 or more teeth **Teeth type:** Permanent	27-65	*Group 1:* *Group 4*	164 151	3.5 0.7	0 68.9	0 15.2	0.6 11.3	0.6 1.3	22.6 3.3	76.2 0	
Forrest 1956	Not stated **Teeth type:** Permanent	12-14	*Group 1:* *Group 2:* *Group 3:* *Group 4:* *Group 5:* *Group 4*	51 62 92 114 119 145	5.8 3.5 2.0 0.1-0.2 0.9 0.1	4 8 34 70 81 100	16 10 22 14 10 0	12 29 32 3 6 0	2 16 4 2 2 0	35 26 8 11 1 0	31 11 0 0 0 0	2.5 1.88 0.7 0.45 0.17 0.00

C6: Fluorosis Studies: Individual Study Results

Study Details	Method in which Indices were Applied	Age	Exposure Group	Number of Subjects	Fluoride Level	Normal	Questionable	Very Mild	Mild	Mod	Severe	CFI (SD)
Forrest 1965	Not stated **Teeth type:** Permanent	8	*Group 1:* *Group 4*	91 130	1 <=0.2	88 92	9 2	3 4	0 1	0 2	0 0	
Grimaldo 1995	Classified according to 2 most severely affected teeth **Teeth type:** Permanent	11-13	*Group 1:* *Group 2:* *Group 3:* *Group 4*	58 58 67 16	>2.0 1.2-2.0 0.7-1.2 <0.7	1.72 8.62 13.43 31.25		1.72 12.1 22.4 18.8	13.8 27.6 37.3 25.0	20.7 24.1 14.9 6.3	62.07 27.59 11.94 18.75	
Grobler 1986	Not stated **Teeth type:** Permanent	12-13	*Group 1:* *Group 4*	34 33	3.7 0.62	0 9.1	2.9 33.3	0 30.3	5.9 21.2	17.6 3.1	73.6 3.0	4.5 1.8
Haavikko 1974	For overall %, % children with enamel defects given. For Dean's score % fluorosis of each defect in tooth population given **Teeth type:** Permanent	10-11	*Group 1:* *Group 2:* *Group 3:* *Group 4*	57 62 34 51	1.08 0.41 0.11 0.05	34.6 66.1 87.3 72.0	25.7 15.6 3.3 16.8	13.3 11.0 3.3 7.4	4.2 0.0 0.8 1.1	11.4 2.8 0.2 0.4	10.9 5.0 5.2 4.2	
Heller 1997	Not stated **Teeth type:** Permanent	7-17	*Group 1:* *Group 2:* *Group 3:* *Group 4*	772 6728 1793 6239	>1.2 0.7-1.2 0.3-0.7 <0.3	28.1 33.6 47.4 59.8	30.5 36.5 31.0 26.6	27.2 22.5 17.3 10.7	7.0 5.8 3.1 2.4	5.3 1.3 1.2 0.4	2.0 0.0 0.0 0.1	0.8 0.58 0.43 0.3
Hong 1990	Classified according to 2 most severely affected teeth **Teeth type:** Permanent	6-15	*Group 1:* *Group 4*	3066 4087	0.6 0.08	81.3 95.8	11.0 2.9	5.8 0.9	1.9 0.4	0 0	0 0	0.15 0.03
Ibrahim 1995	Fluorosis scoring based on maxillary central incisors. If there was a difference between the right and left incisor the higher of the two scores was given. Questionable category not used **Teeth type:**	7-16	*Group 1:* *Group 4*	58 55	2.56 0.25	0 9	0 0	15 53	31 29	47 7	7 2	2.44 1.4
Kunzel 1976	Labial surfaces **Teeth type:** Permanent	9-10	*Group 1:* *Group 2:* *Group 3:* *Group 4*	37 26 66 145	2.3-3.6 1.1-1.6 0.6-0.8 0.1	19 65.4 84.8 91.1	21.6 27.0 9.2 8.9	18.9 3.8 4.5 0	5.4 3.8 1.5 0	29.7 0 0 0	5.4 0 0 0	1.51 0.25 0.12 0.04
Leverett 1986	Only posterior teeth displaying bilaterally symmetrical evidence of classical fluorosis **Teeth type:** Permanent	12-17	*Group 1:* *Group 4*	729 564	1.0 <=0.3	73.1 95.6		22.6 2.7	3.2 1.1	1.1 0.6		
Mella 1992	Not stated **Teeth type:** Permanent	18-22	*Group 1:* *Group 4*	46 72	>0.3 <=0.3	47.8 44.4		34.8 37.6	6.5 12.5	10.9 5.5		0.76 0.81
Mella 1994	Criteria of Russell (2 most severely affected teeth, choose least severely affected one) **Teeth type:** Permanent	12	*Group 1:* *Group 2:* *Group 3:* *Group 4*	171 203 125 194	2.2 0.0 1.0 0.3	38.6 80.8 44 96.8	14.0 9.3 30.4 0	33.3 7.3 21.6 2.1	13.5 1.5 2.4 2.1	0.6 0.5 1.6 0.0	0 0 0 0	
Nanda 1974	Not stated **Teeth type:** Permanent (excluding third molars)	6-17	*Group 1:* *Group 2:* *Group 3:* *Group 4*	66 134 499 710	>1.21 0.81-1.2 0.41-0.8 0-0.4	18 24 38 38	16 35 38 50	26 18 18 11	17 16 5 1	23 7 1 0	0 0 0 0	

C6: Fluorosis Studies: Individual Study Results

Study Details	Method in which Indices were Applied	Age	Exposure Group	Number of Subjects	Fluoride Level	Normal	Questionable	Very Mild	Mild	Mod	Severe	CFI (SD)
Ray	Not stated	Not	*Group 1:*	75	>2	62.7	16	8	6.7	6.7		
1982	**Teeth type:**	stated	*Group 2:*	471	1-2	64.2	18.9	9.6	4.0	3.4		
	Permanent		*Group 4*	964	<1	78.2	14.0	4.4	2.0	1.6		
Russell	Fluorosis rating by individuals	20-44	*Group 1:*	385	2.5	16.4		45.2	28.3	8.3	1.8	
1951	**Teeth type:**		*Group 4*	155	<0.1	100		0	0	0	0	
	Permanent											
Scheinin	Not stated – only present CFI	11	Group1	172	0.00-0.10							0.33
(1964)			Group2	206	0.11-0.39							0.41
			Group3	199	0.4-0.99							0.68
			Group4	195	1.00-1.59							0.95
			Group5	211	1.60 -							0.29
Segreto	All erupted teeth showing 50% or more of buccal & /	7-12 &	*Group 1:*	90	2.7	8.9	8.9	42.2	33.3	6.7	0.0	1.33
1984	or lingual surface of the crown examined for	14-18	*Group 2:*	170	2.7	20.0	4.1	32.4	30.0	13.5	0.0	1.35
	fluorosis. Classification on severest form of mottling		*Group 3:*	200	2.7	2.5	7.0	52.0	34.5	4.0	0.0	1.37
	for 2/> teeth. Age groups have been grouped together		*Group 4:*	223	0.3	81.2	10.3	8.5	0.0	0.0	0.0	0.14
	in the study.		*Group 5:*	190	4.3	0.5	4.7	32.6	30.5	31.1	0.5	1.91
	Teeth type:		*Group 6:*	113	3.1	12.4	10.6	44.2	28.3	4.4	0.0	1.19
	Permanent		*Group 7:*	67	2.9	4.5	1.5	19.4	41.8	32.8	0.0	2.02
			Group 8:	103	0.3	60.2	31.1	6.8	1.9	0.0	0.0	0.26
			Group 9:	301	2.5	20.9	13.3	38.2	24.2	3.3	0.0	1.03
			Group 10:	109	2.3	17.4	4.6	37.6	25.7	14.7	0.0	1.35
			Group 11:	23	2.3	21.7	4.3	21.7	39.1	13.0	0.0	1.41
			Group 12:	361	0.4	92.1	5.6	2.4	0.0	0.0	0.0	0.05
			Group 13:	128	1.4	52.3	32.0	14.8	0.8	0.0	0.0	0.32
			Group 14:	187	1.3	39.0	28.3	21.4	10.2	1.1	0.0	0.59
			Group 15:	211	1.3	49.8	21.3	22.3	5.7	0.9	0.0	0.47
			Group 16:	361	1.0	39.6	21.1	36.6	2.5	0.3	0.0	0.53
Sellman	The severest form of dental fluorosis recorded for 2	12-14	*Group 1:*	25	1.0	60	20	16	0	4	0	
1957	or more teeth		*Group 2:*	55	1.0-1.3	62	31	7	0	0	0	
	Teeth type:		*Group 3:*	69	1.3	65	29	6	0	0	0	
	Permanent		*Group 4*	145	0.3-0.5	78	18	3	1	0	0	
Villa (1998)	Not stated – only present CFI	15	Group1	150	0.07							0.16
			Group2	203	0.21							0.36
			Group3	158	0.55							0.37
			Group4	155	0.93							1.01
			Group5	132	1.10							0.14
Wenzel	Not stated	12-15	*Group 1:*	127	2.4	5	26	39	15	8	7	1.33
1982	**Teeth type:**		*Group 2:*	50	1.0	14	60	26				0.56
	Permanent		*Group 3:*	116	<0.2	96	4					0.02
			Group 4									
Zheng	Not stated	12-17	*Group 1:*	600	0.6-1.2	42.7	28.7	13.7	6.5	5..5	2.9	
1986	**Teeth type:**		*Group 2:*	300	0.4-1.2	38.3	16.7	11.7	11.7	11.3	10.3	
	Not stated		*Group 3:*	450	0.2	82	8.9	6.4	1.6	1.1	0	
			Group 4	300	0.2	97	1.3	1.0	0.7	0	0	
Zimmermann	Not stated	12-14	*Group 1:*	352	1.2	57	26	15	2			
1954	**Teeth type:**		*Group 4*	220	0.2	100	0	0	0			
	Permanent											

C6: Fluorosis Studies: Individual Study Results

e. Thylstrup and Fejerskov Index

Study Details	Method in which Indices were Applied	Age	Exposure Group	Fluoride Level	Number of Subjects	Fluorosis Score									
						0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	8	9
Correia Sampaio 1999	Buccal faces of upper central incisors and lower first molars, teeth>1/3 crown visible **Teeth type:** Permanent	6-11	*Group 1:* *Group 2:* *Group 4*	>1.0 0.7-1.0 <0.7	126 360 164	29 39 70	37 34 27	10 16 4	14 8 1	7 2	4 1	1 0	1 0		
de Crousaz 1982	Vestibular faces of permanent incisors and the occlusal surfaces of molars 16 and 46. The most severely affected incisor was scored **Teeth type:** Permanent	6-13	*Group 1:* *Group 4*	1 Low	73 280	63 73	25 17	9 8	3 2	0 0	0 0	0 0	0 0	0 0	0 0
Gaspar 1995	Vestibular surfaces of all teeth **Teeth type:** Permanent	10-14	*Group 1:* *Group 4*	0.7 <0.2	211 200	79 98	4 0	14 1	2 0.5	0 0	0 0.5	0 0	0 0	0 0	0 0
Riordan 1991	Fluorosis present if fluorosis-like markings present and bilaterally symmetrical on upper anterior teeth. Labial surface of upper left incisor teeth scored using T & F **Teeth type:** Permanent	12	*Group 1:* *Group 4*	0.8 <0.2	338 321	59.8 67.0	29.0 25.5	8.9 6.9	2.4 0.6						

f. Tooth Surface Index of Fluorosis (TSIF)

Study Details	Method in which Indices were Applied	Age	Exposure Group	Fluoride Level	Number of Subjects	Fluorosis Score							
						0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Clark 1993	Not stated **Teeth type:** Permanent	School aged	*Group 1:* *Group 4:*	1.2 <0.1	621 510	35 45	55 48	7 5	<1 <1	<1 <1	1 <1	<1 0	
Jackson 1999	Surfaces had to be fully erupted to be examined **Teeth type:** Permanent	7-10	*Group 1:* *Group 2:* *Group 4:*	4.0 1.0 0.2	57 77 81	2 29 72	35 49 22	16 17 4	28 5 3	11 0 0	9 0 0		
		11-14	*Group 1:* *Group 2:* *Group 4:*	4.0 1.0 0.2	48 45 48	0 47 60	29 47 31	19 0 8	31 7 0	13 0 0	8 0 0	0 0 0	
Levine 1989	Central incisors **Teeth type:** Permanent	9-10	*Group 1:* *Group 4:*	1 <0.1	483 600	16.6 38.8	60.4 50.7	13.7 6.2	4.6 1.2	2.7 1.8	1.0 0.5	0.4 0.5	

C6: Fluorosis Studies: Individual Study Results

Study Details	Method in which Indices were Applied	Age	Exposure Group	Fluoride Level	Number of Subjects	Fluorosis Score							
						0	1	2	3	4	5	6	7
Selwitz 1998	% distribution of TSIF scores for participants, and % surfaces fluoresced **Teeth type:** Permanent	13-16	*Group 1:* *Group 2:* *Group 4:*	1 <0.3 <0.3	93 24 60	85.0 97.9 90.9	13.1 1.9 8.1	1.6 0.2 0.7	0.3 0.0 0.4				
		8-10	*Group 1:* *Group 2:* *Group 4:*	1 <0.3 <0.3	167 104 47	81.4 81.7 82.3	14.4 12.6 15.2	2.8 3.4 2.2	1.3 2.3 0.3				
Vignarajah 1993	All tooth surfaces, excluding 2nd molars **Teeth type:** Permanent	12-14	*Group 1:* *Group 4:*	0.6-1 0.1-0.3	123 154	84.1 95.2	8.3 3.9	4.3 0.5	3.3 0.4				

g. % Prevalence of Fluorosis

Study Details	Method in which Indices were Applied	Age	Exposure Group Number of Subjects	Fluoride Level	Number of Subjects	% Prevalence
Adair 1999	Dean's method used for identifying fluorosis, "questionable" teeth included with "normal" category of fluorosis **Teeth type:** Not stated	11-13	*Group 1:* *Group 4:*	0.5-1.2 <0.1	17 34	46 21
		8-10	*Group 1:* *Group 4:*	0.5-1.2 0.1	65 79	57 53
Al-Alousi 1975	At least one mottled incisor. Distribution of mottled teeth according to Al-Alousi index also presented. **Teeth type:** Permanent	12-16	*Group 1:* *Group 4:*	0.9 <0.01	171 178	39 52
Azcurra 1995	Not stated **Teeth type:** Both	6-7	*Group 1:* *Group 2:*	9.05 0.19	50 50	52 0
		12-13	*Group 1:* *Group 2:*	9.05 0.19	50 50	78 0
Brothwell 1999	Incisors **Teeth type:** Permanent	7-8	*Group 1:* *Group 4:*	>=0.7 <0.7	72 646	31 22
Colquhoun 1984	Erupted permanent teeth **Teeth type:** Permanent	7+	*Group 1:* *Group 4:*	1 Low	1955 732	25 4
Ellwood 1995	At least on tooth affected with mild hyper-mineralisation (TF>0) **Teeth type:** Permanent	14	*Group 1:* *Group 2:* *Group 4:*	0.7 0.9 <0.1	196 455 267	62 54 36
Ellwood 1996	Upper permanent first premolars, canines, lateral incisor and central incisors, classified according to highest score recorded for different groups of index teeth **Teeth type:** Permanent	14	*Group 1:* *Group 4:*	0.7 <0.1	196 267	54 36

C6: Fluorosis Studies: Individual Study Results

Study Details	Method in which Indices were Applied	Age	Exposure Group Number of Subjects	Fluoride Level	Number of Subjects	% Prevalence
Heintze 1998	All permanent teeth **Teeth type:** Permanent	5-24	*Group 1:* *Group 4:*	0.9 0.02	430 348	13 2
Ismail 1990	Percentage of students with one or more teeth affected by fluorosis (assessed by TSIF index) **Teeth type:** Permanent **Public School**	11-17	*Group 1:* *Group 4:*	1.0 <0.1	222 251	46 31
	Private School		*Group 1:* *Group 4:*	1.0 <0.1	215 248	58 30
Jolly (1971)	Not stated	5-15		0.7-9.4	Not stated	2-70: increased with increasing water fluoride concentration
Lin 1991	Not stated **Teeth type:** Not stated	7-14	*Group 1:* *Group 2:*	0.88 0.34	250 256	20.8 16
Masztalerz 1990	Not stated **Teeth type:** Permanent	12	*Group 1:* *Group 2:* *Group 4:*	4-7 0.7-0.9 <0.2	101 106 112	82 60 1
Mazzotti (1939)	Not stated	Not stated		0-4.0	20-300	0-100: increased with increasing water fluoride concentration
McInnes 1982	Primary teeth, patient assigned score according to most severely affected tooth - Dean's 0.5, 1 & 2 combined so only % fluorosis presented **Teeth type:** Permanent	1-5	*Group 1:* *Group 4:*	2.2-4.1 0.2	331 177	51 0
Nunn (1994)	Not stated	12	Group1 Group2 Group3 Group4 Group5 Group6	<0.1 0.4-0.6 0.9-1.1 <0.1 0.4-0.6 0.9-1.1	 71 40 57 175 117 147	85 82 98 61 60 69
Ockerse 1941	Number of children with mottled enamel **Teeth type:** Permanent	6-17	*Group 1:* *Group 2:* *Group 4:*	2.46 (av) 6.8 0.38	183 318 767	93 82 15
Rwenyonyi 1998	Buccal surfaces of all permanent teeth **Teeth type:** Permanent **High Altitude**	10-14	*Group 1:* *Group 4:*	2.5 0.5	64 82	84 45
	Low Altitude		*Group 1:* *Group 4:*	2.5 0.5	67 81	67 25

C6: Fluorosis Studies: Individual Study Results

Study Details	Method in which Indices were Applied	Age	Exposure Group Number of Subjects	Fluoride Level	Number of Subjects	% Prevalence
Rwenyonyi 1999	Tooth prevalence of fluorosis calculated based on fluorosis on incisors and first molars **Teeth type:** Not stated **Altitude = 2200-280**	11-14	*Group 1:* *Group 4:*	2.5 0.5	155 82	76 39
	Altitude = 900-1750m		*Group 1:* *Group 4:*	0.5 2.5	163 81	61 21
Szpunar 1988	% with fluorosis (TSIF>=1) **Teeth type:** Permanent	6-12	*Group 1:* *Group 2:* *Group 3:* *Group 4:*	1.2 1.0 0.8 0.0	43 249 133 131	51 49 32 12
Venkateswarlu (1952)	Not stated	3-14		0.3-1.4	38-130	0-56: increased with increasing water fluoride concentration
Wang 1993	Not stated **Teeth type:** Not stated	Not stated	*Group 1:* *Group 2:* *Group 3:* *Group 4:* *Group 5:* *Group 6:* *Group 4:*	1.58 1.85-2.00 0.48 2.55 0.43 0.46 0.43	Not stated	47 69 28 91 23 17 22
Wang 1999	Not stated **Teeth type:** Permanent	10-19	*Group 1:* *Group 4:*	2-4 1.3	12 46	100 15
Warnakulasuriya (1992)	Not stated	14	Group1 Group2 Group3 Group4 Group5	<0.39 0.4-0.59 0.6-0.79 0.8-0.99 >1.0	211 49 32 27 61	51 66 74 80 31

C7: Bone Studies: Baseline Data

1. Cohort and Ecological Studies

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Arnala (1986) **Country of study** Finland **Geographic location** Kuopio, Kotka, and Hamina **Year study started** Not stated **Study length (years)** **Not stated** **Study design:** Ecological	**Outcome:** Hip fracture **Method of outcome assessment:** Case reports from Kuopio, University Central Hospital, Kotka Central Hospital, and Hamina Hospital	**Inclusion criteria** Age 50 years or more **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Water fluoride level *Group 1:* >1.5 (Natural) *Group 2:* 1-1.2 (Artificial) *Control:* <0.3 (Natural) **No of subjects:** *Group 1:* 112903 *Group 2:* 156303 *Control:* 108871 **Age** Over 50
Author (year) Bernstein (1966) **Country of study** England **Geographic location** Mott and Hettinger (high-F), Grafton, Carrington and New Rockford (high F) **Year study started** Not stated **Study length (years)** Not stated **Study design:** Ecological	**Outcome:** Percentage of subjects with one or more collapsed vertebrae **Method of outcome assessment:** Cases identified from x-rays taken of the lateral lumbar area of the spine	**Inclusion criteria** Outpatients willing to participate in study **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Areas both mainly farming and small businesses - author states that populations sampled believed to be of various socio-economic categories such as income and social stratification **Ethnicity:** Mainly German and Scandinavian descent - author states that populations sampled believed to be of similar racial origin **Other confounding factors:** Areas similar climate and geography, both populations had been living in their respective areas for most of their lives, especially in high fluoride area	**Exposure:** Water fluoride level *Group 1:* 4-5.8 (Natural) *Control:* <=0.3 (Natural) **No of subjects:** *Group 1:* 300 *Control:* 715 **Age** Over 45

C7: Bone Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Cauley (1995) **Country of study** USA **Geographic location** Most women from Westmoreland and Washington counties, Pennsylvania **Year study started** Not stated **Study length (years)** Not stated **Study design:** Prospective cohort	**Outcome:** Wrist fracture Hip fracture Nonspine fractures Incident vertebral fractures Oesteoporotic fracture - fractures of hip, wrist, humerus, pelvis, toe, leg, hand, clavicle, rib **Method of outcome assessment:** Participants contacted every 4 months by postcard/telephone to ask if had sustained fracture or fall. If fracture reported participants interviewed, obtained copy of radiographic report which had to specifically mention occurrence of acute fracture	**Inclusion criteria** Women recruited at the Study of Osteoporotic Fractures Pittsburgh clinic Women aged >=65 **Exclusion criteria** Black women	**Other sources of fluoride:** Not stated **Social class:** Education>12 years **Ethnicity:** Black women excluded **Other confounding factors:** Age, BMI, Calcium intake, alcohol, coffee, tea & cola intake, live alone, leave neighborhood >=once per day, self reported health status, health status compared with 1 year ago, functional status, smoke (current/ever), walk for exercise, history of osteoporosis	**Exposure:** Number of years of exposure to fluoridated public water supplies (mean exposed level = 1.0, unexposed = 0.15) *Group 1:* >20 *Group 2:* 11-20 *Group 3:* 1-10 *Control:* 0 **No of subjects:** *Group 1:* 192 *Group 2:* 198 *Group 3:* 438 *Control:* 1248 **Age (mean)** *Group 1:* 71.6 *Group 2:* 70.7 *Group 3:* 71.2 *Control:* 70.8
Author (year) Cooper (1990) **Country of study** England and Wales **Geographic location** Health regions in England and Wales excluding the four Thames regions **Year study started** 1978 **Study length (years)** 4 **Study design:** Ecological	**Outcome:** Hip fracture **Method of outcome assessment:** Cases identified through discharge records	**Inclusion criteria** Patients discharged from hospital with a diagnosis of hip fracture Patients admitted as emergencies Patients aged 45 years and over **Exclusion criteria** Patient who had undergone a revision of arthroplasty	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Discharge rates directly standardised by age and sex within five year age groups using the 1981 population. Association of hip fracture with calcium content of water also investigated.	**Exposure:** Water fluoride level, 38 study areas, levels ranged from 0.05 – 0.93 ppm **No of subjects:** 4121 men, 16,272 women (number of subjects = number of cases per year) **Age** Over 45 years
Author (year) Daniel (1969) **Country of study** USA **Geographic location** Lubbock, Texas (F), Hattiesburg, Mississippi(non-F) **Year study started** 1968 **Study length (years)** 1 **Study design:** Retrospective Cohort	**Outcome:** Stapedal otosclerosis **Method of outcome assessment:** Subjects diagnosed by otolaryngologists and surgically confirmed.	**Inclusion criteria** Patients of otolaryngologists between Jan 1 1968 and November 15 1968 Lifetime residents of study areas **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Median school age completed, % completed 4+ years high school, % unemployed, % employed in manufacturing, % in white collar occupations, median income, occupation **Ethnicity:** % foreign born **Other confounding factors:** Total population and % native population, otolaryngologists in two areas similar in practices	**Exposure:** Water fluoride levels *Group 1:* 1.9 (Natural) *Control:* <0.6 (Natural) **No of subjects:** *Group 1:* 726 *Control:* 810 **Age** *Group 1:*range: 1 - 88, mean: 34.3 for males and 37.4 for females *Control:* range: 1- 85, mean: 32.6 for males and 40.3 for females

C7: Bone Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Danielson (1992) **Country of study** USA **Geographic location** Brigham city (F), Logan and Cedar City (non-F), Utah **Year study started** 1984 **Study length (years)** 6 **Study design:** Ecological	**Outcome:** Hip fracture requiring hospitalisation **Method of outcome assessment:** Utah Peer Review Organisation maintains computerised database of all Medicare admissions and discharges in Utah since 1984, data on hip fracture incidence and age-specific populations obtained from this register and used to calculate hip fracture rates	**Inclusion criteria** Patients aged >=65 Medicare recipients **Exclusion criteria** Hip fractures listed as other than first diagnosis second hip fractures) ICD 9 code for surgical revision of hip fracture Patients with metastatic cancer	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Smoking (no significant differences between fluoridated and non-fluoridated counties)	**Exposure:** Level of water fluoridation *Group 1:* 1 (Artificial) *Control:* <0.3 (Natural) **Year of fluoridation:** 1966, 3 year interruption **No of subjects:** Not stated **Age** Over 65 years of age
Author (year) Jacobsen (1992) **Country of study** USA **Geographic location** Throughout USA **Year study started** 1984 **Study length (years)** 3 **Study design:** Ecological	**Outcome:** Discharge for hip fracture defined as ICD code 820.0 - 820.9 **Method of outcome assessment:** Discharge records of HCFA for persons covered under Medicare and discharges from VA hospitals for persons classified as above, denominator data provided by Bureau of Census - county estimates of 1985 pop. Of white women by 5 year age group & then 85+	**Inclusion criteria** White men and women aged >65 Patients covered under Medicare programme or discharged from VA hospitals Counties with centralised water system **Exclusion criteria** ZIP code from Puerto Rico or missing or country of residency was out of scope Alaska, Hawaii and Virginia	**Other sources of fluoride:** Not stated **Social class:** % of 65+ pop below poverty level, % land in farms, **Ethnicity:** White men and women only **Other confounding factors:** Latitude centroid, water hardness index (measure of calcium carbonate), January sunlight	**Exposure:** % of population served with fluoridated water (level at which considered fluoridated not stated), fluoridated if changed from <10% to more than 66% within 3 year period *Group 1:* >60% *Control:* <10% **No of subjects:** *Group 1:* 40 000 000 *Control:* 30 000 000 **Age** Over 65 measured in 5 year age groups
Author (year) Jacqmin-Gadda (1998) **Country of study** France **Geographic location** Gironde and Dordogne **Year study started** Not stated **Study length (years)** Not stated **Study design:** Prospective cohort	**Outcome:** Non-hip fractures Hip fracture **Method of outcome assessment:** Subjects visited at 1, 3 and 5 years after baseline and interviewed about fractures, also completed postal survey on fractures that required hospitalisation, Physician required to confirm fracture when details weren't clear.	**Inclusion criteria** Subjects included in a previous cohort study (Paquide study on ageing) Random sample of subjects selected from the study in a 3-step procedure with stratification by age, sex, and size of urban unit **Exclusion criteria** Subjects who used medication that may be prescribed as a treatment for osteoporosis	**Other sources of fluoride:** Not stated **Social class:** Subjects asked information on profession in questionnaire, Dordogne is a more rural area **Ethnicity:** Not stated **Other confounding factors:** Age, sex, BMI, tobacco consumption, spirit and wine consumption, current participation in sports, visual and auditory impairment, psychotropic and non psycotropic drug use	**Exposure:** Weighted mean (takes into account level of fluoride and duration of use of water supply & hourly flow of each supply) water fluoride level *Group 1:* >0.25 *Group 2:* 0.11-0.25 *Control:* 0.05-0.11 **No of subjects:** Not stated **Age** 74.8 years (mean)

C7: Bone Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Jacqmin-Gadda (1995) **Country of study** France **Geographic location** Gironde and Dordogne **Year study started** Not stated **Study length (years)** Not stated **Study design:** Ecological	**Outcome:** Any fractures Hip fracture **Method of outcome assessment:** Data collected on fracture history at time of baseline survey	**Inclusion criteria** Men and women aged 65 years or more enrolled in a previous cohort study (the Paquide study on ageing) Subjects living at home **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** age, sex, BMI, smoking and physical activity	**Exposure:** Water level *Group 1:* 0.11-1.83 *Control:* <0.11 **No of subjects:** Not stated **Age** 65+
Author (year) Karagas (1996) **Country of study** USA **Geographic location** USA **Year study started** 1986 **Study length (years)** 4 **Study design:** Ecological	**Outcome:** Fracture of the proximal humerus Ankle fracture Fracture of the distal forearm Hip fracture (ICD9 820-820.9) **Method of outcome assessment:** Cases identified from hospital discharge records or emergency room visit diagnoses	**Inclusion criteria** US Medicare population Patients aged 65 to 89 years Areas with municipal water supplies that could be classified according to fluoridation status **Exclusion criteria** Non-white races Patients enrolled in Medicare with Rail board eligibility Patients not enrolled in both hospital and outpatient programmes Patients enrolled in health maintenance organisations	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Subjects classified according to county of residence. Proportion of residents receiving fluoridated water at levels >=0.7ppm *Group 1:* 67% (both) *Control:* <10% (Natural) **Year of fluoridation:** **No of subjects:** Not stated **Age** 65-89
Author (year) Karjalainen (1982) **Country of study** Finland **Geographic location** Kuopio (F) & surrounding low fluoride areas **Year study started** 1974 **Study length (years)** 3 **Study design:** Retrospective Cohort	**Outcome:** Incidence of otosclerosis **Method of outcome assessment:** Patients identified through same otolaryngological clinic	**Inclusion criteria** Patients treated in same otolaryngological clinic **Exclusion criteria** Patients who lived for a long time outside the study area	**Other sources of fluoride:** Author states no significant sources of fluoride other than drinking water **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Water fluoride content *Group 1:* 0.95-0.99 (Artificial) *Control:* 0.02-0.32 (Natural) **No of subjects:** *Group 1:* 71180 *Control:* 181833 **Age** Mean age 39.6 in F area, 38.8 in low F area

C7: Bone Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Kelsey (1971) **Country of study** USA **Geographic location** Connecticut **Year study started** 1960 **Study length (years)** 6 **Study design:** Ecological	**Outcome:** Incidence of slipped epiphysis **Method of outcome assessment:** Use of diagnostic indexes in all general hospitals in and near the state and in Newington hospital for children operating room log books.	**Inclusion criteria** Connecticut residents Aged <25 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Water fluoride level *Group 1:* 1 (Artificial) *Control:* low(Natural) **Year of fluoridation:** Mainly 1960, few small areas fluoridated earlier **No of subjects:** *Group 1:* 967972 *Control:* 3168269 **Age** < 25 years old
Author (year) Korns (1969) **Country of study** USA **Geographic location** Newburgh (F), Kingston (non-F), New York State **Year study started** 1964 **Study length (years)** 2 **Study design:** Ecological	**Outcome:** Wrist fracture Cervical, intertrochanteric or subcapital hip fractures **Method of outcome assessment:** Identification of cases from hospital records, confirmed from X-ray records	**Inclusion criteria** Residents of study areas since 1945 White only for hip fracture data Residents over 40 years old **Exclusion criteria** Subtrocanteric, or shaft of the femur fractures Pathological features: related to metastatic cancer Second fractures	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** White residents only included for hip fracture, all races included for wrist fracture **Other confounding factors:** % pop resident in study areas since 1945 approximately same in both areas (+-60%)	**Exposure:** Water fluoride level *Group 1:* 1-0.2 (Artificial) *Control:* 0.05 (Natural) **Year of fluoridation:** 1945 **No of subjects:** *Group 1:* 6215 *Control:* 5051 **Age** Over 40 years (data also given as incident cases in 5 year age groups, but rates only provided for over 40s combined)
Author (year) Kroger (1994) **Country of study** Finland **Geographic location** Kuopio province - Kuopio (F), surrounding area (non-F) **Year study started** 1980 **Study length (years)** 9 **Study design:** Retrospective Cohort	**Outcome:** Other fractures Wrist fracture Ankle fracture All fractures **Method of outcome assessment:** Reported by women	**Inclusion criteria** Pre-menopausal women aged 47-56 living in study area Random stratified sample of those willing to undergo bone densitometry selected from total cohort **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Age, weight, years since last menstruation, parity, calcium intake, physical demands of work, overall physical activity, HRT, walking/running, alcohol intake, height, menopausal status, smoking & leisure exercise	**Exposure:** Water fluoride level. Exposed had >10 years exposure, control no exposure *Group 1:* 1.2 (Artificial) *Control:* 0-0.3 (Natural) **No of subjects:** *Group 1:* 969 *Control:* 2253 **Age** Fluoride group mean 53.2 (sd=2.8), non-fluoride group mean 53.5 (sd = 2,8), p=0.031

C7: Bone Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Kurttio (1999) **Country of study** Finland **Geographic location** Finland **Year study started** 1981 **Study length (years)** 13 **Study design:** Ecological	**Outcome:** ICD 8 & 9 code for hip fracture of 820 **Method of outcome assessment:** The cohort was linked to the hospital discharge register using personal identification numbers, all hospital types were included in the study	**Inclusion criteria** Villages and squares where more than 90% of the population was not provided with a municipal water system Subjects born between 1900-1930 (age 51-81 at start of study) Subjects who had lived at the same address at least from 1967-1980 First hip fractures in which the main diagnosis was hip fracture **Exclusion criteria** Subjects who had a hip fracture between January 1978 and December 1980 Subjects from urban areas	**Other sources of fluoride:** Not stated **Social class:** Occupation in 1970, 1975 and 1980 measured for all subjects **Ethnicity:** Not stated **Other confounding factors:** Birth year, sex area of residence	**Exposure:** Estimated water fluoride level of well (see study for further details of method of estimation) *Group 1:* >1.5 (Natural) *Group 2:* 1.1-1.5 (Natural) *Group 3:* 0.5-1.0 (Natural) *Group 4:* 0.3-0.5 (Natural) *Group 5:* 0.11-0.30(Natural) *Control:* <0.10(Natural) **Year of fluoridation:** **No of subjects:** *Group 1:* 11759 *Group 2:* 30497 *Group 3:* 66448 *Group 4:* 26820 *Group 5:* 219627 *Control:* 554621 **Age** 51-81 at start of study
Author (year) Lehmann (1998) **Country of study** Germany **Geographic location** Chemnitz (Karl-Marx-Stadt) and Halle **Year study started** 1987 **Study length (years)** 2 **Study design:** Ecological	**Outcome:** Femoral neck or trochanteric fracture, ICD code 820.0, 820.2, 820.8 **Method of outcome assessment:** All patients hospitalised for hip fracture in study areas identified through hospital records	**Inclusion criteria** Aged >=35 **Exclusion criteria** Hip fractures after adequate trauma Pathological fractures	**Other sources of fluoride:** Not stated **Social class:** Not stated, but both cities are heavy industrial bases of similar size <100 km apart **Ethnicity:** Not stated, but stated as homogenous and low mobility amongst population of the 2 communities **Other confounding factors:** Age, weight, height, BMI, alcohol, smoking, calcium intake, menarche, pre-menopausal, postmenopausal, years since menopause, parity, oral contraceptive use	**Exposure:** Water fluoride level, also looks at length of exposure to fluoridated water in years *Group 1:* 0.77-1.2 (Artificial) *Control:* 0.08-0.36 (Natural) **Year of fluoridation:** 1959 **No of subjects:** *Group 1:* 120035 *Control:* 54162 **Age** Mean 37.8 in men, 39.1 in women in Halle, and 42.9 in men in Chemnitz, 40.7 in women. Results presented refer to over 60s only - incidence same in both cities up to age 60

C7: Bone Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Li (1999) **Country of study** China **Geographic location** 6 rural areas of China **Year study started** Not stated **Study length (years)** Not stated **Study design:** Retrospective cohort	**Outcome:** Hip fracture All fractures **Method of outcome assessment:** Subjects questioned about location, nature, frequency and circumstances of fracture sustained since age 20	**Inclusion criteria** 25 years or more continuous residence in study areas Lifetime exposure to specified fluoride level in drinking water Age 50+ **Exclusion criteria** Not stated	**Other sources of fluoride:** None of the subjects used fluoride containing toothpaste or mouthwashes, use of packaged beverages and canned food was minimal. Tea drinking reported by 13.5% of subjects - fluoride content of tea largely determined by fluoride content of water used **Social class:** Environment, culture, ethnic background, social structure and economic conditions of all populations had not changed significantly over the past several decades **Ethnicity:** Not stated **Other confounding factors:** Age, gender, BMI, alcohol consumption, smoking and level of physical activity	**Exposure:** Water fluoride level *Group 1:* 4.32-7.97 (Natural) *Group 2:* 2.62-3.56 (Natural) *Group 3:* 1.45-2.19 (Natural) *Group 4:* 1.00-1.06 (Natural) *Group 5:* 0.58-0.73 (Natural) *Control:* 0.25-0.34 (Natural) **No of subjects:** *Group 1:* 1501 *Group 2:* 1051 *Group 3:* 1574 *Control:* 1370 *Group 1:* 1407 *Group 2:* 1363 **Age** Mean aged varied from 61.3 to 64.0
Author (year) Madans (1983) **Country of study** USA **Geographic location** USA **Year study started** 1973 **Study length (years)** 4 **Study design:** Ecological	**Outcome:** Hip fracture **Method of outcome assessment:** Cases identified through National Health Interview Survey (NHIS) hospital episode records - white persons hospitalised at least once in the last 12 months for whom hip fracture was the reason for hospitalisation	**Inclusion criteria** White people who participated in the NHIS **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** White people only **Other confounding factors:** Not stated	**Exposure:** Proportion of population exposed to fluoridated water at a level of 0.7ppm or more *Group 1:* >=80%(Both) *Control:* <20%(both) **No of subjects:** *Group 1:* 39844 *Control:* 56470 **Age** All ages

C7: Bone Studies: Baseline Data

<table>
<tr><th>Study Details</th><th>Outcome Details</th><th>Inclusion/Exclusion Criteria</th><th>Confounding Factors</th><th>Baseline Data</th></tr>
<tr><td rowspan="2">Author (year)
McClure (1944)
Country of study
USA
Geographic location
Lubbock, Texas; Oklahoma City, Oklahoma; Indianapolis, Ind; Fort Myer, Virginia; Manchester, New Hampshire
Year study started
Not stated
Study length (years)
Not stated
Study design:
Retrospective cohort</td>
<td>Outcome:
All fractures
Method of outcome assessment:
Men interviewed during physical examination regarding fracture history at any time in their lives</td>
<td>Inclusion criteria
Men reporting for physical examination at US military services induction centres
Exclusion criteria
Not stated</td>
<td>Other sources of fluoride:
Not stated
Social class:
Not stated
Ethnicity:
Not stated
Other confounding factors:
Height and weight measured</td>
<td>Exposure:
Water fluoride level
Group 1: 2.0 - 5.0(Natural)
Group 2: 0.3-1.0(Natural)
Group 3: 0.5-1.0 (Natural)
Group 4: 0.0-0.5 (Natural)
Group 5: 0.2 (Natural)
Group 6: 0.0(Natural)
Group 7: 0.0 (Natural)
Control: 0.0(Natural)
No of subjects:
Group 1: 210
Group 2: 213
Group 3: 246
Group 1: 286
Group 1: 190
Group 2: 138
Group 3: 365
Control: 232
Age
19-23</td></tr>
<tr><td>Outcome:
All fractures
Method of outcome assessment:
Boys interviewed during school physical examination regarding fracture history at any time in their lives</td>
<td>Inclusion criteria
High school boys aged 15-17
Continuous residents
Exclusion criteria
Not stated</td>
<td>Other sources of fluoride:
Not stated
Social class:
Not stated
Ethnicity:
Not stated
Other confounding factors:
Height and weight measured</td>
<td>Exposure:
Water fluoride level
Group 1: 1.9 (Natural)
Group 2: 1.7 (Natural)
Group 3: 1.7-1.9 (Natural)
Group 4: 1.2 (Natural)
Group 5: 0.5 (Natural)
Group 6: 0.1 (Natural)
Group 7: 0.0 (Natural)
Control: 0.0-0.1 (Natural)
No of subjects:
Group 1: 207
Group 2: 909
Group 3: 297
Group 4: 248
Group 5: 218
Group 6: 206
Group 7: 203
Control: 409
Age
15-17 years</td></tr>
</table>

C7: Bone Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Niessen (1986) **Country of study** USA **Geographic location** 4 metropolitan counties with pop >4 million (F), 27 rural communities pop approx. 500 000 (non-F) **Year study started** 1980 **Study length (years)** 2 **Study design:** Ecological	**Outcome:** Fracture of the humerus, radius, ulna, tibia, fibula, femur & pelvis **Method of outcome assessment:** Number of fractures obtained from Medicaid fracture data	**Inclusion criteria** White women aged 65 or more Michigan Medicaid recipients **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Percentage of pop. receiving fluoridated water *Group 1:* >=0.89 *Group 2:* >=0.89 (excluding Wayne county) *Control:* <=0.15 **Year of fluoridation:** Not stated **No of subjects:** *Group 1:* 3902 *Group 2:* 1727 *Control:* 1155 **Age** Not stated
Author (year) Phipps (1999) **Country of study** USA **Geographic location** Portland, OR, Minneapolis, MN, Baltimore, MD, Monongahela Valley, PA **Year study started** 1986 **Study length (years)** 9 **Study design:** Prospective cohort	**Outcome:** All non-vertebral fractures Hip fracture Humerus Incident vertebral fractures Wrist fracture **Method of outcome assessment:** Participants contacted every 4 months by postcard/telephone to ask if had sustained fracture or fall. If fracture reported participants interviewed, obtained copy of radiographic report which had to specifically mention occurrence of acute fracture	**Inclusion criteria** White women aged 65 or more Completion of residence history questionnaire **Exclusion criteria** Women unable to walk without assistance Women who had bilateral hip replacement Women with mixed/unknown exposure to fluoridated water Fractures due to major trauma, e.g. traffic accident	**Other sources of fluoride:** Not stated **Social class:** % with education beyond elementary school **Ethnicity:** White women only **Other confounding factors:** Age, BMI, weight, exercise, muscle strength, fall in last year, surgical menopause, calcium & alcohol intake, functional status, current smoker, history of osteoporosis/non-insulin dependent diabetes, oestrogen, thiazide diuretic & thyroid hormone use	**Exposure:** Number of years of exposure to fluoridated public water supplies *Group 1:* >20 *Control:* 0 **Year of fluoridation:** 1971 **No of subjects:** Not stated **Age** Not stated
Author (year) Simonen (1985) **Country of study** Finland **Geographic location** Kuopio (F) and Jyvaskyla (non-F) **Year study started** 1967 **Study length (years)** 11 **Study design:** Ecological	**Outcome:** Femoral-neck fracture **Method of outcome assessment:** Cases identified from hospital discharge data for Finland. All cases recorded under ICD codes 820.00 and 820.10 included in the study, only records with main diagnosis of hip fracture and first admissions for fractures included	**Inclusion criteria** Residents of study areas aged 50 or more Cases where diagnosis of hip fracture was the main diagnosis **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Distribution of occupations compared between 2 study areas **Ethnicity:** Not stated **Other confounding factors:** Areas similar in water hardness (calcium and magnesium water content)	**Exposure:** Water fluoride level *Group 1:* 1 (Artificial) *Control:* <0.1 (Natural) **Year of fluoridation:** 1959 **No of subjects:** *Group 1:* 17591 *Control:* 14701 **Age** 50+

C7: Bone Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Sowers (1991) **Country of study** USA **Geographic location** Rural communities in north-western Iowa **Year study started** 1983 **Study length (years)** 6 **Study design:** Prospective cohort	**Outcome:** Hip fracture incidence Fracture incidence **Method of outcome assessment:** Reported during interview.	**Inclusion criteria** Women resident in study areas for >=5 years Consumed public water Ambulatory Aged 20-80 **Exclusion criteria** Pregnant women No wrist or forearm fractures in previous 2 years	**Other sources of fluoride:** Toothpaste, mouthrinses (amount of products & quantity used not assessed in study), >80% of participants in control and high Ca communities used F toothpaste, 39% of women in exposed group used F products **Social class:** Author reports that areas similar with respect to mean income and occupational categories **Ethnicity:** All women of Northern European origin, author states no ethnic difference among communities **Other confounding factors:** Age, HRT, oral contraceptive use, frequency of surgical menopause, estimated nutrients from diet and supplements, domestic ion exchange water conditioning systems	**Exposure:** Fluoride level (mg/L) *Group 1:* 4 *Control:* 1 **Year of fluoridation:** **No of subjects:** *Group 1:* 230 *Control:* 158 **Age** 20-35 and 55-80
Author (year) Suarez-Almazor (1993) **Country of study** Canada **Geographic location** Edmonton(high-F), Calgary (low-F), Alberta **Year study started** 1981 **Study length (years)** 6 **Study design:** Ecological	**Outcome:** Hip fracture **Method of outcome assessment:** Total number of admission identified from hospital records with discharge diagnosis of hip fracture ICD-9 820.0-820.9	**Inclusion criteria** Aged >=45 Primary, secondary or tertiary discharge for hip fracture Resident in study areas **Exclusion criteria** Transfers to other hospitals Discharge diagnosis code 905.3 or 733.8	**Other sources of fluoride:** Not stated **Social class:** Calgary: service & administrative occupational structure, Edmonton: manufacturing & processing base **Ethnicity:** Ethnic composition of two areas reasonably similar - multiple origins, British, French, German. Dutch, Ukrainian, Aboriginal & Chinese **Other confounding factors:** % married, population density, oestrogen therapy, body build, alcohol & tobacco use, calcium water content	**Exposure:** Water fluoride levels *Group 1:* 1 (Artificial) *Control:* 0.3 (Natural) **Year of fluoridation:** 1967 **No of subjects:** *Group 1:* 336423 *Control:* 340331 **Age** 45-64 65+

C7: Bone Studies: Baseline Data

2. Case-Control Studies

Study Details	Case and Control Selection	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Hillier (2000) **Country of study** England **Geographic location** Cleveland **Year study started** Not stated **Year study ended** Not stated	**Case-definition:** Patients with diagnosed fractures of the femoral neck that were through or above the lesser trochanter and not caused by cancer identified through ward admission books for Hartlepool General, North Tees General and Middlesbrough General Hospitals **Method of control selection:** Randomly selected from list of all members of the study population registered National Health Service general practitioners **Matching:** Age (in 5 year bands) and sex **Ratios of cases to controls:** 1:1	**Inclusion criteria** Residents of Cleveland aged 50 years or more Score of 6 or more on Hodkinson abbreviated mental test **Exclusion criteria** Not stated	**Other sources of fluoride:** Dietary sources of fluoride **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Demographic variables, BMI, lifetime residential history, physical activity, recent medication, dietary sources of calcium, age at menopause, smoking, alcohol consumption	**Number of subjects** *Cases:* 514 *Controls 1:* 527 **Age range (mean)** Not stated **Exposure 1:** Average drinking water concentration of fluoride: <0.9 **Exposure 2:** Average drinking water concentration of fluoride: >= 0.9 **Exposure 3:** Odds ratio adjusted for all potential confounders
Author (year) Kelsey (1971) **Country of study** USA **Geographic location** Colorado, Arizona, New Mexico, Texas **Year study started** 1953 **Year study ended** Not stated	**Case-definition:** Cases of slipped epiphysis identified though diagnostic indexes and operating room log books of 21 hospitals included in study, in Arizona, Texas, Colorado and New Mexico **Method of control selection:** Two sets of controls: orthopaedic (1) & other (2) - next patients admitted to orthopaedic/other service after the slipped epiphysis patient **Matching:** Matched on sex and age within 2 years **Ratios of cases to controls:** 1:1	**Inclusion criteria** Aged <25 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Number of subjects per outcome group:** Arizona: 56 Texas: 33 New Mexico: 11 Colorado: 41 **Exposure:** Water fluoride level

C8: Bone Studies: Individual Study Results

1. Cohort and Ecological Studies

a. Studies which present adjusted outcomes

Study Details	Outcome	Group	Exposure	Crude Risk Males/ 100 000	Crude Risk Females/ 100 000	Summary Measure (CI): Details	Male	Female
Cauley (1995)	Hip fracture	*Group 1:* *Group 2:* *Group 3:* *Control:*	>20 11-20 1-10 0		1041.7 1010.2 2283.2 2163.5	**Measure used:** Relative Risk **Variables controlled for:** Age, BMI, total calcium intake (diet plus supplement), history of osteoporosis), surgical menopause, history of falls in past year, drinks per week. Education, current oestrogen use, current thiazide use, ever used bottled water		0.44 (0.1, 1.86) 0.58 (0.14, 2.48) 0.89 (0.42, 1.92) 1.0
	Incident vertebral fractures	*Group 1:* *Group 2:* *Group 3:* *Control:*	>20 11-20 1-10 0					1.63 (0.57, 4.67) 0.58 (0.21, 1.60) 1.02 (0.55, 1.88) 1.0
	Nonspine fractures	*Group 1:* *Group 2:* *Group 3:* *Control:*	>20 11-20 1-10 0		14062.5 16161.6 20319.6 17708.3			0.73(0.48,1.12) 1.04 (0.71, 1.52) 1.10(0.85, 1.42) 1.0
	Oesteoporotic fracture - fractures of hip, wrist, humerus, pelvis, toe, leg, hand, clavicle, rib	*Group 1:* *Group 2:* *Group 3:* *Control:*	>20 11-20 1-10 0		11458.3 12121.2 15753.4 14262.8			0.74 (0.46,1.19) 0.96 (0.67. 1.54) 1.04 (0.77, 1.38) 1.0
	Wrist fracture	*Group 1:* *Group 2:* *Group 3:* *Control:*	>20 11-20 1-10 0		3125 3030.3 4337.9 3525.6			0.95 (0.40,2.25) 0.81 (0.32, 2.04) 1.17 (0.67, 2.05) 1.0
Danielson (1992)	Hip fracture requiring hospitalisation	*Group 1:* *Control:*	1 <0.3			**Measure used:** Relative Risk **Variables controlled for:** Age	1.41 (1.00-1.81) 1.0	1.27 (1.08-1.46) 1.0
Jacobsen (1992)	Discharge for hip fracture defined as ICD code 820.0 - 820.9	*Group 1:* *Control:*	>60% <10%			**Measure used:** Regression Coefficient **Variables controlled for:** 5-level index of ground water hardness, % of people aged 65+ living below the poverty level, % of land in agricultural use, % of population served with fluoridated water, mean hours of sunlight in January and latitude at centroid of the county	-0.002 (p=0.0138)	
Cooper (1990)	Hip fracture	*38 study areas*	0.05-0.93			**Method Used** Direct **Standard Population** Discharge rates directly standardised by age and sex within 5 year age groups using the 1981 population	Standardised rates ranged from 2.17 to 0.88, no association with water fluoride level was found	

C8: Bone Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Crude Risk Males/ 100 000	Crude Risk Females/ 100 000	Summary Measure (CI): Details	Male	Female
Jacqmin-Gadda (1995)	Any fractures	*Group 1:* *Control:*	0.11-1.83 <0.11			**Measure used:** Odds ratio	0.98 (0.80-1.21) 1	
	Hip fracture	*Group 1:* *Control:*	0.11-1.83 <0.11			**Variables controlled for:** Age, sex and BMI	1.86 (1.02-3.36) 1	
Jacqmin-Gadda (1998)	Hip fracture	*Group 1:* *Group 2:* *Control:*	>0.25 0.11-0.25 0.05-0.11			**Measure used:** Odds ratio **Variables controlled for:**	2.43 (1.11-5.33) 3.25 (.66-6.38) 1	
	Non-hip fractures	*Group 1:* *Group 2:* *Control:*	>0.25 0.11-0.25 0.05-0.11			Age, sex, BMI, smoking, spirit consumption, use of non-psychotropic drugs, hypnotic drug use, antidepressive drug use, neuroleptic drug use and area	1.05 (0.74-1.51) 0.88 (0.63-1.22) 1.0	
Karagas (1996)	Ankle fracture	*Group 1:* *Group 2:* *Group 3:* *Control:*	67% <10%			**Measure used:** Relative Risk **Variables controlled for:** Not stated, possible age and sex standardised rates	1.01(0.87-1.16) 1.00	1.00(0.92-1.08) 1.00
	Fracture of the distal forearm	*Group 1:* *Group 2:* *Group 3:* *Control:*	67% <10%				1.16 (1.02-1.33) 1.0	No association 1.0
	Fracture of the proximal humerus	*Group 1:* *Group 2:* *Group 3:* *Control:*	67% <10%				1.23(1.06-1.43) 1.0	No association 1.0
	Hip fracture (ICD9 820-820.9)	*Group 1:* *Control:*	67% <10%			**Variables controlled for:** Demographic, census division, age group and gender (not clear whether results presented are controlled for these, but infer from methods section that these are the results presented)	1.00(0.92-1.09) 1.00	1.01(0.96-1.06) 1.00
Karjalainen (1982)	Incidence of otosclerosis	*Group 1:* *Group 2:* *Group 3:* *Control:*	0.95-0.99 0.02-0.32			**Measure used:** Rate ratio **Variables controlled for:** Crude rate ratio		0.93 1
Kurttio (1999)	ICD 8 & 9 code for hip fracture of 820	*Group 1:* *Group 2:* *Group 3:* *Group 4:* *Group 5:* *Control:*	>1.5 1.1-1.5 0.5-1.0 0.3-0.5 0.11-0.30 <0.10	189.0 7140.6 210.3 141.7 191.9 9166.2	399.7 386.9 403.3 410.2 352.9 333.6	**Measure used:** Rate ratio **Variables controlled for:** Age and area	0.98 (0.61-1.60) 0.67 (0.46-0.97) 1.03 (0.81-1.32) 0.72 (0.51-1.02) 1.05 (0.9-1.22) 1.0	1.08 (0.8-1.46) 1.08 (0.88-1.32) 1.12 (0.96-1.31) 1.12 (0.93-1.34) 0.93 (0.84-1.02) 1.0

C8: Bone Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Crude Risk Males/ 100 000	Crude Risk Females/ 100 000	Summary Measure (CI): Details	Male	Female
Li (1999)	All fractures	*Group 1:* *Group 2:* *Group 3:* *Group 4:* *Group 5:* *Control:*	4.32-7.02 2.62-3.56 1.45-2.19 1.00-1.06 0.58-0.73 0.25-0.34	7395.1 6089.41 6035.6 5109.5 6396.6 7410.1		**Measure used:** Odds ratio **Variables controlled for:** Age and gender, relative to 1.00-1.06 fluoride group	1.47 (p=0.01) 1.18 (0.35) 1.17 (p=0.33) 1.00 1.25 (p=0.17) 1.50 (p=0.01)	
	Hip fracture	*Group 1:* *Group 2:* *Group 3:* *Group 4:* *Group 5:* *Control:*	4.32-7.97 2.62-3.56 1.45-2.19 1.00-1.06 0.58-0.73 0.25-0.34	1199.2 761.2 889.5 365.0 426.4 366.8		**Measure used:** Odds ratio **Variables controlled for:** Age and BMI, relative to 1.00-1.06 fluoride group	3.26 (p=0.02) 1.73 (p=0.34) 2.13 (p=0.15) 1.00 1.12 (0.85) 0.99 (0.99)	
Phipps (1999)	All non-vertebral fractures	*Group 1:* *Control:*	>20 0			**Measure used:** Relative Risk **Variables controlled for:** Age, current oestrogen/thiazide/thyroid hormone use, history of osteoporosis, weight, walks, calcium intake, alcohol intake, history of falls in past year, smoking status surgical menopause, muscle strength, non-insulin dep. dependent diabetes, education		0.96(0.83, 1.10) 1.0
	Hip fracture	*Group 1:* *Control:*	>20 0					0.69(0.5, 0.96) 1.0
	Humerus	*Group 1:* *Control:*	>20 0					1.15(0.80, 1.63) 1.0
	Incident vertebral fractures	*Group 1:* *Control:*	>20 0					0.74(0.55, 0.99) 1.0
	Wrist fracture	*Group 1:* *Control:*	>20 0					1.3(1.02, 1.7) 1.0
Simonen (1985)	Femoral-neck fracture	*Group 1:* *Control:*	1 <0.1			**Measure used:** Rate ratio **Variables controlled for:** Age	1.0 2.5(1.6-3.9)	1.0 1.5 (1.2-1.8)
Sowers (1991)	Fracture incidence	*Group 1:* *Group 2:* *Group 3:* *Control:*	4 (age 20-35) 1 (age 20-35) 4 (age 55-80) 1 (age 55-80)		13432.8 8108.1 19018.4 9090.9	**Measure used:** Relative Risk **Variables controlled for:** Age and Quatelet index (weight/height*height)		1.81 (0.45-8.22) 1.0 2.11(1.01-4.43) 1.0

b. Studies which present standardised results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Risk (Males)/ 100 000	Crude Risk (Females)/ 100 000	Standardisation: Methods	Standardised rate: Male	Standardised rate: Female
Jacobsen (1992)	Discharge for hip fracture defined as ICD code 820.0 - 820.9	*Group 1:* *Control:*	% of population served with fluoridated water	>60% <10%			**Method used** Direct **Standard population** Entire US population aged 65 years and older	4.71(4.59-4.83) 3.99(3.88-4.10)	8.62(8.51-8.73) 7.85(7.74-7.96)

C8: Bone Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Risk (Males)/ 100 000	Crude Risk (Females)/ 100 000	Standardisation		
							Methods	Standardised rate	
Simonen (1985)	Femoral-neck fracture	*Group 1:* *Control:*	Water fluoride level	1 <0.1			**Method used** Direct **Standard population** Not stated, standardised on age and sex	2.5 7.0	6.0 9.0
Suarez-Almazor (1993)	Hip fracture	*Group 1:* *Control:*	Water fluoride levels	1 0.3	508.8 447.0	953.8 1008.5	**Method used** Direct **Standard population** Edmonton	5.09 4.52	9.54 9.91
		Group 1: *Control:*	Water fluoride levels	1 0.3	58.9 53.2	59.8 68.1	**Method used** Direct **Standard population** Edmonton	0.59 0.55	0.6 0.71

c. Studies which present crude data only

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Risk /100 000	
					Male	Female
Arnala (1986)	Hip fracture	*Group 1:* *Group 2:* *Control:*	Water fluoride level	>1.5 1-1.2 <0.3		124.0 119.0 124.0
Bernstein (1966)	Prevalence of subjects with one or more collapsed vertebrae	*Group 1:* *Control:*	Water fluoride level	4-5.8 <=0.3	30120.5 31410.3	5223.9 20347.4
Daniel (1969)	Stapedal otosclerosis	*Group 1:* *Control:*	Water fluoride level	1.9 <0.6		1928.4 7284.0
Kelsey (1971)	Incidence of slipped epiphysis	*Group 1:* *Control:*	Water fluoride level	1 low	5.6 4.7	1.3 2.1
Korns (1969)	Cervical, intertrochanteric or subcapital hip fractures	*Group 1:* *Control:*	Water fluoride level	1-1.2 0.05	613.915 351.5	1271.2 1392.62
	Wrist fracture	*Group 1:* *Control:*		1-0.2 0.05	40 99.0	354.0 372.0
Kroger (1994)	Wrist fracture	*Group 1:* *Control:*	Water fluoride level. Exposed had >10 years exposure, control no exposure	1.2 0-0.3		4437.6 3107.0
	Other fractures	*Group 1:* *Control:*		1.2 0-0.3		8359.1 8122.5
	Ankle fracture	*Group 1:* *Control:*		1.2 0-0.3		2476.8 2174.9
	All fractures	*Group 1:* *Control:*		1.2 0-0.3		15273.5 13404.3
Lehmann (1998)	Femoral neck or trochanteric fracture, ICD code 820.0, 820.2, 820.8	*Group 1:* *Control:*	Water fluoride level, also looks at length of exposure to fluoridated water in years	0.77-1.2 0.08-0.36	161.2 177.2	382.4 458.1

C8: Bone Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Risk /100 000	
					Male	Female
Madans (1983)	Hip fracture	*Group 1:* *Control:*	Proportion of population exposed to fluoridated water at a level of 0.7ppm or more	>=80% <20%	110.9 100.0	220.1 239.6
McClure (1944)	All fractures	*Group 1:* *Group 2:* *Group 3:* *Group:4*	Water fluoride level	2.0 - 5.0 0.3-1.0 0.5-1.0 0.0-0.5	30526.3 29710.1 27397.3 25862.1	
		Group 1: *Group 2:* *Group 3:* *Group 4:* *Group5:* *Group 6:* *Group:7* *Group 8* *Group 9* *Group 10* *Group:11* *Group 12:*		0.2 0.0 0.0 1.9 1.7 1.7-1.9 1.2 0.5 0.1 0.0 0.0-0.1 0.0	28095.2 24882.6 28861.8 27053.1 31111.1 28282.8 25403.2 24311.9 21359.2 25123.2 23227.4 32517.5	
Niessen (1986)	Fracture of the humerus, radius, ulna, tibia, fibula, femur & pelvis	*Group 1:* *Group 2:* *Control:*	Water fluoride level	>=0.89 >=0.89 (excluding Wayne county) <=0.15		9431.1 8106.5 7878.8
Sowers (1991)	Hip fracture incidence	*Group 1:* *Group 2:* *Group 3:* *Control:*	Fluoride level (mg/L)	4 1 4 1		1492.5 0 3067.5 0

2. Case-Control Studies

Study Details	Outcome	Number of Subjects per Group	Exposures	Level of Exposure in Cases	Level of Eposure in Control 1	Level of Exposure in Control 2	OR for Exposure
Hillier (2000)	Patients with diagnosed fractures of the femoral neck that were through or above the lesser trochanter and not caused by cancer identified through ward admission books for Hartlepool General, North Tees General and Middlesbrough General Hospitals	514	**Exposure 1:** Water fluoride: <0.9 **Exposure 2:** Water fluoride: >= 0.9 **Exposure 3:** Odds ratio adjusted for all potential confounders	380 80	346 77		1.0 1.0 (0.7-1.5)
Kelsey (1971) **Texas**	Cases of slipped epiphysis identified though diagnostic indexes and operating room log books of 21 hospitals included in study	33	**Exposure 1:** Water fluoride level	2.064	2.188	2.118	
New Mexico		11		0.727	0.636	0.500	
Colorado		41		1.051	0.995	1.005	
Arizona		56		0.564	0.366	0.607	

C9: Cancer Studies: Baseline Data

1. Cohort and Ecological Studies

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Chilvers (1985) **Country of study** UK **Geographic location** 67 small areas in England **Year study started** 1969 **Study length (years)** 4 **Study design:** Ecological	**Outcome:** Cancer mortality from oesophagus, lung, ovary, skin, stomach, pancreas, breast, rectum, bladder, buccal cavity, kidney and intestinal cancer and cancer mortality from all causes **Method of outcome assessment:** Population figures and numbers of deaths provided by OPCS (ONS)	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** High fluoride areas matched with low fluoride areas for urban/rural status, and as far as possible for population size, as far as possible areas chosen to be geographically close, furthest apart 85 miles, age.	**Exposure:** Water fluoride level *Group 1:* >=1.0(Natural) *Group 2:* 0.5-0.99(Natural) *Group 3:* <=0.2 (Natural) *Group 4:* <=0.1(Natural) **No of subjects:** Not stated **Age** Not stated
Author (year) Cohn (1992) **Country of study** USA **Geographic location** New Jersey **Year study started** 1979 **Study length (years)** 8 **Study design:** Ecological	**Outcome:** Cases of osteosarcoma **Method of outcome assessment:** Cases identified from New Jersey Cancer Registry, 1980 census used as source of population data.	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Results presented by age and sex	**Exposure:** Proportion of the population receiving fluoridated water from at least the early 1970s to 1987 *Group 1:* >85% *Control:* <10% **No of subjects:** *Group1:* 218588 *Control:* 502759 **Age** <20
Author (year) Glattre (1979) **Country of study** Norway **Geographic location** 70 Municipalities in Southern Norway **Year study started** 1971 **Study length (years)** 4 **Study design:** Ecological	**Outcome:** Mortality from oral or pharyngeal cancer (ICD 140-149) **Method of outcome assessment:** Age-adjusted mortality rate for oral and pharyngeal cancer provided by the Central Bureau of Statistics of Norway	**Inclusion criteria** Areas where > 80% of population get water from registered supplies **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Smoking and alcohol consumption, working and consuming water outside the home, urban and rural differences, differences in population size, age.	**Exposure:** Weighted average fluoride concentration of registered water supplies *Group 1:* 0.11-0.50(Natural) *Group 2:* 0.06-.010(Natural) *Group 4:* 0-0.05(Natural) **No of subjects:** *Group 1:* 207300 *Group 2:* 811600 *Group 4:* 931800 **Age** Not stated

C9: Cancer Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Hoover (1976) **Country of study** USA **Geographic location** Texas **Year study started** 1950 **Study length (years)** 19 **Study design:** Ecological	**Outcome:** Mortality from cancer of the nose and nasal sinuses, eye, brain, connective tissue, colon, bladder, oesophagus, skin, uterus, liver and bile duct, rectum, ovary, stomach, nasopharynx, lung, thyroid, cervix, bone, kidney, lip, breast, larynx, leukaemia, pancreas, testis, salivary gland, prostate, mouth and throat, other and unspecified sites, and, all sites. Also mortality from melanoma, lymphoma, Hodgkin's disease, multiple myeloma and cancer of other endocrine organs. **Method of outcome assessment:** Age-race and sex- specific numbers of cancer deaths, coded according to the ICD were provided by the National Center for Health statistics	**Inclusion criteria** White subjects only **Exclusion criteria** Counties with artificially fluoridated water	**Other sources of fluoride:** Not stated **Social class:** Counties subdivided by percent urbanisation and socio-economic categories based on median number of years of school completed by the adult population of each county **Ethnicity:** White subjects only **Other confounding factors:** Age	**Exposure:** Level of fluoride that >2/3 of the population were exposed to *Group 1:* >=2.0 (Natural) *Group 2:* 1.3-1.9 (Natural) *Group 3:* 0.7-1.2 (Natural) *Group 4:* <0.7 (Natural) **No of subjects:** Not stated **Age** All ages
Author (year) Hrudey (1990) **Country of study** Canada **Geographic location** Calgary (non F) and Edmonton (F), Alberta **Year study started** 1970 **Study length (years)** 18 **Study design:** Ecological	**Outcome:** Osteosarcoma incidence **Method of outcome assessment:** Cases identified through Alberta Cancer Board cancer registry	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Age	**Exposure:** Water fluoride content *Group 1:* 1(Artificial) *Group 4:* 0.3(Natural) **Year of fluoridation:** 1967 **No of subjects:** *Group 1:* 9629630 *Group 4:* 10000000 **Age** All ages
Author (year) Kinlen (1975) **Country of study** UK **Geographic location** England and Wales **Year study started** 1961 **Study length (years)** 7 **Study design:** Ecological	**Outcome:** Kidney, stomach, oesophagus, bone, colon, bladder, thyroid, breast and rectum cancer **Method of outcome assessment:** Cancer incidence data supplied by OPCS from National cancer registration scheme	**Inclusion criteria** Local authority districts with water fluoride > 1ppm Group 4 areas for each high fluoride area, with water fluoride <0.2 ppm Group 4 area, area nearest of similar size Similar procedure for areas of high/medium (0.5-0.99), with matched Group 4 areas <0.1ppm **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Areas matched on urban/rural, age standardised, presented by sex.	**Exposure:** Water fluoride level *Group 1:* 1 *Group 2:* 0.5-0.99 *Group 3:* <0.2 (Natural) *Group 4:* <0.1(Natural) **No of subjects:** *Group 1:* 482398 *Group 2:* 779054 *Group 3:* 510045 *Group 4:* 896625 **Age** All ages

C9: Cancer Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Lynch (1985) **Country of study** USA **Geographic location** Iowa **Year study started** 1969 **Study length (years)** 12 **Study design:** Ecological	**Outcome:** Incidence of breast cancer, bladder cancer, prostate cancer, colon cancer, lung cancer, rectum cancer, cancer of all other sites and cancer of all sites combined **Method of outcome assessment:** Cases of cancer identified through the Iowa Cancer Information System, population data provided by the census bureau for 1970 & 1980, Rushton's estimates for inter-census years used for other years. Address algorithm used to classify cancer case exposure	**Inclusion criteria** Areas with 1970 pop >1000 Fluoride concentration maintained at 0.9-1.2 ppm from time of initiation of fluoridation Divided into 2 groups: 1970 pops > and < 10 000 **Exclusion criteria** Areas that failed to maintain fluoridation programmes for any period of > 6 months	**Other sources of fluoride:** **Social class:** Education, marital status, occupation, foreign born, family income **Ethnicity:** 98.5% of Iowa's 1970 population was white, so no race adjustment performed **Other confounding factors:** Initiation of water treatment processes, water samples analysed for several volatile organics, trace elements and heavy metals, primary source of drinking water, distance to nearest city with pop. > 25 00, % change in pop between 1980 and 1970	**Exposure:** **Study 1:** Length of time from initiation of artificial water fluoridation until 1981 **Low population (<10 000) group:** *Group 1:* 0-9(Artificial) *Group 2:* 10-19(Artificial) *Group 3:* 20+ (Artificial) **High population group:** *Group 1:* <20(Artificial) *Group 2:* >20(Artificial) **Study 2:** Natural water fluoride level, and minimum length of exposure to this fluoride level *Group 1:* <=0.5, exp. 1968-81(Natural) *Group 2:* >=1.0, exp. 1968-81(Natural) *Group 3:* <=0.5, exp. 1950-81 (Natural) *Group 4:* >=1.0, exp. 1950-81(Natural) **Age:** All ages
Author (year) Mahoney (1991) **Country of study** USA **Geographic location** New York state, exclusive of New York City **Year study started** 1975 **Study length (years)** 12 **Study design:** Ecological	**Outcome:** Bone cancer incidence Osteosarcoma incidence **Method of outcome assessment:** United States census data used to provide population denominator figures, cases of bone cancer identified through New York State Cancer Registry	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Fluoridated water *Group 1:* High(Artificial) *Group 2:* Low(Natural) *Group 3:* High(Artificial) *Group 4:* Low(Natural) **Year of fluoridation:** **No of subjects:** *Group 1:* 17600000 *Group 2:* 7500000 *Group 3:* 17403846 *Group 4:* 9142857 **Age** <30 given in exposed 1 & 2, 30 + given in exposed 3 & 4

C9: Cancer Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Richards (1979) **Country of study** Australia **Geographic location** 10 fluoridated and 10 non-fluoridated areas in New South Wales **Year study started** 1970 **Study length (years)** 2 **Study design:** Ecological	**Outcome:** Deaths from Malignant neoplasms **Method of outcome assessment:** Deaths from malignant neoplasms obtained from Australian Bureau of Statistics. Annual average number of deaths used as numerator, population at 1971 census used as denominator.	**Inclusion criteria** None stated **Exclusion criteria** Areas which had been fluoridated for <5 years Areas with naturally fluoridated water supplies	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Areas matched on population size where possible, age and sex.	**Exposure:** Water fluoride level *Group 1:* High(Artificial) *Group 4:* Low(Natural) **No of subjects:** *Group 1:* 163616 *Group 4:* 192322 **Age** Not stated
Author (year) *Smith (1980) **Country of study** USA **Geographic location** 20 US cities, 10 F, 10 non-F **Year study started** 1950 **Study length (years)** 20 **Study design:** Ecological	**Outcome:** Deaths from cancer **Method of outcome assessment:** Not stated	**Inclusion criteria** 10 largest fluoridated cities in US 10 largest non-fluoridated cities in US, with death rates >155 per 100 000 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Group 4 led for using indirect standardisation **Other confounding factors:** Age, sex	**Exposure:** Water fluoride level, exposed 1 & 2 used for 1950 data, exposed 3 & 4 for 1970 data (study before after not traditional cohort) *Group 1:* Low(Natural) *Group 2:* Low(Natural) *Group 3:* High (Artificial) *Group 4:* Low(Natural) **Year of fluoridation:** **No of subjects:** *Group 1:* 11885800 *Group 2:* 6290100 *Group 3:* 10766600 *Group 4:* 7347700 **Age** All ages

C9: Cancer Studies: Baseline Data

2. Before-After Studies

Study Details	Outcome Details	Inclusion/ Exclusion Criteria	Confounding Factors	Baseline Group Characteristics	Final Group Characteristics
Author (year) *Chilvers (1983) **Country of study** USA **Geographic location** 35 US cities **Year study started** 1950 **Year study ended:** 1970	**Outcome:** Death from cancer **Method of outcome assessment:** Numbers of deaths from cancer abstracted from successive volumes of Vital Statistics in the United States	**Inclusion criteria** 10 largest fluoridated cities in US 10 largest non-fluoridated cities in US, with death rates >155 per 100 000 10 additional fluoridated and 5 additional non-fluoridated areas 5 additional Group 4 areas **Exclusion criteria** None stated 10 additional fluoridated and 5 additional non-fluoridated areas	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Standardised for ethnic group **Other confounding factors:** Rates also standardised for age and sex	**Fluoride level (ppm):** *Group 1:*Low (Natural) *Group 4:* Low (Natural) **Year fluoridation initiated:** 1951-1964 **No of subjects:** Not stated **Age** Not stated	**Fluoride level (ppm):** *Group 1:*High (Artificial) *Group 4:* Low(Natural) **No of subjects:** Not stated **Age** Not stated
Author (year) *Chilvers (1982) **Country of study** USA **Geographic location** 20 US cities 10 F, 10 non-F **Year study started** 1958 **Year study ended:** 1972	**Outcome:** Mortality from cancer of the digestive organs, respiratory system, breast, genital organs, urinary organs, leukaemia and aleukaemia, other malignant neoplasms and all malignant neoplasms **Method of outcome assessment:** Deaths from cancer by site, obtained from: Vital statistics of the United States, deaths from 1958-62 related to 1960 pop data and from 1968-72 related to 1970 pop data.	**Inclusion criteria** 10 largest fluoridated cities in US 10 largest non-fluoridated cities in US, with death rates >155 per 100 000 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Results standardised for ethnic group **Other confounding factors:** Standardised for age and sex	**Fluoride level (ppm):** *Group 1:*Low *Group 4:* Low **No of subjects:** Not stated **Age** Not stated	**Fluoride level (ppm):** *Group 1:*High *Group 4:* Low **No of subjects:** Not stated **Age** Not stated
Author (year) Cook-Mozaffari (1981) **Country of study** England **Geographic location** Birmingham (F), London, Bristol, Liverpool, Manchester, Leeds, Sheffield (Non-F) **Year study started** 1959 **Year study ended:** 1978	**Outcome:** Age adjusted cancer deaths males and females, 1959-63 & 1969-73 and for 1969-73 & 1974-78 **Method of outcome assessment:** Cancer data taken from Registrar General' area mortality tables & from volumes of Statistical Review of England and Wales, Pop. Data by age & sex obtained from 1961 & 1971 national censuses & estimates for individual years from OPCS	**Inclusion criteria** Cities with populations > 400 000 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Age standardised and sex stratified	**Fluoride level (ppm):** *Group 1:*Low (Natural) *Group 4:* Low (Natural) **Year fluoridation initiated:** 1964 **No of subjects:** Not stated **Age** Not stated	**Fluoride level (ppm):** *Group 1:*High (Artificial) *Group 4:* Low(Natural) **No of subjects:** Not stated **Age** Not stated *:*

C9: Cancer Studies: Baseline Data

Study Details	Outcome Details	Inclusion/ Exclusion Criteria	Confounding Factors	Baseline Group Characteristics	Final Group Characteristics
Author (year) *Doll (1977) **Country of study** USA **Geographic location** Twenty cities in America, 10 of which had fluoridated water **Year study started** 1950 **Year study ended:** 1970	**Outcome:** Deaths from cancer **Method of outcome assessment:** Not stated	**Inclusion criteria** 10 largest fluoridated cities in US 10 largest non-fluoridated cities in US, with death rates >155 per 100 000 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Raw data presented separately for whites and non-whites **Other confounding factors:** Age, sex	**Fluoride level (ppm):** *Group 1:*Low *Group 4:* low **No of subjects:** *Group 1:* 11885800 *Group 4:* 6290000 **Age** Not stated	**Fluoride level (ppm):** *Group 1:*High *Group 4:* Low **No of subjects:** *Group 1:* 10767000 *Group 4:* 7348000 **Age** Not stated
Author (year) Goodall (1980) **Country of study** New Zealand **Geographic location** Auckland, Manukau, Hamilton, Wellington, Waimairi County, Dunedin (F), Whangarei, Wanganui, Nelson and Christchurch city (Non-F) **Year study started** 1961 **Year study ended:** 1976	**Outcome:** Cancer mortality **Method of outcome assessment:** Registered cancer deaths	**Inclusion criteria** Aged 45 or more **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Rates standardised for age and sex	**Exposure:** Water fluoride level *Group 1:* low (natural) *Control:* low (natural) **No of subjects:** *Group 1:*1470791 *Control:*73 228 **Age** 45+	**Exposure:** Water fluoride level *Group1:* high (artificial) *Control:* low (natural) **No of subjects:** *Group 1:*180 855 *Control:* 7 901 **Age** 45+
Author (year) Hoover (1991) **Country of study** USA **Geographic location** Areas in US covered by the SEER programme with known water fluoride concentrations **Year study started** 1973 **Year study ended:** 1987	**Outcome:** Incidence of osteosarcoma (males only) and bone and joint cancers (both sexes) **Method of outcome assessment:** Cases reported to to Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI)	**Inclusion criteria** Cases of bone and joint cancers and osteosarcoma reported to the SEER programme of the National Cancer Institute **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:*<10% pop, <0.3 (Natural) *Group 3:*>60% pop, F<1955 (Artificial) *Group 4:* >60% pop, F>=1966 (Artificial) **No of subjects:** Not stated **Age** All ages	**Fluoride level (ppm):** *Group 1:*<10% pop, <0.3 (Natural) *Group 3:*>60% pop, F<1955(Artificial) *Group 4:* >60% pop, F>=1966(Artificial) **No of subjects:** Not stated **Age** All ages

C9: Cancer Studies: Baseline Data

Study Details	Outcome Details	Inclusion/ Exclusion Criteria	Confounding Factors	Baseline Group Characteristics	Final Group Characteristics
Author (year) Schlesinger (1956) **Country of study** USA **Geographic location** Newburgh & Kingston, New York State **Year study started** 1944 **Year study ended:** 1954	**Outcome:** Deaths from cancer **Method of outcome assessment:** Not stated	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:* *Group 4:* **Year fluoridation initiated:** 1945 **No of subjects:** Not stated **Age** All	**Fluoride level (ppm):** *Group 1:*1-1.2 (Artificial) *Group 4:* <0.2(Natural) **No of subjects:** Not stated **Age** All
Author (year) Raman (1977) **Country of study** Canada **Geographic location** Areas in Canada, selected as outlined in inclusion criteria (pop. >25 000) **Year study started** 1954 **Year study ended:** 1973	**Outcome:** Mortality from cancer (all malignant neoplasms) **Method of outcome assessment:** Cases identified through Heath Division of Statistics, Candad, data, population data provided from census data	**Inclusion criteria** Urbanised core of each Census Metropolitan area Sections of fringe (area outside core) also included if a municipality of >25000 was in this area or a portion of a municipality listed as urbanised core lay in the fringe **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Age and sex	**Fluoride level (ppm):** *Group 1:*fluoridated <1959 (Artificial) *Group 2:* Fluoridated 1959-63(Artificial) *Group 3:*Fluoridated 1964-67 (Artificial) *Group 4:* Not fluoridated (Natural) **No of subjects:** Not stated **Age** Not stated	**Fluoride level (ppm):** *Group 1:*fluoridated <1959 (Artificial) *Group 2:* Fluoridated 1959-63(Artificial) *Group 3:*Fluoridated 1964-67(Artificial) *Group 4:* Not fluoridated(Natural) **No of subjects:** Not stated **Age** Not stated
Author (year) *Yiamouyiannis (1977) **Country of study** USA **Geographic location** 20 Cities in US, 10 F, 10 non-F **Year study started** 1952 **Year study ended:** 1969	**Outcome:** Death from cancer ages 0-24, 25-44, 45-64 and 65+ **Method of outcome assessment:** State/county/city health departments provided annual cancer deaths, missing data supplied by linear extrapolation/interpolation. Age, race & sex specific pops obtained by linear interpolation of census figures obtained from US Census Bureau	**Inclusion criteria** 10 largest fluoridated cities in US 10 largest non-fluoridated cities in US, with death rates >155 per 100 000 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Author shows that % non-white increased in fluoridated areas over study period, states that regression analysis performed of increase in age-adjusted cancer rate against increase in % white population, found no correlation **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:*Low (Natural) *Group 4:* Low (Natural) **Year fluoridation initiated:** 1952-56 **No of subjects:** Not stated **Age** 0-24, 25-44, 45-64, 65+	**Fluoride level (ppm):** *Group 1:*High (Artificial) *Group 4:* Low(Natural) **No of subjects:** Not stated **Age** 0-24, 25-44, 45-64, 65+

C9: Cancer Studies: Baseline Data
3. Case-Control Studies

Study Details	Case and Group 4 selection	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data	
Author (year) Gelberg (1995) **Country of study** USA **Geographic location** New York State **Year study started** 1978 **Year study ended** 1988	**Case-definition:** Cases of osteosarcoma newly diagnosed from January 1978 to December 1988 identified from the New York Cancer Registry. Results presented separately for questionnaires completed by subjects and parents. **Method of Group 4 selection:** Group 4s were randomly selected from live birth records maintained by the New York State Department of Health, had to survive until matched pairs subject's age at diagnosis **Matching:** Matched by year of birth and sex **Ratios of cases to Group 4s:** 1:1	**Inclusion criteria** Newly diagnosed cases of osteosarcoma Aged less than 24 years at time of diagnosis Resident in New York state excluding New York City **Exclusion criteria** Subjects with pre-existing cancers Resident in New York state excluding New York City	**Other sources of fluoride:** Lifetime exposure to fluoride from tablets, mouthrinses, toothpaste, dental treatments and total fluoride measured in cases and Group 4s **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Number of subjects** *Cases:* 55 *Group 4s 1:* 56 **Age:** <24	**Exposure 1:** Lifetime exposure to water fluoride of 0mg **Exposure 2:** Lifetime exposure to water fluoride of 1-1850mg **Exposure 3:** Lifetime exposure to water fluoride of 1851-3385mg
Author (year) McGuire (1991) **Country of study** USA **Geographic location** Iowa and Nebraska **Year study started** 1980 **Year study ended** 1990	**Case-definition:** Patients diagnosed with osteosarcoma between 1980 and 1990. Cases identified through University of Iowa cancer registry and medical records of division of orthopaedics, St. Joseph's Hospital, Omaha, Nebraska **Method of Group 4 selection:** Patients of appropriate orthopaedic department **Matching:** Age, gender and county of residence at time of diagnosis **Ratios of cases to Group 4s:** 1:1	**Inclusion criteria** Aged<=40 at diagnosis **Exclusion criteria** Patients with any prediagnosis history of radiation therapy Patients with history of kidney dialysis	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Number of subjects** *Cases:* 22 *Group 4s 1:* 22 **Age range (mean)** 0-40	**Exposure 1:** More than 1/3 of life at >0.7ppm **Exposure 2:** Lifetime exposure greater than 0.7ppm **Exposure 3:** More than 1/3 of childhood at 0.7ppm
Author (year) Moss (1995) **Country of study** USA **Geographic location** Wisconsin **Year study started** 1979 **Year study ended** 1989	**Case-definition:** Primary osteosarcoma tumours occurring in Wisconsin reported to the Wisconsin Cancer Reporting System between 1979-89 **Method of Group 4 selection:** 2 groups of Group 4s: brain and nervous system tumours and digestive system cancers, reported to Wisconsin cancer reporting system during the same period as the cases **Matching:** Match according to age in 0-14 year and then 10 year age-groups, until >84, sex and race **Ratios of cases to Group 4s:** 1:4	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Matched on race **Other confounding factors:** Population size, radiation levels, age, sex	**Number of subjects** *Cases:* 167 *Group 4s 1:* 647 *Group 4s 2:* 342 **Age range (mean)** Not stated	**Exposure 1:** Water fluoride level >0.7, estimated according to area of residence **Exposure 2:** Water fluoride level <0.7, estimated according to area of residence **Exposure 3:** Odds ratio adjusted for population, age, radiation and gender

C10: Cancer Studies: Individual Study Results

1. Cohort and Ecological Studies

a. Studies which present indirectly standardised results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Rate (Males)	Crude Rate (Females)	Standardisation						
							Methods	Observed		Expected		SMR	
								M	F	M	F	M	F
Chilvers (1985)	Cancer mortality from cancer of the buccal cavity and pharynx	*Group 1:* *Group 2:* *Group 3:* *Group 4:*	Water fluoride level	>=1.0 0.5-0.99 <=0.2 <=0.1			**Method used** Indirect **Standard population** Standardised mortality ratios provided by OPCS. Where no deaths occurred in area expected deaths calculated by applying England and Wales age-sex specific death rates. Standardised for age.	41 43 42 33	30 21 15 21			102.97 97.57 116.69 77.08	120.91 81.00 64.92 79.00
	Cancer mortality from all causes	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				2426 2525 2255 2632	2039 2169 1957 2236			95.06 89.02 97.06 95.55	96.36 97.18 98.58 97.92
	Cancer mortality from all stomach cancers	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				288 275 234 284	177 180 175 214			97.88 85.10 88.07 90.26	82.8 83.09 89.39 94.43
	Cancer mortality from breast cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1					410 483 396 470				96.78 105.47 98.13 101.66
	Cancer mortality from intestinal cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				162 180 177 189	230 264 221 277			93.51 94.21 113.14 101.62	93.82 104.94 97.69 105.90
	Cancer mortality from kidney cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				38 28 27 41	25 28 19 30			102.11 65.85 77.51 100.23	102.07 108.75 83.09 114.39
	Cancer mortality from lung cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				938 984 841 1035	214 221 181 207			92.97 87.71 91.01 94.80	97.71 95.41 88.21 87.47
	Cancer mortality from oesophagus cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				60 58 53 78	44 50 54 58			86.86 75.56 84.56 104.76	81.19 90.02 108.10 100.33
	Cancer mortality from ovary cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1					136 150 156 130				98.73 100.39 118.72 86.43
	Cancer mortality from pancreas cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				119 110 82 106	106 107 80 87			108.02 90.07 82.02 89.40	108.70 107.04 89.08 83.90

C10: Cancer Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Rate (Males)	Crude Rate (Females)	Standardisation						
							Methods	Observed		Expected		SMR	
								M	F	M	F	M	F
Chilvers (1985) - continued	Cancer mortality from rectum cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				115 133 153 143	103 114 96 117			89.11 93.52 131.86 103.26	93.49 101.23 94.43 99.64
	Cancer mortality from skin cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				19 21 22 23	30 16 26 25			97.59 93.96 120.79 107.15	142.81 69.98 129.32 108.10
	Cancer mortality from bladder cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.0 0.5-0.99 <=0.2 <=0.1				110 99 100 129	41 45 50 47			96.48 79.78 98.79 106.63	88.67 95.93 117.54 95.53
Hoover (1976)	Mortality from cancer of all sites	*Group 1:* *Group 2:* *Group 3:* *Group 4:*	Level of fluoride that >2/3 of the population were exposed to	>=2.0 1.3-1.9 0.7-1.2 <0.7			**Method used** Indirect **Standard population** The entire 1970 US population (5 year age-groups to 74, then 75-84 and 85+)					0.9 1.0 1.0 1.0	0.9 1.0 1.0 1.0
	Mortality from cancer of the testis	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=1.3 0.7-1.2 <0.7								1.6 0.7 1.1 0.9	
	Mortality from cancer of the nose and nasal sinuses	*Group 1:* *Group 2:* *Group 4:*		>=2.0 1.3-1.9 0.7-1.2 <0.7								0.8 1.1 1.1	2.0 0.7 1.2
	Mortality from cancer of the oesophagus	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=2.0 1.3-1.9 0.7-1.2 <0.7								0.8 0.9 1.0 1.1	0.6 1.0 1.0 1.2
	Mortality from cancer of the ovary	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=2.0 1.3-1.9 0.7-1.2 <0.7									0.9 1.0 1.0 1.1
	Mortality from cancer of the pancreas	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=2.0 1.3-1.9 0.7-1.2 <0.7								1.1 1.1 1.0 1.0	1.2 0.9 1.0 1.1
	Mortality from cancer of the prostate	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=2.0 1.3-1.9 0.7-1.2 <0.7								1.1 1.0 1.0 1.0	
	Mortality from cancer of the rectum	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		>=2.0 1.3-1.9 0.7-1.2 <0.7								0.6 1.0 1.0 1.1	0.8 0.9 1.1 1.0

C10: Cancer Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Rate (Males)	Crude Rate (Females)	Standardisation						
							Methods	Observed		Expected		SMR	
								M	F	M	F	M	F
Hoover (1976) - continued	Mortality from other lymphoma	*Group 1:*		>=2.0								0.9	1.1
		Group 2:		1.3-1.9								1.0	1.1
		Group 3:		0.7-1.2								1.1	1.0
		Group 4:		<0.7								0.8	1.0
	Mortality from cancer of the stomach	*Group 1:*		>=1.3								1.1	1.0
		Group 2:		0.7-1.2								1.1	1.0
		Group 3:		<0.7								1.0	1.0
		Group 4:										1.0	1.0
	Mortality from cancer of the lung	*Group 1:*		>=2.0								0.8	1.0
		Group 2:		1.3-1.9								1.0	1.0
		Group 3:		0.7-1.2								1.0	1.0
		Group 4:		<0.7								1.0	0.9
	Mortality from cancer of the thyroid	*Group 1:*		>=2.0								1.1	0.7
		Group 2:		1.3-1.9								1.2	1.3
		Group 4:		0.7-1.2								0.8	0.6
				<0.7									
	Mortality from cancer of the uterus	*Group 1:*		>=2.0									0.8
		Group 2:		1.3-1.9									1.1
		Group 3:		0.7-1.2									1.0
		Group 4:		<0.7									1.0
	Mortality from Hodgkin's disease	*Group 1:*		>=2.0								1.4	1.4
		Group 2:		1.3-1.9								0.7	0.6
		Group 3:		0.7-1.2								1.1	1.1
		Group 4:		<0.7								1.0	1.1
	Mortality from leukaemia	*Group 1:*		>=2.0								1.0	0.9
		Group 2:		1.3-1.9								1.0	0.9
		Group 3:		0.7-1.2								1.0	1.1
		Group 4:		<0.7								1.0	1.0
	Mortality from melanoma	*Group 1:*		>=1.3								1.3	1.0
		Group 2:		0.7-1.2								1.2	1.2
		Group 3:		<0.7								0.9	1.0
		Group 4:										1.0	0.9
	Mortality from multiple myeloma	*Group 1:*		>=2.0								0.7	1.7
		Group 2:		1.3-1.9								1.2	1.5
		Group 3:		0.7-1.2								0.9	0.9
		Group 4:		<0.7								1.2	0.9
	Mortality from cancer of the salivary gland	*Group 1:*		>=2.0								0.9	1.5
		Group 2:		1.3-1.9								1.2	1.0
		Group 4:		0.7-1.2								0.9	1.1
				<0.7									
	Mortality from cancer of the colon	*Group 1:*		>=1.3								0.9	1.0
		Group 2:		0.7-1.2								1.0	1.0
		Group 3:		<0.7								1.0	1.0
		Group 4:										1.0	1.1

C10: Cancer Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Rate (Males)	Crude Rate (Females)	Standardisation						
							Methods	Observed		Expected		SMR	
								M	F	M	F	M	F
Hoover (1976) - continued	Mortality from cancer of other endocrine cancers	*Group 1:*										1.4	1.6
		Group 2:										0.9	0.9
		Group 4:										1.0	1.0
	Mortality from cancer of the bladder	*Group 1:*		>=2.0								1.0	0.7
		Group 2:		1.3-1.9								1.1	1.2
		Group 3:		0.7-1.2								1.0	1.0
		Group 4:		<0.7								1.0	0.9
	Mortality from cancer of the bone	*Group 1:*		>=2.0								0.6	0.8
		Group 2:		1.3-1.9								1.2	0.9
		Group 3:		0.7-1.2								1.0	1.1
		Group 4:		<0.7								1.0	0.9
	Mortality from cancer of the brain	*Group 1:*		>=2.0								0.7	0.7
		Group 2:		1.3-1.9								1.0	1.1
		Group 3:		0.7-1.2								1.0	1.0
		Group 4:		<0.7								1.2	1.2
	Mortality from cancer of the nasopharynx	*Group 1:*		>=1.3								0.9	
		Group 2:		0.7-1.2								0.9	
		Group 3:		<0.7								1.8	
		Group 4:											
	Mortality from cancer of the cervix	*Group 1:*		>=2.0									0.9
		Group 2:		1.3-1.9									1.0
		Group 3:		0.7-1.2									1.1
		Group 4:		<0.7									0.9
	Mortality from cancer of the mouth and throat	*Group 1:*		>=2.0								0.7	0.9
		Group 2:		1.3-1.9								0.8	1.2
		Group 3:		0.7-1.2								1.0	1.0
		Group 4:		<0.7								1.1	1.0
	Mortality from cancer of the connective tissue	*Group 1:*		>=2.0								1.8	1.9
		Group 2:		1.3-1.9								1.5	0.9
		Group 3:		0.7-1.2								0.9	1.1
		Group 4:		<0.7								1.0	0.9
	Mortality from cancer of the eye	*Group 1:*		>=1.3								1.0	1.6
		Group 2:		0.7-1.2								0.9	0.7
		Group 4:		<0.7								1.5	1.3
	Mortality from cancer of the kidney	*Group 1:*		>=2.0								0.6	1.2
		Group 2:		1.3-1.9								1.2	1.0
		Group 3:		0.7-1.2								1.0	1.0
		Group 4:		<0.7								1.1	1.0
	Mortality from cancer of the larynx	*Group 1:*		>=2.0								1.3	1.1
		Group 2:		1.3-1.9								0.6	1.1
		Group 3:		0.7-1.2								1.1	0.7
		Group 4:		<0.7								1.1	
	Mortality from cancer of the lip	*Group 1:*		>=2.0								2.4	
		Group 2:		1.3-1.9								0.9	
		Group 3:		0.7-1.2								0.9	
		Group 4:		<0.7								1.1	

C10: Cancer Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Rate (Males)	Crude Rate (Females)	Standardisation						
							Methods	Observed		Expected		SMR	
								M	F	M	F	M	F
Hoover (1976) - continued	Mortality from cancer of the liver and bile duct	*Group 1:*		>=2.0								0.8	0.9
		Group 2:		1.3-1.9								0.8	0.7
		Group 3:		0.7-1.2								1.1	1.1
		Group 4:		<0.7								1.0	0.9
	Mortality from other skin cancer	*Group 1:*		>=2.0								0.9	0.7
		Group 2:		1.3-1.9								1.0	0.8
		Group 3:		0.7-1.2								1.0	1.0
		Group 4:		<0.7								1.0	1.1
	Mortality from cancer of the breast	*Group 1:*		>=2.0									1.0
		Group 2:		1.3-1.9									1.0
		Group 3:		0.7-1.2									1.0
		Group 4:		<0.7									1.0
Kinlen (1975)	Thyroid cancer	*Group 1:*	Water fluoride level	1	9.3		**Method used** Indirect **Standard population** Not stated, standardised for age and sex					1.05	
		Group 2:		0.5-0.99	6.9							0.79	
		Group 3:		<0.2	11.2							1.27	
		Group 4:		<0.1	9.4							1.02	
	Bone cancer	*Group 1:*		1	3.7							1.00	
		Group 2:		0.5-0.99	3.9							1.06	
		Group 3:		<0.2	3.7							1.02	
		Group 4:		<0.1	3.5							0.94	
	Breast cancer	*Group 1:*		1	117.5							0.92	
		Group 2:		0.5-0.99	128.2							1.06	
		Group 3:		<0.2	127.4							1.08	
		Group 4:		<0.1	123.2							0.97	
	Colon cancer	*Group 1:*		1	80.0							0.96	
		Group 2:		0.5-0.99	78.7							1.03	
		Group 3:		<0.2	75.5							0.99	
		Group 4:		<0.1	80.2							1.00	
	Kidney cancer	*Group 1:*		1	26.7							1.01	
		Group 2:		0.5-0.99	25.4							1.00	
		Group 3:		<0.2	25.7							1.02	
		Group 4:		<0.1	26.0							0.98	
	Oesophagus cancer	*Group 1:*		1	15.1							0.87	
		Group 2:		0.5-0.99	16.8							1.02	
		Group 3:		<0.2	14.3							0.87	
		Group 4:		<0.1	19.7							1.13	
	Stomach cancer	*Group 1:*		1	77.7							0.88	
		Group 2:		0.5-0.99	94.1							1.15	
		Group 3:		<0.2	64.1							0.9	
		Group 4:		<0.1	90.9							1.05	
	Bladder cancer	*Group 1:*		1	89.1							1.00	
		Group 2:		0.5-0.99	81.1							0.96	
		Group 3:		<0.2	87.1							1.06	
		Group 4:		<0.1	87.7							1.00	

C10: Cancer Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Rate (Males)	Crude Rate (Females)	Standardisation: Methods	Observed M	Observed F	Expected M	Expected F	SMR M	SMR F
Kinlen (1975) - continued	Rectum cancer	*Group 1:*		1	56.6							0.93	
		Group 2:		0.5-0.99	62.4							1.11	
		Group 3:		<0.2	51.8							0.94	
		Group 4:		<0.1	57.9							0.99	
Lynch (1985)	Cancer of all other sites	*Group 1:*	Length of time from initiation of artificial water fluoridation until 1981, in the high population group	<20			**Method used** Indirect **Standard population** 1970 State of Iowa site-sex specific five-year age-specific population counts					1.050	1.041
		Group 4:		>20								1.146	1.094
	Incidence of bladder cancer	*Group 1:*		<20								1.085	1.192
		Group 4:		>20								1.176	1.236
	Incidence of breast cancer	*Group 1:*		<20									1.073
		Group 4:		>20									1.126
	Incidence of colon cancer	*Group 1:*		<20								1.092	1.031
		Group 4:		>20								1.149	1.120
	Incidence of cancer (all sites)	*Group 1:*		<20								1.082	1.066
		Group 4:		>20								1.172	1.125
	Incidence of rectum cancer	*Group 1:*		<20								1.003	1.040
		Group 4:		>20								1.193	1.026
	Incidence of prostate cancer	*Group 1:*		<20								1.027	
		Group 4:		>20								1.061	
	Incidence of lung cancer	*Group 1:*		<20								1.208	1.310
		Group 4:		>20								1.331	1.451
	Incidence of colon cancer	*Group 1:*	Length of time from initiation of artificial water fluoridation until 1981, in the low population (<10 000) group	0-9								1.131	1.035
		Group 2:		10-19								1.088	1.018
		Group 3:		20+								0.993	1.093
	Incidence of breast cancer	*Group 1:*		0-9									1.050
		Group 2:		10-19									1.080
		Group 3:		20+									1.019
	Incidence of bladder cancer	*Group 1:*		0-9								1.276	0.865
		Group 2:		10-19								1.036	0.892
		Group 3:		20+								1.031	1.164
	Incidence of rectum cancer	*Group 1:*		0-9								1.101	1.005
		Group 2:		10-19								1.010	1.121
		Group 3:		20+								1.006	0.927
	Incidence of cancer (all sites)	*Group 1:*		0-9								1.053	1.016
		Group 2:		10-19								1.044	1.044
		Group 3:		20+								1.074	1.039
	Incidence of cancer of all other sites	*Group 1:*		0-9								0.983	0.999
		Group 2:		10-19								1.029	1.026
		Group 3:		20+								1.107	1.052
	Incidence of prostate	*Group 1:*		0-9								0.951	
		Group 2:		10-19								1.073	
		Group 3:		20+								1.135	
	Incidence of lung cancer	*Group 1:*		0-9								1.155	1.014
		Group 2:		10-19								1.007	1.091
		Group 3:		20+								1.027	0.895

C10: Cancer Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Rate (Males)	Crude Rate (Females)	Standardisation						
							Methods	Observed		Expected		SMR	
								M	F	M	F	M	F
Lynch (1985) - continued	Incidence of bladder cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*	Natural water fluoride level, and minimum length of exposure to this fluoride level (Groups 1& 2: 1968-81, Group 3 & Group 4 1950-81)	<=0.5 >=1.0 <=0.5 >=1.0								1.083 0.924 1.101 1.034	1.161 1.142 1.179 1.355
	Incidence of breast cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		<=0.5 >=1.0 <=0.5 >=1.0									0.960 0.978 0.987 1.043
	Incidence of prostate cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		<=0.5 >=1.0 <=0.5 >=1.0								1.079 1.020 1.107 1.167	
	Incidence of rectum cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		<=0.5 >=1.0 <=0.5 >=1.0								1.308 0.938 1.276 0.967	1.106 1.053 1.053 0.967
	Incidence of cancer from all sites	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		<=0.5 >=1.0 <=0.5 >=1.0								1.101 1.033 1.110 1.100	1.023 1.024 1.035 1.055
	Incidence of lung cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		<=0.5 >=1.0 <=0.5 >=1.0								1.047 1.088 1.034 1.038	0.918 1.051 0.873 1.020
	Incidence of colon cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		<=0.5 >=1.0 <=0.5 >=1.0								1.040 1.214 1.023 1.280	1.019 1.009 1.029 1.038
	Incidence of cancer of all other sites	*Group 1:* *Group 2:* *Group 3:* *Group 4:*		<=0.5 >=1.0 <=0.5 >=1.0								1.134 0.995 1.155 1.076	1.057 1.042 1.073 1.062
Richards (1979)	Deaths from Malignant neoplasms	*Group 1:* *Group 4:*	Water fluoride level	High Low	146.7 176.8		**Method used** Indirect **Standard population** Annual average number of deaths with the census population of 1971 used to calculate 1971 SMRs & applied to population of selected study areas	240 340		262 359		91.6 94.9	

C10: Cancer Studies: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Rate (Males)	Crude Rate (Females)	Standardisation						
							Methods	Observed		Expected		SMR	
								M	F	M	F	M	F
Smith (1980)	Deaths from cancer	*Group 1:* *Group 2:* *Group 3:* *Group 4:*	Water fluoride level, exposed 1 & 2 used for 1950 data, exposed 3 & 4 for 1970 data	Low Low High Low	180.8 179.0 217.4 194.2		**Method used** Indirect **Standard population** Cancer death rates for the whole of US, using 1950 rates for 1950 data and 1970 rates for 1970 data. Standardised for age, sex, ethnic origin	180.8 179.0 217.4 194.2 Expected Cancer Death rate 1950 F: 1.0 Non-F: 1.0		146.9 155.5 217.4 168.9 Expected Cancer Death rate 1970 F: 0.96 Non-F: 1.0			

b. Studies which present directly standardised results

Study Details	Outcome	Group	Exposure	Crude Risk Males/ 100 000	Crude Risk Females/ 100 000	Summary Measure (CI):		
						Details	Male	Female
Glattre (1979)	Mortality from oral or pharyngeal cancer (ICD 140-149)	*Group 1:* *Group 2:* *Group 4:*	0.11-0.50 0.06-.010 0-0.05			**Method used** Direct **Standard population** Age standardised mortality rate (standard error of the mean)	3.4 (0.81) 4.7 (0.90) 5.3 (0.99)	0.6 (0.24) 1.1 (0.43) 1.5 (0.34)

c. Studies which present crude results only

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Risk /100 000	
					Male	Female
Cohen (1992)	Osteosarcoma incidence	*Group 1:* *Control:*	% of the population exposed to fluoridated water	>85% <10%	1.35 0.40	0.35 0.35
Hrudey (1990)	Osteosarcoma incidence	*Group 1:* *Group 4:*	Water fluoride content	1 0.3	0.27 0.29	
Mahoney (1991) (SMSA data for fluoridated areas used, in order to best match the data from non-fluoridated areas)	Osteosarcoma incidence Age <30	*Group 1:* *Group 2:*	Water fluoride level	High Low	0.43 0.44	0.25 0.32
	Age >30	*Group 3:* *Group 4*		High Low	0.29 0.33	0.22 0.24
	Bone cancer incidence Age < 30	*Group 1:* *Group 2:*	Fluoridated water	High Low	0.90 0.97	0.64 0.67
	Age >30	*Group 3:* *Group 4:*		High Low	1.04 1.24	0.8 0.70

C10: Cancer Studies: Individual Study Results

2. Before-After Studies

Study Details	Outcome Presented	Group	Fluoride Level	Outcome 1	Outcome 2	Outcome 3	Outcome 4
Chilvers (1983)	Mean standardised mortality ratios for 1950 and 1970, US 1960 population used as standard			**Death from cancer (SE)**			
		Baseline:					
		Group 1: *Group 4:*	Low Low	120.54 116.80			
		Final:					
		Group 1: *Group 4*	High Low	123.84 120.18			
Chilvers (1982)	Standardised mortality ratios presented. Indirect standardisation carried out simultaneously for age (0-1, 1-4, 5-14) , sex and ethnic group (white & non-white). Specific rates used were total US 1960			**Digestive organs (SE)**	**Respiratory system (SE)**	**Breast (SE)**	**Genital organs (SE)**
		Baseline:					
		Group 1: *Group 4:*	Low Low	125.31 109.92	135.71 130.89	119.90 112.56	109.27 106.62
		Final:					
		Group 1: *Group 4*	High Low	106.72 96.05	199.17 195.53	120.89 114.67	92.97 97.25
				Urinary organs (SE)	**Leukaemia and aleukaemia (SE)**	**Other malignant neoplasms (SE)**	**All malignant neoplasms (SE)**
		Baseline:					
		Group 1: *Group 4:*	Low Low	125.51 114.82	104.56 108.01	115.64 115.74	121.31 113.87
		Final:					
		Group 1: *Group 4*	High Low	118.79 109.20	102.01 103.07	136.40 130.94	124.03 118.43
Cook-Mozaffari (1981)	Age adjusted rate, adjusted using geometric mean of average annual rates for England and Wales for each study period, age groups 0-4 & then 10 year groups up to 85+. SMRs multiplied by age-standardised death rates for England and Wales to give rate			**Age adjusted cancer deaths males, 1959-63 & 1969-73 (SE)**	**Age adjusted cancer deaths females, 1959-63 & 1969-73 (SE)**	**Age adjusted cancer deaths males, 1969-73 & 1974-78 (SE)**	**Age adjusted cancer deaths females, 1969-73 & 1974-78 (SE)**
		Baseline:					
		Group 1: *Group 4:*	Low Low	201.6 211.2	121.9 120.1	211.5 220.7	128.8 128.1
		Final:					
		Group 1: *Group 4*	High Low	214.3 223.9	129.7 128.6	213.5 215.7	130.2 129.9
Doll (1977)	Age (10 year groups), sex and ethnic group (white/non-white) standardised (standard, specific national cancer-mortality rates for US) ratio of observed to expected deaths from cancer			**Deaths from cancer (SE)**			
		Baseline:					
		Group 1: *Group 4:*	Low low	01.23 01.15			
		Final:					
		Group 1: *Group 4*	High Low	01.18 01.17			

C10: Cancer Studies: Individual Study Results

Study Details	Outcome Presented	Group	Fluoride Level	Outcome 1	Outcome 2	Outcome 3	Outcome 4
Goodall (1980)	Crude death rates from cancer per 100 000 population			**Cancer death rate males**	**Cancer death rate females**		
		Baseline:					
		Group 1:	Low	629.5	484.7		
		Group 4:	Low	567.7	501.4		
		Final:					
		Group 1:	High	691.1	463.2		
		Group 4	low	733.5	511.9		
Hoover (1991)	Age adjusted incidence rates for 1973-80 and 1981-87			**Incidence of osteosarcoma (males only) (SE)**	**Incidence of bone and joint cancers (both sexes) (SE)**		
		Baseline:					
		Group 1:	<10% pop, <0.3	0.29	0.90		
		Group 2:	>60% pop, F<1955	0.32	0.90		
		Group 4:	>60% pop, F>=1966	0.35	0.83		
		Final:					
		Group 1:	<10% pop, <0.3	0.30	0.85		
		Group 2:	>60% pop, F<1955	0.42	0.86		
		Group 4	>60% pop, F>=1966	0.45	0.93		
Schlesinger (1956)	Crude death rate			**Deaths from cancer (SE)**	**(SE)**		
		Baseline:					
		Group 1:		219.0	221.2		
		Group 4:		169.0	264.4		
		Final:					
		Group 1:	1-1.2	221.0			
		Group 4	<0.2	264.4			
Raman (1977)	Age standardised results using the 1971 Canada population as standard			**Mortality from cancer (all malignant neoplasms) - males (SE)**	**Mortality from cancer (all malignant neoplasms) - females (SE)**		
		Baseline:					
		Group 1:	F <1959	161.1	146.0		
		Group 2:	F 1959-63	193.4	167.1		
		Group 3:	F 1964-67	159.5	134.9		
		Group 4:	Not fluoridated	177.0	165.2		
		Final:					
		Group 1:	F <1959	170.5	136.9		
		Group 2:	F 1959-63	181.2	132.9		
		Group 3:	F 1964-67	166.9	122.9		
		Group 4	Not fluoridated	179.5	137.2		
Yiamouyiannis (1977)	Crude death rates			**Death from cancer ages 0-24 (SE)**	**Deaths from cancer ages 25-44 (SE)**	**Deaths from cancer ages 45-64 (SE)**	**Deaths from cancer ages 65+ (SE)**
		Baseline:					
		Group 1:	Low	9.7	49.96	338.3	1032.8
		Group 4:	Low	9.69	47.33	323.5	974.4
		Final:					
		Group 1:	High	7.30	47.15	375.1	1069.9
		Group 4	Low	7.20	44.67	347.2	977.6

C10: Cancer Studies: Individual Study Results

3. Case-Control Studies

Study Details	Outcome	Number of Subjects per Group	Exposures	Level of Exposure in Cases	Level of Exposure in Group 4 1	OR for Exposure
Gelberg (1995)	Cases of osteosarcoma newly diagnosed from January 1978 to December 1988 identified from the New York Cancer Registry. Questionnaire completed by subjects.	55	**Exposure 1:** Lifetime exposure to water fluoride of 0 **Exposure 2:** Lifetime exposure to water fluoride of 1-1850mg **Exposure 3:** Lifetime exposure to water fluoride of 1851-3385mg	21 15 14	29 11 12	1.00 2.31(0.74, 7.20) 2.07(0.53, 8.02)
	Questionnaire completed by parents.	110		40 32 26	57 16 23	1.00 4.13(1.65, 10.35) 1.84(0.81, 4.2)
McGuire (1991)	Patients diagnosed with osteosarcoma between 1980 and 1990. Cases identified through University of Iowa cancer registry and medical records of division of orthopaedics, St. Joseph's Hospital, Omaha, Nebraska	22	**Exposure 1:** More than 1/3 of life at >0.7ppm **Exposure 2:** Lifetime exposure greater than 0.7ppm **Exposure 3:** More than 1/3 of childhood at 0.7ppm			0.14 (0.02, 1.22) 0.33 (0.04, 2.50) 0.33 (0.04, 2.50)
Moss (1995)	Primary osteosarcoma tumours occurring in Wisconsin reported to the Wisconsin Cancer Reporting System between 1979-1989	167	**Exposure 1:** Water fluoride level >0.7, estimated according to area of residence **Exposure 2:** Water fluoride level <0.7, estimated according to area of residence **Exposure 3:** Odds ratio adjusted for population, age, radiation and gender	110 57	695 294	1.0(0.6-1.5)

C11: Other Adverse Effects Studies: Baseline Data

1. Cohort and Ecological Studies

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Berry (1958) **Country of study** England **Geographic location** Essex county subdivided into fluoridated and non-fluoridated areas **Year study started** 1945 **Study length (years)** 9 **Study design:** Ecological	**Outcome:** Number of births with Down's syndrome per 1000 births **Method of outcome assessment:** Information sought from institutions, death certificates, records of medical officers of health authorities, personal knowledge of health visitors	**Inclusion criteria** Children born in study areas during study period Mothers living in study area at time of birth **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Water fluoride level *Group 1:* 0.7-1.1 *Group 2:* 1.9-2.0 *Group 3:* 0.9 *Group 4:* <0.2 *Group 5:* <0.2 *Group 6:* <0.2 *Group 7:* <0.2 *Control:* <0.2 **No of subjects:** *Group 1:* 20760 *Group 2:* 14710 *Group 3:* 9492 *Group 4:* 12620 *Group 5:* 11587 *Group 6:* 22452 *Group 7:* 14873 *Control:* 6870
Author (year) Erickson (1978) **Country of study** USA **Geographic location** Georgia **Year study started** 1960-1973 **Study length (years)** 13 **Study design:** Ecological	**Outcome:** Incidence of Down syndrome and other congenital malformations **Method of outcome assessment:** Cases identified through the Metropolitan Atlanta Congenital Malformations Surveillance Program and National Cleft Lip and Palate Intelligence service. Data for Down syndrome was supplemented by a retrospective ascertainment (using multiple sources) of children born between 1960 and 1967.	**Inclusion criteria** Birth of white children only Areas in which mothers' usual place of residence at birth of child permitted determination of exposure to fluoridated water **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** White children only **Other confounding factors:** Down syndrome results stratified on maternal age	**Exposure:** Water fluoride content *Group 1*: High (Artificial) *Control*: Low (Natural) **Year of fluoridation:** 1951-1969 **No of subjects:** Metropolitan area *Group 1:* 95254 *Control:* 25373 NIS surveillance areas *Group 1:* 234300 *Control:* 1032100
Author (year) Erickson (1978) **Country of study** USA **Geographic location** Selected fluoridated and non-fluoridated cities in USA **Year study started** 1969 **Study length (years)** 3 **Study design:** Ecological	**Outcome:** Deaths from all causes classified into 34 categories **Method of outcome assessment:** Computer tapes containing information abstracted from all United States death certificates for years 1969-1971 made available by United States National Center for Health Statistics	**Inclusion criteria** Cities with 1957 populations >250 000 Black and white racial groups only **Exclusion criteria** Cities with mixed fluoridation status Cities with supplies fluoridated since 1965	**Other sources of fluoride:** Not stated **Social class:** Median education, median income, % of workforce employed in manufacturing **Ethnicity:** Black and white racial groups only **Other confounding factors:** Population density	**Exposure:** Water fluoride level *Group 1:* >0.7 *Control:* <0.7(Natural) **No of subjects:** *Group 1:* 15972817 *Control:* 11106746 **Age** All ages, age, sex and race standardised rates presented

C11: Other Adverse Effects Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Erickson (1980) **Country of study** USA **Geographic location** 27 fluoridated, 17 non fluoridated US cities **Year study started** 1973 **Study length (years)** 2 **Study design:** Ecological	**Outcome:** Number of lives births with Down's Syndrome Number of live births with congenital malformations (excluding Down's syndrome) **Method of outcome assessment:** Data from birth certificates obtained from US Nation Center for Health Statistics, denominator number of live births in study areas	**Inclusion criteria** Cities with 1970 populations >=250 000 Cities fluoridated for >= 5 years by 1973 **Exclusion criteria** Cities with mixed fluoridation status States which do not report birth defects on birth certificates Cities fluoridated for <5 years by 1973	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** White births only **Other confounding factors:** Not stated	**Exposure:** Water fluoride level *Group 1:* >=0.7 *Control:* <0.7(Natural) **No of subjects:** *Group 1:* 432580 *Control:* 204185 **Age** Not stated
Author (year) Farkas (1983) **Country of study** Hungary **Geographic location** Kunszentmarton (F), Kiskunmajsa (non-F) **Year study started** **Study length (years)** **Study design:** Retrospective cohort	**Outcome:** Median age at menarche **Method of outcome assessment:** Data collected from children	**Inclusion criteria** Girls resident in study areas **Exclusion criteria** Twins and gypsy children of another ethnic group	**Other sources of fluoride:** Not stated **Social class:** Not stated, author states that areas similar in respects other than water fluoride level **Ethnicity:** Children of other ethnic origin excluded (assume means only hungarian children included) **Other confounding factors:** Not stated	**Exposure:** Water fluoride level *Group 1:* 1.09(Natural) *Group 2:* () *Group 3:* () *Control:* 0.17(Natural) **Year of fluoridation:** **No of subjects:** *Group 1:* 337 0 0 *Group 2:* 0 0 *Group 3:* 0 0 *Control:* 467 0 0 **Age** 10-19.5
Author (year) Forbes (1997) **Country of study** Canada **Geographic location** Ontario **Year study started** Not stated **Study length (years)** Not stated **Study design:** Ecological	**Outcome:** Alzheimer's disease reported as the underlying cause of death Rate of impaired mental functioning **Method of outcome assessment:** Data obtained from death certificate, place of death used to estimate water supply	**Inclusion criteria** Subjects enrolled in the Ontario Longitudinal Study of Ageing **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Levels of aluminium, iron and silica in water, water pH and source of water	**Exposure:** Water fluoride level *Group 1:* >=0.98 *Group 2:* 0.5-0.98 *Control:* <0.5 **No of subjects:** Not stated **Age** Age 85+ **Exposure:** Water fluoride level *Group 1:* >=0.8 *Control:* <0.8(Natural) **No of subjects:** *Group 1:* 397 *Control:* 144 **Age** All subjects were aged 76 years

C11: Other Adverse Effects Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Griffith (1963) **Country of study** Wales **Geographic location** Anglesey **Year study started** 1960 **Study length (years)** Not stated **Study design:** Ecological	**Outcome:** Anaemia during pregnancy **Method of outcome assessment:** Results of haemoglobin tests taken during clinic visits used to calculate incidence of anaemia, defined as haemoglobin level below 75 (units not stated) at any time	**Inclusion criteria** Pregnant women that could be allocated to one of two water supplies Pregnant women for whom a clinic record was available which included at least one estimate of haemoglobin level **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Parity and stage of pregnancy	**Exposure:** Water fluoride level *Group 1:* 1.0(Artificial) *Control:* <0.1(Natural) **No of subjects:** Not stated **Age** Not stated
Author (year) Hagan (1954) **Country of study** USA **Geographic location** 32 paired fluoride and non-fluoride cities in the US **Year study started** 1949 **Study length (years)** 1 **Study design:** Ecological	**Outcome:** Average yearly deaths from all causes **Method of outcome assessment:** Number of deaths in study areas obtained from vital statistics of the United States	**Inclusion criteria** Cities with 1950 census populations >10 000 **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Rates adjusted for race **Other confounding factors:** Rates also adjusted for age & sex	**Exposure:** Cities where majority of analyses of water supply indicate the presence of fluoride at following levels: *Group 1:* >=0.7 *Control:* <=0.25 **Year of fluoridation:** **No of subjects:** *Group 1:* 892625 *Control:* 1297500 **Age** Results standardised for age
Author (year) Jacqmin-Gadda (1994) **Country of study** France **Geographic location** Gironde and Dordogne **Year study started** Not stated **Study design:** Ecological	**Outcome:** Cognitive impairment (used as major clinical sign of Alzheimer's) **Method of outcome assessment:** Mini-mental state examination used as measure of cognitive mental status, total score ranges from 0-30 cognitive impairment defined as a score <24	**Inclusion criteria** Men and women aged 65 years and older **Exclusion criteria** Areas where water samples could not be collected	**Other sources of fluoride:** Not stated **Social class:** Principal lifetime occupation, educational level **Ethnicity:** Not stated **Other confounding factors:** Age and sex, water fluoride levels of calcium, aluminium and pH	**Exposure:** Water fluoride level *Group 1:* 0.6-2.03 (Natural) *Group 2:* 0.11-0.6 (Natural) *Group3:* 0.07-0.11 (Natural) *Group4:* 0.03-0.07 (Natural) **No of subjects:** *Group 1:* 626 *Group 2:* 1417 *Group 3:* 812 *Group 4:* 635

C11: Other Adverse Effects Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Jooste (1999) **Country of study** South Africa **Geographic location** Victoria West and Williston (Low fluoride), Carnarvon and Frazerburg (Medium fluoride), Brandvlei and Kenhardt (high fluoride) **Year study started** Not stated **Study design:** Cross Sectional	**Outcome:** % Prevalence of goitre **Method of outcome assessment:** All children examined by same physician to assess size of thyroid gland and incidence of goitre according to standard criteria	**Inclusion criteria** All 6, 12, and 15 year old children Lifetime residents of study areas **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Use of iodised and non-iodised salt for cooking, height, weight, urinary iodine levels, water iodine levels, salt iodine levels	**Exposure:** Water fluoride level *Group 1:* 2.6(Natural) *Group 2:* 1.7(Natural) *Group 3:* 0.9 (Natural) *Group 3:* 1.1(Natural) *Group 5:* 0.3(Natural) *Control:* 0.5(Natural) **No of subjects:** *Group 1:* 183 *Group 2:* 94 *Group 3:* 87 *Group 4:* 95 *Group 5:* 85 *Control:* 127 **Age** Ages 6, 12 and 15
Author (year) Needleman (1974) **Country of study** USA **Geographic location** Massachusetts **Year study started** 1950 **Study length (years)** 17 **Study design:** Ecological	**Outcome:** Cases of Down's syndrome **Method of outcome assessment:** Cases identified through maternity and paediatric hospitals, the Massachusetts Departments of Public and Mental Health, private nurseries and school for mentally retarded children, karyotyping laboratories and several miscellaneous sources	**Inclusion criteria** Children born with Down's syndrome **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Water fluoride level (artificially fluoridated areas fluoridated at some point during study period), status defined by the fluoride level of mother's residence 9 months before birth *Group 1:* 1(Artificial) *Control:* <0.3 (Natural) **Year of fluoridation:** **No of subjects:** *Group 1:* 81017 *Control:* 1752435 **Age** Maternal mean age in fluoride area = 34.0, in non-fluoride area = 33.2

C11: Other Adverse Effects Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Rapaport (1957) **Country of study** USA **Geographic location** Areas with different water fluoride levels in Wisconsin, North and South Dakota and Illinois **Year study started** Not stated **Study length (years)** Not stated **Study design:** Ecological	**Outcome:** Prevalence of Down's syndrome **Method of outcome assessment:** Alive subjects with Down's syndrome identified through institutions in North and South Dakota (cases living in the community not identified)	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Exposure:** Water fluoride level *Group 1:* >3 *Control:* <3 **No of subjects:** *Group 1:* 31575 *Control:* 467685
	Method of outcome assessment: Alive subjects with Down's syndrome identified through institutions in Illinois			*Group 1:* 0.1-0.2 *Control:* 0.0 **No of subjects:** *Group 1:* 670120 *Control:* 77049
	Method of outcome assessment: Alive subjects with Down's syndrome identified through institutions in North Dakota			*Group 1:* 1.6-2.6 *Group 2:* 1.0-1.2 *Group 3:* 0.4-0.7 *Control:* 0.3 **No of subjects:** *Group 1:* 41618 *Group 2:* 210628 *Group 3:* 196258 *Control:* 151167
	Method of outcome assessment: Alive subjects with Down's syndrome identified through institutions in Wisconsin			*Group 1:* 2.8 *Group 2:* 1.4 *Group 3:* 0.5 *Control:* 0.1 **No of subjects:** *Group 1:* 52735 *Group 2:* 21538 *Group 3:* 51189 *Control:* 1076876

C11: Other Adverse Effects Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Rapaport (1963) **Country of study** USA **Geographic location** Illinois **Year study started** 1950 **Study length (years)** 6 **Study design:** Ecological	**Outcome:** Infant mortality **Method of outcome assessment:** Infant mortality data provided by the Public Health department of the state of Wisconsin from January 1946 until December 1956	**Inclusion criteria** All cases children with Down's syndrome born during study period Town (of mother's residence) size 10 000 - 100 000 **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Maternal age, effect of other minerals in water: iron, magnesium, manganese, calcium	**Exposure:** Water fluoride level *Group 1:* >2.0(Natural) *Control:* <1.0(Natural) **Year of fluoridation:** **No of subjects:** *Group 1:* 15515 *Control:* 11935
	Outcome: Incidence of Down's syndrome per 100 000 births **Method of outcome assessment:** All cases of Down's syndrome born during study period identified from birth and death certificates, registers of specialist medical educational state institutions	**Inclusion criteria** All cases children with Down's syndrome born during study period Town (of mother's residence) size 10 000 - 100 000 **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Maternal age, effect of other minerals in water: iron, magnesium, manganese, calcium	**Exposure:** Water fluoride level for area in which mother was living at time of birth *Group 1:* 1.0-2.6 *Group 2:* 0.3-0.7 *Group 3:* 0.1-0.2 *Control:* 0.0 **Year of fluoridation:** **No of subjects:** *Group 1:* 67053 *Group 2:* 70111 *Group 3:* 132665 *Control:* 63521
Author (year) Still (1980) **Country of study** USA **Geographic location** Anderson (low F), Horry (High F), York (low F); South Carolina **Year study started** 1971 **Study length (years)** 8 **Study design:** Ecological	**Outcome:** Primary degenerative dementia **Method of outcome assessment:** First admissions to South Carolina Dept. of Mental Health Hospitals from study areas between 1/7/1971 and 30/6/1979, with DSM codes listed. Mean pop. estimates provided by office of Co-operative Health Statistics, South Carolina Budget & Control Board	**Inclusion criteria** All first admission to the South Carolina Department of Mental Health from the study areas Patients aged 55 or more **Exclusion criteria** Patients resident in study areas for <10 years before first admission	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Reported as white/non-white **Other confounding factors:** Chloride, magnesium and calcium water content	**Exposure:** Water fluoride level *Group 1:* 4.18 *Group 3:* 0.49 *Control:* 0.61 **No of subjects:** *Group 1:* 17161.2 *Group 3:* 23419.2 *Control:* 16856.1 **Age** 55 or more

C11: Other Adverse Effects Studies: Baseline Data

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Zhao (1996) **Country of study** China **Geographic location** Sima (high F), Xinghua (lower F) **Year study started** Not stated **Study length (years)** Not stated **Study design:** Cross-sectional	**Outcome:** IQ **Method of outcome assessment:** IQ of all children was measured using official intelligence quotient (IQ) tests lasting 40 minutes	**Inclusion criteria** Children whose mothers lived in study areas while pregnant Children aged 7-14 **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Author states that occupations, living standards and social customs of residents of the two study areas are similar **Ethnicity:** Not stated **Other confounding factors:** Educational level of parents	**Exposure:** Water fluoride level *Group 1:* 4.12 *Control:* 0.91 **Year of fluoridation:** **No of subjects:** *Group 1:* 160 *Control:* 160 **Age** 7-14

2. Before/After Studies

Study Details	Outcome Details	Inclusion/ Exclusion Criteria	Confounding Factors	Baseline Group Characteristics	Final Group Characteristics
Author (year) Briner (1966) **Country of study** Chile **Geographic location** La Serena (natural-F), Curico (Artificial F) and San Fernando (low-F) **Year study started** 1953 **Year study ended:** 1963	**Outcome:** Mortality **Method of outcome assessment:** Census figures used to provide information on number of deaths and population figures	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:*low (Natural) *Group 2:* 0.6-0.7(Natural) *Control:* low (Natural) **Year fluoridation initiated:** 1953 **No of subjects:** *Group 1:* 46017 *Group 2:* 51267 *Control:* 35560 **Age** All	**Fluoride level (ppm):** *Group 1:*1 (Artificial) *Group 2:* 0.6-0.7(Natural) *Control:* low(Natural) **No of subjects:** *Group 1:* 58612 *Group 2:* 64927 *Control:* 42952 **Age** All
Author (year) Overton (1954) **Country of study** USA **Geographic location** Newburgh (F), Kingston (non-F), New York State **Year study started** 1939 **Year study ended:** 1952	**Outcome:** Infant mortality Still births **Method of outcome assessment:** Cases identified through routinely collected mortality data	**Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Areas similar in general racial, social and economic conditions **Ethnicity:** Areas similar in racial structure **Other confounding factors:** Not stated	**Fluoride level (ppm):** *Group 1:*low (Natural) *Control:* low (Natural) **Year fluoridation initiated:** 1945 **No of subjects:** Not stated **Age** Not stated	**Fluoride level (ppm):** *Group 1:*1-1.2 (Artificial) *Control:* low(Natural) **No of subjects:** Not stated **Age** Not stated

C11: Other Adverse Effects Studies: Baseline Data

Study Details	Outcome Details	Inclusion/ Exclusion Criteria	Confounding Factors	Baseline Group Characteristics	Final Group Characteristics
Author (year) Rogot (1978) **Country of study** USA **Geographic location** 484 urban areas of US **Year study started** 1950 **Year study ended:** 1970	**Outcome:** Mortality **Method of outcome assessment:** Number of deaths obtained from official vital statistics for years 1949-50 (baseline), 1959-61 (not extracted) and 1969-71 (final)	**Inclusion criteria** Cities with populations >25 000 Areas with reliable mortality data by cause for study years **Exclusion criteria** Cities of uncertain fluoridation status	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Standardised for race **Other confounding factors:** Standardised for age and sex	**Fluoride level (ppm):** *Group 1:*Low *Group 2:* >=0.7(Natural) *Control:* <0.7 (Natural) **Year fluoridation initiated:** 1945-69 **No of subjects:** *Group 1:* 37700000 *Group 2:* 2100000 *Control:* 17900000 **Age** Not stated	**Fluoride level (ppm):** *Group 1:*>=0.7 (Artificial) *Group 2:* >=0.7(Natural) *Control:* <0.7(Natural) **No of subjects:** *Group 1:* 40500000 *Group 2:* 4000000 *Control:* 22400000 **Age** Not stated
Author (year) Schatz (1976) **Country of study** Chile **Geographic location** Curico (F), San Fernando (non-F) & La Serena(natural-F) **Year study started** 1954 **Year study ended:** 1964	**Outcome:** Mortality **Method of outcome assessment:** Statistics (pop. data & number of deaths) obtained directly from annual reports from the demographic department of the Chilean government	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** La Serena has different kind of soil and much warmer and drier climate than other 2 study areas	**Fluoride level (ppm):** *Group 1:*low (Natural) *Group 2:* 0.67(Natural) *Control:* low (Natural) **Year fluoridation initiated:** 1953 **No of subjects:** *Group 1:* 46500 *Group 2:* 50600 *Control:* 19500 **Age** Not stated	**Fluoride level (ppm):** *Group 1:*High (Artificial) *Group 2:* 0.67(Natural) *Control:* low(Natural) **No of subjects:** *Group 1:* 37600 *Group 2:* 46900 *Control:* 24300 **Age** Not stated
	Method of outcome assessment: 11 yearly average number of stillbirths + infant deaths per 1000 total births before (1943-53) and after (1954-64) water fluoridation was introduced in Curico			**No of subjects:** *Group 1:* 1575 *Group 2:* 1560 *Control:* 1140	**No of subjects:** *Group 1:* 2450 *Group 2:* 1510 *Control:* 1088

C11: Other Adverse Effects Studies: Baseline Data

Study Details	Outcome Details	Inclusion/ Exclusion Criteria	Confounding Factors	Baseline Group Characteristics	Final Group Characteristics
Author (year) Schatz (1976) **Country of study** Chile **Geographic location** Curico (F), San Fernando (non-F) & La Serena(natural-F) **Year study started** 1943 **Year study ended:** 1964	**Method of outcome assessment:** Statistics (pop. data & number of deaths) obtained directly from annual reports from the demographic department of the Chilean government	As above	As above	**No of subjects:** *Group 1:* 46500 *Group 2:* 50600 *Control:* 19500	**No of subjects:** *Group 1:* 37600 *Group 2:* 46900 *Control:* 24300
	Method of outcome assessment: 11 yearly average number of stillbirths + infant deaths per 1000 total births before (1943-53) and after (1954-64) water fluoridation was introduced in Curico			**No of subjects:** *Group 1:* 1575 *Group 2:* 1560 *Control:* 1140	**No of subjects:** *Group 1:* 2450 *Group 2:* 1510 *Control:* 1088
Author (year) Weaver (1944) **Country of study** England **Geographic location** Tynemouth (non-F), Southshields (F) **Year study started** 1930 **Year study ended:** 1939	**Outcome:** Mortality **Method of outcome assessment:** Crude death rates obtained from Medical Officers of Health for 2 study areas	**Inclusion criteria** None stated **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Author stated that no appreciable difference in age & sex distributions of 2 areas. In Registrar General's "area computability factor" in 1939 Tynemouth was 1.11 and South Shields 1.12	**Fluoride level (ppm):** *Group 1:*1.4 (Natural) *Control:* <0.25 (Natural) **No of subjects:** Not stated **Age** Not stated	**Fluoride level (ppm):** *Group 1:*1.4 (Natural) *Control:* 0.25(Natural) **No of subjects:** Not stated **Age** Not stated

3. Case Control Studies

Study Details	Case and Control Selection	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Dick (1999) **Country of study** New Zealand **Geographic location** New Zealand **Year study started** 1987 **Year study ended** Not stated	**Case-definition:** Postneonatal deaths attributed to SIDS **Method of control selection:** Representative sample of controls from all births within study area **Matching:** Not stated **Ratios of cases to controls:** 1:4	**Inclusion criteria** Babies enrolled in the New Zealand cot death study **Exclusion criteria** If date of death/nominated sleep occurred during change from usual fluoridation status of area Difference in fluoridation status between 2 postnatal addresses	**Other sources of fluoride:** Method of infant feeding **Social class:** Occupational status, marital status, age mother left school **Ethnicity:** Not Stated **Other confounding factors:** Age, region, time, season, sex, birthweight, gestation, ethnicity, twin, age of mother at infant's birth & first pregnancy, no. previous pregancies, smoking, alcohol, caffeine, antenatal clinics, maternal weight, sleep position, bed sharing, hospital admissions	**Number of subjects** *Cases:* 379 *Controls 1:* 1550 **Age range (mean)** Not stated **Exposure 1:** >80% of population served with fluoridated water (artificially fluoridated to 1ppm) **Exposure 2:** <20% of population served with fluoridated water (artificially fluoridated to 1ppm)

C11: Other Adverse Effects Studies: Baseline Data
4. Cross-Sectional Studies

Study Details	Outcome Details	Inclusion/Exclusion Criteria	Confounding Factors	Baseline Data
Author (year) Jolly (1971) **Country of study** India **Geographic location** The Punjab **Year study started** Not stated	**Outcome:** Skeletal fluorosis (%)	**Inclusion criteria** School children **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.7-9.4 **No of subjects (min-max):** Not stated **Age** Not stated
Author (year) Gedalia (1963) **Country of study** Israel **Geographic location** Upper Galilee (non-f), Western Galilee (non-F), Kiriath Motzkin (F), Kiriath Bialik (medium F) **Year study started** Not stated	**Outcome:** % with enlarged thyroid	**Inclusion criteria** Lifetime residents of study areas (girls only) **Exclusion criteria** None stated	**Other sources of fluoride:** Not stated **Social class:** Not stated **Ethnicity:** Not stated **Other confounding factors:** Iodine water level - areas with lowest levels of iodine had highest levels of Goitre, areas with highest levels of iodine also had highest levels of fluoride	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.1-0.9 **No of subjects (min-max):** 410-979 **Age** Aged 7-18 years **Sex** Girls only
Author (year) Lin (1991) **Country of study** China **Geographic location** Langan and Jiayi (non-F), Xinyuan (F) **Year study started** Not stated	% with goitre	**Inclusion criteria** School children aged 7 to 14 years **Exclusion criteria** Not stated	**Other sources of fluoride:** Not stated **Social class:** Low socioeconomic status, mean annual income of about 200 yuan **Ethnicity:** Not stated **Other confounding factors:** Not stated	**Fluoride measure:** Fluoride level **Fluoride level (min-max):** 0.34-0.88 **No of subjects (min-max):** 250-256 **Age** Aged 7-14 years

C12: Other Adverse Effects: Individual Study Results

1. Cohort and Ecological Studies

a. Studies which present adjusted outcomes

Study Details	Outcome	Group	Exposure	Crude Risk Males/ 100 000	Crude Risk Females/ 100 000	Summary Measure (CI): Details	Male	Female
Erickson (1978)	Deaths from all causes classified into 34 categories	*Group 1:* *Control:*	>0.7 <0.7	3572.8 3160.8		**Measure used:** Rate ratio **Variables controlled for:** Age-sex-race standardised mortality rates controlled for city population density and median education, weighted for black and white 1970 populations,	1.01 1	
Forbes (1997)	Alzheimer's disease reported as the underlying cause of death	*Group 1:* *Group 2:* *Control:*	>=0.98 0.5-0.98 <0.5			**Measure used:** Odds ratio **Variables controlled for:** Aluminium, iron and silica content of drinking water, water pH and water source	1.22 (1.00-1.47) 0.80 (0.59-1.07) 1.0	
	Rate of impaired mental functioning	*Group 1:* *Control:*	>=0.8 <0.8		38035.3 48611.1	**Measure used:** Odds ratio **Variables controlled for:** Water concentrations of aluminium and iron, water pH and source	0.49 (0.27-0.89) 1.0	
Griffith (1963)	Anaemia during pregnancy	*Group 1:* *Group 2:* *Group 3:* *Control:*	1.0 <0.1			**Measure used:** Rate difference **Variables controlled for:** Not controlled for any variables		2.03 (SE = 3.57)

b. Studies which present standardised results

Study Details	Outcome	Group	Exposure	Exposure Level	Crude Risk Males/ 100 000	Crude Risk Females/ 100 000	Standardisation: Methods	SMR M	SMR F	Standardised rate M	Standardised rate F
Erickson (1978)	Deaths from all causes classified into 34 categories	*Group 1:* *Control:*	Water fluoride level	>0.7 <0.7	3572.8 3160.7		**Method used** Indirect **Standard population** Deaths and populations of all cities pooles	1156.0 1102.4			
Erickson (1980)	Births with congenital malformations	*Group 1:* *Control:*	Water fluoride level	>=0.7 <0.7	650.5 650.4		**Method used** Indirect **Standard population** Age-specific rates in all study areas combined			65.1 65.0	
	Births with Down's Syndrome	*Group 1:* *Control:*	Water fluoride level	>=0.7 <0.7	41.1 44.1					4.1 4.4	
Hagan (1954)	Average yearly deaths from all causes	*Group 1:* *Control:*	Water fluoride level	>=0.7 <=0.25			**Method used** Direct **Standard population** 1950 US population, results standardised for age, sex and race (stated that used indirect, but actually used direct method)	1010.6 1005.0			

C12: Other Adverse Effects: Individual Study Results

c. Studies which present crude results only

<table>
<tr><th rowspan="2">Study Details</th><th rowspan="2">Outcome</th><th rowspan="2">Group</th><th rowspan="2">Exposure</th><th rowspan="2">Exposure level</th><th colspan="2">Crude Risk /100 000</th></tr>
<tr><th>Male</th><th>Female</th></tr>
<tr><td>Berry (1958)</td><td>Number of births with Down’s syndrome per 1000 births</td><td>Group 1:</td><td>Water fluoride level</td><td>0.7-1.1</td><td colspan="2">159.0</td></tr>
<tr><td></td><td></td><td>Group 2:</td><td></td><td>1.9-2.0</td><td colspan="2">122.4</td></tr>
<tr><td></td><td></td><td>Group 3:</td><td></td><td>0.9</td><td colspan="2">137.0</td></tr>
<tr><td></td><td></td><td>Group 4:</td><td></td><td><0.2</td><td colspan="2">190.2</td></tr>
<tr><td></td><td></td><td>Group 5:</td><td></td><td><0.2</td><td colspan="2">164.0</td></tr>
<tr><td></td><td></td><td>Group 6:</td><td></td><td><0.2</td><td colspan="2">164.8</td></tr>
<tr><td></td><td></td><td>Group 7:</td><td></td><td><0.2</td><td colspan="2">107.6</td></tr>
<tr><td></td><td></td><td>Group 8:</td><td></td><td><0.2</td><td colspan="2">131.0</td></tr>
<tr><td></td><td></td><td>Group 9:</td><td></td><td><0.2</td><td colspan="2">153.4</td></tr>
<tr><td>Erickson (1976)</td><td>Number of births with Down’s syndrome per 10 000 births: data from Metropolitan Atlanda (1960-1973)</td><td>Group 1:
Control:</td><td>Water fluoride level</td><td>High
Low</td><td colspan="2">9.9
8.5 (p<0.05)</td></tr>
<tr><td></td><td>Number of births with Down’s syndrome per 10 000 births: Data from NIS surveillance areas (1961-1966)</td><td>Group 1:
Control:</td><td></td><td>High
Low</td><td colspan="2">4.9
5.1 (p<0.05)</td></tr>
<tr><td></td><td>Number of births with All congenital malformations per 10 000 births: data from Metropolitan Atlanda (1960-1973)</td><td>Group 1:
Control:</td><td></td><td>High
Low</td><td colspan="2">292.6
270 (p<0.05)</td></tr>
<tr><td></td><td>Number of births with All congenital malformations per 10 000 births: Data from NIS sureillance areas (1961-1966)</td><td>Group 1:
Control:</td><td></td><td>High
Low</td><td colspan="2">96.6
102.0(p>0.05)</td></tr>
<tr><td>Needleman (1974)</td><td>Cases of Down's syndrome</td><td>Group 1:
Control:</td><td>Water fluoride level</td><td>1
<0.3</td><td colspan="2">153.1
133.8</td></tr>
<tr><td>Rapaport (1957)</td><td>Prevalence of Down’s syndrome</td><td>Group 1:
Control:</td><td>Water fluoride level</td><td>0.1-0.2
0.0</td><td colspan="2">6.0
3.9</td></tr>
<tr><td></td><td>Prevalence of Down’s syndrome</td><td>Group 1:
Control:</td><td></td><td>>3
<3</td><td colspan="2">34.8
15.2</td></tr>
<tr><td></td><td>Prevalence of Down’s syndrome</td><td>Group 1:
Group 2:
Group 3:
Control:</td><td></td><td>2.8
1.4
0.5
0.1</td><td colspan="2">30.3
32.5
25.4
13.5</td></tr>
<tr><td></td><td>Prevalence of Down’s syndrome</td><td>Group 1:
Group 2:
Group 3:
Control:</td><td>Water fluoride level</td><td>1.6-2.6
1.0-1.2
0.4-0.7
0.3</td><td colspan="2">14.4
11.4
12.2
6.6</td></tr>
<tr><td>Rapaport (1963)</td><td>Infant mortality</td><td>Group 1:
Control:</td><td>Water fluoride level</td><td>>2.0
<1.0</td><td colspan="2">979.7
775.0</td></tr>
<tr><td></td><td>Incidence of Down's syndrome per 100 000 births</td><td>Group 1:
Group 2:
Group 3:
Control:</td><td>Water fluoride level for area in which mother was living at time of birth</td><td>1.0-2.6
0.3-0.7
0.1-0.2
0.0</td><td colspan="2">71.6
47.1
39.2
23.6</td></tr>
<tr><td>Jooste (1999)</td><td>% Prevalence of goitre</td><td>Group 1:
Group 2:
Group 3:
Group 4:
Group 5:
Group 6:</td><td>Water fluoride level</td><td>2.6
1.7
0.9
1.1
0.3
0.5</td><td colspan="2">28961.7
27659.6
18390.8
5263.2
15294.1
17322.8</td></tr>
<tr><td>Farkas (1983)</td><td>Median age at menarche</td><td>Group 1:
Control:</td><td>Water fluoride level</td><td>1.09
0.17</td><td></td><td>12.78
12.79</td></tr>
</table>

C12: Other Adverse Effects: Individual Study Results

Study Details	Outcome	Group	Exposure	Exposure level	Crude Risk /100 000	
					Male	Female
Jacqmin – Gadda (1994)	Cognitive impairment (used as major clinical sign of Alzheimer's)	*Group 1:* *Group 2:* *Group 3:* *Control:*	Water fluoride level	0.6-2.03 0.11-0.6 0.07-0.11 0.03-0.07		23801.9 24417.8 22906.4 25511.8
Still (1980)	Primary degenerative dementia	*Group 1:* *Group 2:* *Control:*	Water fluoride level	4.18 0.49 0.61	26.1 159.2 140.3	31.6 171.5 133.6
Zhao (1996)	IQ	*Group 1:* *Control:*	Water fluoride level	4.12 0.91	98.1 (13.2) 105.8 (15.0)	97.3 (12.9) 105.0 (15.0)

2. Before-After Studies

Study Details	Outcome Presented	Group	Fluoride level	Outcome 1	Outcome 2
Briner (1966)	Crude mortality rates (per 10 000) for 1953 and 1963			**Mortality (SE)**	
		Baseline:			
		Group 1: *Group 2:* *Control:*	low 0.6-0.7 low	180 130 140	
		Final:			
		Group 1: *Group 2:* *Control*	1 0.6-0.7 low	175 110 116	
Overton (1954)	Incident rate per 1000 live births for infant mortality and per 100 live and still births for still births			**Infant mortality (SE)**	**Still births (SE)**
		Baseline:			
		Group 1: *Control:*	low low	36.4 43.1	27 27.7
		Final:			
		Group 1: *Control*	1-1.2 low	27.6 30.6	18.7 18.8
Rogot (1978)	Average mortality ratios for deaths from all causes, indirectly standardised for age, sex and race using US specific rates for 3 year period 1959-61			**Mortality (SE)**	
		Baseline:			
		Group 1: *Group 2:* *Control:*	Low >=0.7 <0.7	1.13 1.19 1.16	
		Final:			
		Group 1: *Group 2:* *Control*	>=0.7 >=0.7 <0.7	0.97 0.96 0.99	

C12: Other Adverse Effects: Individual Study Results

Study Details	Outcome Presented	Group	Fluoride level	Outcome 1	Outcome 2
Schatz (1976)	Number of deaths per year for 1954 and 1964			**Mortality (SE)**	
		Baseline:			
		Group 1:	low	837	
		Group 2:	0.67	596	
		Control:	low	441	
		Final:			
		Group 1:	High	886	
		Group 2:	0.67	647	
		Control	low	487	
Schatz (1976) (continued)	Average yearly number of stillbirths and infant deaths per 1000 total births (number of subjects = number of births)			**Mortality (SE)**	
		Baseline:			
		Group 1:	low	335	
		Group 2:	0.67	275	
		Control:	low	198	
		Final:			
		Group 1:	high	457	
		Group 2:	0.67	273	
		Control	low	204	
Weaver (1944)	Crude death rates for deaths from all-causes			**Mortality (SE)**	
		Baseline:			
		Group 1:	1.4	12.9	
		Control:	<0.25	11.9	
		Final:			
		Group 1:	1.4	13.4	
		Control	<0.25	12.1	

3. Case-Control Studies

Study Details	Outcome	Number of Subjects per Group	Exposures	Level of Exposure in Cases	Level of Exposure in Control 1	OR for Exposure
Dick (1999)	Postneonatal deaths attributed to SIDS	379	**Exposure 1:** >80% of population served with fluoridated water (artificially fluoridated to 1ppm) **Exposure 2:** <20% of population served with fluoridated water (artificially fluoridated to 1ppm)	227 152	944 606	1.19 (0.82-1.74) 1.0

C12: Other Adverse Effects: Individual Study Results

4. Cross –Sectional Studies

Study Details	Outcome Details	Exposure	Water Fluoride Level	Number of Subjects	Results (% prevalence)
Jolly (1971)	Skeletal fluorosis (%)	Fluoride level	0.7-9.4	Not stated	The prevalence of skeletal fluorosis showed and increase with increasing water fluoride levels. The prevalence of skeletal fluorosis ranged from 45 at water fluoride levels of 0.7ppm to 70% at levels of 9.4ppm
Gedalia (1963)	% with enlarged thyroid	Fluoride level	<0.1 <0.3 0.3 0.7 – 0.9	692 979 604 410	17 30 2.6 4.7
Lin (1991)	Goitre	Fluoride level	0.88 0.34	250 256	91 82

APPENDIX D

Validity Assessment Scoring and Definition of Terms in the Tables

Cohort, Before-After, Ecological, and Cross-Sectional Study Designs

Prospective	Was the study prospective? Was it planned and started prior to the outcome of interest occurring? Score = 1 or 0
Study Design	The study design hierarchy for this review = cohort > before-after > ecological > cross-sectional. Scores range Scores range between 0.25-1, with cohort = 1, cross-sectional = 0.25
Fluoride Measurement	Was the Fluoride level reliably measured? Scores range between 0-1.
Confounding Factors	Were confounding factors addressed (measured)? Scores range between 0-1, with 3 or more factors measured = 1.
Control for Confounding	Was there adjustment for the possible effect of confounding factors in the analysis? Scores range between 0-1, with stratification by age and sex = 0.5, other types of analysis (e.g. regression) = 1.
Blinding	Were those measuring outcomes (e.g. fluorosis) blind to the exposure status of the person being assessed? Score = 0 or 1
Baseline Survey	Was the baseline survey at the point of initiation or discontinuation of water fluoridation? Score = 0 or 1
Follow-Up	Was the final survey an adequate time after the initiation or discontinuation of water fluoridation to assess effects (2 years for caries, 5 years for other effects)? Score = 0 or 1
Score	Sum of the scores of the above questions. Total score is out of 8 possible.
Level of Evidence	A, B or C based on the levels defined in the methods section.

Case-Control Study Designs

Disease Validated	Was the disease state of the cases reliably assessed and validated? Score = 0 or 1
Cases in Series	Are the cases representative of a series (or is there a potential for selection bias)? Score = 0 or 1
Controls Similar	Are the controls selected from a similar population to the cases? Score = 0 or 1
Controls Disease-Free	Is there evidence that the controls are free from disease? Score = 0 or 1
Confounding Factors	Are cases and controls comparable with respect to confounding factors? Scores range between 0-1, with 3 or more factors measured = 1
Exposure Assessment Similar	Was exposure (e.g. to fluoridated water) assessed in the same way for cases and controls? Score = 0 or 1
Response Rate Adequate	Was the response rate adequate (meaning numbers of people included into the study out of those possible)? Score = 0 or 1
Non-Response Similar	Was the non-response rate the same in cases and controls? Score = 0 or 1
Statistical Analysis	Was an appropriate statistical analysis performed (e.g. use of matching)? Score = 0 or 1
Score	Sum of the scores of the above questions. Total score is out of 9 possible.
Level of Evidence	A, B or C based on the levels defined in the methods section.

Caries Study Validity Assessment (Score out of 8)

Author	Year	Prospective	Fluoride Measurement	Confounding factors	Control for confounding	Blinding	Baseline survey	Final survey	Follow-up	Score	Level of evidence
Hardwick	1982	1	1	1/2	1/4	1	1	1	1	6.8	B
Maupomé	2000	1	0	1	1	0	1	1	1	6.0	B
Kunzel	1997	1	1	1/2	1/4	0	1	1	1	5.8	B
Seppa	1998	1	1	1/2	1/4	0	1	1	1	5.8	B
Beal	1981	1	1	1/4	1/4	0	1	1	1	5.5	B
DHSS	1969	1	1	1/4	1/4	0	1	1	1	5.5	B
Kalsbeek	1993	1	0	1/2	1/2	1/2	1	1	1	5.5	B
Adriasola	1959	1	2/3	1/4	1/4	0	1	1	1	5.2	B
Loh	1996	1	1/3	1/2	1/4	0	1	1	1	5.1	B
Backer Dirks	1961	1	0	0	0	1	1	1	1	5.0	B
Attwood	1988	1	1/3	1/4	1/4	0	1	1	1	4.8	B
Beal	1971	1	1/3	1/4	1/4	0	1	1	1	4.8	B
Guo	1984	1	0	1/2	1/4	0	1	1	1	4.8	B
Alvarez-Ubilla	1959	1	0	1/4	1/4	0	1	1	1	4.5	B
Arnold	1956	1	0	1/4	1/4	0	1	1	1	4.5	B
Ast	1951	1	0	1/4	1/4	0	1	1	1	4.5	B
Blayney	1960	1	0	1/4	1/4	0	1	1	1	4.5	B
Brown	1965	1	0	1/4	1/4	0	1	1	1	4.5	B
Hobbs	1994	1	0	1/4	1/4	0	1	1	1	4.5	B
Wragg	1999	1	0	1/4	1/4	0	1	1	1	4.5	B
Pot	1974	0	0	1/2	1/2	0	1	1	1	4.0	B
Gray	1999	1	0	1/4	1/4	0	1	1	0	3.5	B

Social Class Studies: Validity

Author	Year	Prospective	Study design	Fluoride Measurement	Confounding factors	Control for confounding	Blinding	Baseline Survey	Follow -Up	Score	Level of Evidence
Beal	1971	1	1/3	1/4	1/4	0	1	1	1	4.8	B
DHSS	1969	1	3/4	1	1/4	1/4	0	1	1	5.3	B
Gray	2000	1	3/4	0	1/4	1/4	0	1	1	4.3	B
Holdcroft	1999	1	3/4	0	1/4	1/4	0	1	1	4.3	B
Evans	1996	0	1/4	0	1/2	1/2	0	0	0	1.3	C
Rugg-Gunn	1977	0	1/4	0	1/2	1/2	0	0	0	1.3	C
Bradnock	1984	0	1/4	0	1/4	1/4	0	0	0	0.8	C
Carmichael	1989	0	1/4	0	1/4	1/4	0	0	0	0.8	C
Murray	1984	0	1/4	0	1/4	1/4	0	0	0	0.8	C
Murray	1991	0	1/4	0	1/4	1/4	0	0	0	0.8	C
Provart	1995	0	1/4	0	1/4	1/4	0	0	0	0.8	C
Riley	1999	0	1/4	0	1/4	1/4	0	0	0	0.8	C
Jones	1997	0	1/4	0	1/4	1/4	0	0	0	0.8	C
Jones	2000	0	1/4	0	1/4	1/4	0	0	0	0.8	C

Fluorosis Study Validity Assessment (Score out of 8)

Author	Year	Prospective	Study Design	Fluoride Measurement	Confounding Factors	Control for Confounding	Blinding	Baseline Survey	Follow -Up	Score	Level of Evidence
Kumar	1999	1	3/4	0	1	1	0	1	1	5.8	B
Jackson	1999	1	3/4	0	1	1/2	1	0	1	5.3	C
Rugg-Gunn	1997	0	1/4	1	1/2	1	1	0	1	4.8	C
Brothwell	1999	0	1/4	2/3	1/2	1	1	0	1	4.4	C
Chen	1989	1	3/4	2/3	0	0	1	0	1	4.4	C
Butler	1985	0	1/4	1	1	1	0	0	1	4.3	C
Correia Sampaio	1999	0	1/4	1	1	1	0	0	1	4.3	C
Heifetz	1988	1	3/4	1	1/4	1/4	0	0	1	4.3	C
Ismail	1990	0	1/4	1	1	1	0	0	1	4.3	C
Heller	1997	0	1/4	2/3	1	1	0	0	1	3.9	C
Milsom	1990	0	1/4	0	1	1/2	1	0	1	3.8	C
Segreto	1984	0	1/4	1	1	1/2	0	0	1	3.8	C
Szpunar	1988	0	1/4	1/3	1	1	0	0	1	3.6	C

Author	Year	Prospective	Study Design	Fluoride Measurement	Confounding Factors	Control for Confounding	Blinding	Baseline Survey	Follow -Up	Score	Level of Evidence
Heintze	1998	0	1/4	1	1	1/4	0	0	1	3.5	C
McInnes	1982	0	1/4	1	1	1/4	0	0	1	3.5	C
Stephen	1999	0	1/4	0	1	1/4	1	0	1	3.5	C
Adair	1999	0	1/4	2/3	1/2	0	1	0	1	3.4	C
Scheinin	1964	0	1/4	2/3	1/4	1/4	1	0	1	3.4	C
Selwitz	1995	0	1/4	2/3	1	1/2	0	0	1	3.4	C
Angelillo	1999	0	1/4	0	1	1	0	0	1	3.3	C
Chen	1993	0	1/4	1	0	0	0	1	1	3.3	C
Colquhoun	1984	0	1/4	0	1	1	0	0	1	3.3	C
Haavikko	1974	0	1/4	1	1/2	1/2	0	0	1	3.3	C
Ibrahim	1995	0	1/4	1	1	0	0	0	1	3.3	C
Kunzel	1976	0	1/4	1	0	0	1	0	1	3.3	C
Mella	1994	0	1/4	0	1/2	1/2	1	0	1	3.3	C
Nunn	1994	0	1/4	1/3	1/2	1/4	1	0	1	3.3	C
Riordan	1991	0	1/4	0	1	1	0	0	1	3.3	C
Villa	1998	0	1/4	1	1	0	0	0	1	3.3	C
Ellwood	1996	0	1/4	0	1/4	1/2	1	0	1	3.0	C
Russell	1951	0	1/4	1	1/2	1/4	0	0	1	3.0	C
Sellman	1957	0	1/4	1	1/2	1/4	0	0	1	3.0	C
Warnakulasuriya	1992	0	1/4	2/3	1	0	0	0	1	2.9	C
Booth	1991	0	1/4	0	1	1/2	0	0	1	2.8	C
Ellwood	1995	0	1/4	0	1/4	1/4	1	0	1	2.8	C
Forrest	1965	0	1/4	0	1/4	1/4	1	0	1	2.8	C
Ockerse	1941	0	1/4	1	1/2	0	0	0	1	2.8	C
Ray	1982	0	1/4	1	1/2	0	0	0	1	2.8	C
Rwenyonyi	1999	0	1/4	0	1	1/2	0	0	1	2.8	C
Jolly	1971	0	1/4	2/3	1/2	1/4	0	0	1	2.7	C
Driscoll	1983	0	1/4	1	1/4	0	0	0	1	2.5	C
Masztalerz	1990	0	1/4	0	1	1/4	0	0	1	2.5	C
Selwitz	1998	0	1/4	1	1/4	0	0	0	1	2.5	C
Nanda	1974	0	1/4	2/3	1/2	0	0	0	1	2.4	C
Clarkson	1992	0	1/4	0	1/2	1/2	0	0	1	2.3	C
de Crousaz	1982	0	1/4	0	0	0	1	0	1	2.3	C

Author	Year	Prospective	Study Design	Fluoride Measurement	Confounding Factors	Control for Confounding	Blinding	Baseline Survey	Follow -Up	Score	Level of Evidence
Eklund	1987	0	1/4	0	1	0	0	0	1	2.3	C
Grimaldo	1995	0	1/4	1	0	0	0	0	1	2.3	C
Hong	1990	0	1/4	0	1	0	0	0	1	2.3	C
Jackson	1975	0	1/4	0	0	0	1	0	1	2.3	C
Rwenyonyi	1998	0	1/4	0	1/2	1/2	0	0	1	2.3	C
Zimmermann	1954	0	1/4	1	0	0	0	0	1	2.3	C
Al-Alousi	1975	0	1/4	0	1/2	1/4	0	0	1	2.0	C
Wang	1993	0	1/4	0	1/4	1/2	0	0	1	2.0	C
Mazzotti	1939	0	1/4	2/3	0	0	0	0	1	1.9	C
Spadaro	1955	0	1/4	2/3	0	0	0	0	1	1.9	C
Venkateswarlu	1952	0	1/4	2/3	0	0	0	0	1	1.9	C
Azcurra	1995	0	1/4	0	1/4	1/4	0	0	1	1.8	C
Clarkson	1989	0	1/4	0	1/4	1/4	0	0	1	1.8	C
Downer	1994	0	1/4	0	1/4	1/4	0	0	1	1.8	C
Forrest	1956	0	1/4	0	1/2	0	0	0	1	1.8	C
Gaspar	1995	0	1/4	0	1/4	1/4	0	0	1	1.8	C
Grobler	1986	0	1/4	0	1/2	0	0	0	1	1.8	C
Leverett	1986	0	1/4	0	1/4	1/4	0	0	1	1.8	C
Mella	1992	0	1/4	1/3	1/4	0	0	0	1	1.8	C
Vignarajah	1993	0	1/4	0	1/2	0	0	0	1	1.8	C
Clark	1993	0	1/4	0	1/4	0	0	0	1	1.5	C
Lin	1991	0	1/4	0	1/4	0	0	0	1	1.5	C
Cutress	1985	0	1/4	0	1/4	0	0	0	1	1.5	C
Levine	1989	0	1/4	0	1/4	0	0	0	1	1.5	C
Nunn	1992	0	1/4	0	1/4	0	0	0	1	1.5	C
Goward	1982	0	1/4	0	0	0	0	0	1	1.3	C
Wang	1999	0	1/4	0	0	0	0	0	1	1.3	C
Wenzel	1982	0	1/4	0	0	0	0	0	1	1.3	C
Zheng	1986	0	1/4	0	0	0	0	0	1	1.3	C

Case Control Study Design (Score out of 9)

Author	Year	Disease Validated	Cases in Series	Controls Similar	Controls Disease-Free	Confounding Factors	Exposure Assessment Similar	Response Rate Adequate	Non-Response Similar	Statistical Analysis	Score	Level of Evidence
Skotowski	1995	1	1	1	1	1/2	1	1	1	0	7.5	C

Bone Effects Study Validity Assessment (Score out of 8)

Author	Year	Prospective	Study Design	Fluoride Measurement	Confounding Factors	Control for Confounding	Blinding	Baseline Survey	Follow -Up	Score	Level of Evidence
Cauley	1995	1	1	1	1	1	0	0	1	6.0	C
Jacqmin-Gadda	1998	1	1/2	1	1	1	0	0	1	5.5	C
Sowers	1991	1	1	1/3	1	1	0	0	1	5.3	C
Jacqmin-Gadda	1995	0	1	1	1	1	0	0	1	5.0	C
Li	1999	0	1	1	1	1	0	0	1	5.0	C
Kurttio	1999	0	1/2	1	1	1	0	0	1	4.5	C
Phipps	1999	0	1	1/3	1	1	0	0	1	4.3	C
Kelsey	1971	0	1/2	1/3	1/2	1/2	0	1	1	3.8	B
Lehmann	1998	0	1/2	1	1	1/4	0	0	1	3.8	C
Danielson	1992	0	1/2	2/3	1	1/2	0	0	1	3.7	C
Karjalainen	1982	0	1	2/3	1/2	1/2	0	0	1	3.7	C
Bernstein	1966	0	1/2	0	1/2	1/2	1	0	1	3.5	C
Cooper	1990	0	1/2	1/3	1	1/2	0	0	1	3.3	C
Jacobsen	1992	0	1/2	1/3	1	1/2	0	0	1	3.3	C
Niessen	1986	0	1/2	1/3	1	1/4	0	0	1	3.1	C
Suarez-Almazor	1993	0	1/2	0	1	1/2	0	0	1	3.0	C
Kroger	1994	0	1	0	1/2	1/4	0	0	1	2.8	C
Madans	1983	0	1/2	1/3	1/2	1/2	0	0	1	2.8	C
McClure	1944	0	1	1/3	1/4	1/4	0	0	1	2.8	C
McClure	1944	0	1	1/3	1/4	1/4	0	0	1	2.8	C
Daniel	1969	0	1	0	1/4	1/4	0	0	1	2.5	C
Korns	1969	0	1/2	0	1/2	1/2	0	0	1	2.5	C
Simonen	1985	0	1/2	0	1/2	1/2	0	0	1	2.5	C
Arnala	1986	0	1/2	0	0	0	0	0	1	1.5	C
Karagas	1996	0	1/2	0	0	0	0	0	1	1.5	C

Bone Fracture Studies: Case Control Study Design (Score out of 9)

Author	Year	Disease Validated	Cases in Series	Controls Similar	Controls Disease-Free	Confounding Factors	Exposure Assessment Similar	Response Rate Adequate	Non-Response Similar	Statistical Analysis	Score	Level of Evidence
Hillier	2000	0	1	1	0	1	1	0	0	0	4	C
Kelsey	1971	1	1	1	0	1/2	0	0	0	0	3.5	C

Cancer Study Validity Assessment (Score out of 8)

Author	Year	Prospective	Study Design	Fluoride Measurement	Confounding Factors	Control for Confounding	Blinding	Baseline Survey	Follow-Up	Score	Level of Evidence
Chilvers	1982	0	3/4	0	1	1	0	1	1	4.8	B
Doll	1977	0	3/4	0	1	1	0	1	1	4.8	B
Smith	1980	0	1/2	1/3	1	1	0	1	1	4.8	B
Lynch	1985	0	1/2	2/3	1	1	0	0	1	4.2	C
Yiamouyiannis	1977	0	3/4	1/3	1	0	0	1	1	4.1	C
Hrudey	1990	0	1/2	0	1/2	1	0	1	1	4.0	B
Kinlen	1975	0	1/2	1	1/2	1	0	0	1	4.0	C
Chilvers	1983	0	3/4	0	1	1	0	0	1	3.8	C
Glattre	1979	0	1/2	1/3	1	1	0	0	1	3.8	C
Hoover	1976	0	1/2	1/3	1	1	0	0	1	3.8	C
Chilvers	1985	0	1/2	0	1	1	0	0	1	3.5	C
Goodall	1980	0	1/2	0	1/2	1/2	0	1	1	3.5	C
Cook-Mozaffari	1981	0	3/4	0	1	1/2	0	0	1	3.3	C
Hoover	1991	0	3/4	1/3	1/4	1	0	0	1	3.3	C
Tate	1977	0	3/4	0	1/2	1	0	0	1	3.3	C
Richards	1979	0	1/2	1/3	1/4	1	0	0	1	3.1	C
Mahoney	1991	0	1/2	1/3	1	0	0	0	1	2.8	B
Schlesinger	1956	0	3/4	0	0	0	0	1	1	2.8	C

Case Control Study Design (Score out of 9)

Author	Year	Disease Validated	Cases in Series	Controls Similar	Controls Disease-Free	Confounding Factors	Exposure Assessment Similar	Response Rate Adequate	Non-Response Similar	Statistical Analysis	Score	Level of Evidence
Moss	1995	0	1	1	0	1	1	1	0	1	6.0	C
Gelberg	1995	0	1	1	0	1/4	1	0	0	1	4.3	C
McGuire	1991	0	1	1	0	1/2	1	0	0	0	3.5	C

Other Effects Study Validity Assessment (Score out of 8)

Author	Year	Prospective	Study Design	Fluoride Measurement	Confounding Factors	Control for Confounding	Blinding	Baseline Survey	Follow-Up	Score	Level of Evidence
Jacqmin-Gadda	1994	0	1/2	1	1	1	0	0	1	4.5	C
Rogot	1978	0	3/4	1/3	1	1	0	0	1	4.1	C
Forbes	1997	0	1/2	1	1/2	1	0	0	1	4.0	C
Briner	1966	0	3/4	0	1/2	1/2	0	1	1	3.8	C
Erickson	1978	0	1/2	1/3	1	1	0	0	1	3.8	C
Erickson	1980	0	1/2	0	1	1	0	0	1	3.5	C
Erickson	1976	0	1/2	0	1	1	0	0	1	3.5	C
Hagan	1954	0	1/2	0	1	1	0	0	1	3.5	C
Still	1980	0	1/2	0	1	1/2	0	0	1	3.0	C
Overton	1954	0	3/4	0	0	0	0	1	1	2.8	C
Schatz	1976	0	3/4	0	0	0	0	1	1	2.8	C
Jolly	1971	0	1/4	2/3	1/2	1/4	0	0	1	2.7	C
Gedalia	1963	0	1/4	0	1	1/4	0	0	1	2.5	C
Zhao	1996	0	1/4	0	1	1/4	0	0	1	2.5	C
Griffith	1963	0	1/2	0	1/2	1/4	0	0	1	2.3	C
Needleman	1974	0	1/2	0	1/4	0	0	0	1	1.8	C
Rapaport	1963	0	1/2	0	1/4	0	0	0	1	1.8	C
Rapaport	1957	0	1/2	0	1/4	0	0	0	1	1.8	C
Jooste	1999	0	1/4	0	1/2	0	0	0	1	1.8	C
Weaver	1944	0	3/4	0	0	0	0	0	1	1.8	C
Lin	1991	0	1.4	0	1.4	0	0	0	1	1.5	C
Farkas	1983	0	1/2	0	0	0	0	0	1	1.5	C
Berry	1958	0	1/2	0	0	0	0	0	1	1.5	C

Case Control Study Design (Score out of 9)

Author	Year	Disease Validated	Cases in Series	Controls Similar	Controls Disease-Free	Confounding Factors	Exposure Assessment Similar	Response Rate Adequate	Non-Response Similar	Statistical Analysis	Score	Level of Evidence
Dick	1999	0	1	0	1	1	1	1	1	1.0	7	C

APPENDIX E
Measurement of Dental Caries

Dental caries is a disease that affects the teeth. It is a destructive disease caused by micro-organisms in plaque. These micro-organisms produce acids through the breakdown of sugars. It is these acids that dissolve the tooth structure. It is possible to arrest this condition in the very early phases. However, progression leads to cavitation of the tooth surface and if not stopped can lead to infection of the tooth pulp (nerve), an abscess and, sometimes, serious facial infection.

Factors affecting the development of caries
Many factors are associated with the development of caries. The primary factors are the frequency and amount of non-milk extrinsic sugars in the diet, the presence of micro-organisms in dental plaque, and the amount of fluoride in the oral environment.

Within the UK there is a strong social gradient associated with the prevalence of dental caries. This is found both in adults and in children. Those who are more deprived have significantly greater levels of disease. There is also geographical variation with the northwest of England, Scotland and Northern Ireland most severely affected. (Pitts, 1998; Kelly, 2000)

Measurement of caries
In the studies included in this review the measurement of dental caries has been undertaken by clinical diagnosis or by the examination of radiographs. The most common method used is to record the number and percentage of people who are caries-free. This means that none of their teeth have been affected by caries. However, sometimes the inverse of this figure is presented, the number of people with decay experience. In areas with a very high prevalence of caries this figure rapidly fails to show any difference between groups of people and it is necessary to introduce a measure of the severity of the disease process.

The use of the 'DMFT' index (decayed missing and filled teeth) acts as a measure of severity (Klein, 1938). This simple index ascribes a count of one to any tooth that is either decayed or missing or filled. Missing teeth are presumed to be due to caries, unless other reasons are noted (e.g. trauma). Thus the minimum score is zero and the maximum is 32. This is applied to the secondary (or permanent) dentition. The 'dmft' index is used for the primary (or deciduous) dentition. Here the minimum is zero and the maximum is 20. Similar indices are used to count surfaces. Instead of ascribing a count of one to a tooth, each tooth surface is counted separately. Posterior teeth have five surfaces and anterior teeth (the canines and incisors) usually have four surfaces but may occasionally be considered as having five. When counting surfaces, the indices are called 'DMFS' or 'dmfs' (decayed, missing, and filled surfaces). The main problem in using the DMFS / dmfs index is in deciding how many surfaces to count for a tooth that is missing. How many of its surfaces were affected by dental caries? This is impossible to deduce retrospectively and so it is prudent to report the DMFT as well as the DMFS. The use of the surface index is used particularly if small differences are expected or if it is thought that only some surfaces of the tooth may be affected. This means that in some cases data are presented separately for different tooth surfaces. For example, the occlusal (or biting) surfaces of the teeth may be presented separately from the smooth surfaces of teeth. In some studies the smooth surfaces are further subdivided into free smooth surfaces (those adjacent to the tongue, palate, cheek or lips) and the approximal (or proximal) surfaces which are those smooth surfaces between the teeth.

In older studies another index is used, which is the 'deft'. This is similar to, but distinct from, the dmft. It is an index, based on the number of decayed, scheduled for extraction, and filled primary teeth. Thus it does not count missing teeth.

The recording of missing teeth in the primary dentition presents a particular problem because they are often being lost naturally as the permanent dentition erupts. Protocols will incorporate criteria that are usually age based as to whether a tooth should be recorded as lost or its permanent successor as unerupted.

The diagnosis of caries shows considerable variation between examiners unless monitored carefully. (Shaw, 1975) Examiners are trained in caries criteria, calibration exercises are undertaken and often a percentage of subjects are re-examined to determine if there has been a shift in diagnostic standards. It should also be noted that different diagnostic thresholds are used in different studies. This makes inter-study comparison complicated.

The use of radiographs can help overcome some of the problems of reproducibility but, cannot provide reliable information on all tooth surfaces. Provided radiographs are taken and developed under standardised conditions they can provide an excellent way of assessing caries. The assessment can easily be undertaken blind. Studies using this technique often concentrate on the approximal surfaces because it is these that can best be assessed radiographically.

Using the DMFT and its variants gives the prevalence of dental caries. If this is recorded at more than two points in time, subtracting one from the other gives a disease increment and the amount of new decay recorded between the two examinations is found.

Clinical and radiographic examination of teeth always underestimates the true amount of caries in a population. This is because early lesions cannot be identified. This is of relevance in studies relating to fluoridation because it is believed that fluoride works by preventing demineralisation and by enhancing remineralisation in the early phase of caries development. In epidemiological studies this will not be measured because the techniques available are not sensitive enough.

Ages selected for the review
Some studies have reported results for each age of child entering the study (i.e. 5 to 17), while others have reported only specific ages. This has led to a vast amount of variable data being generated. In order to be able to make comparisons, data were extracted from children aged 5, 8, 12 and 15 years. If the data were not available the next closest age group was taken. The reasons for selecting these age groups were:

Age 5: The primary dentition is complete and the transition to the permanent dentition is about to start. This is a good time to measure the condition of the primary teeth. Children have often started some form of education and this makes sampling more straightforward.

Age 8: This is a period of the mixed dentition. The primary incisors have been lost and the permanent incisors and first molars have erupted. This allows the condition of the primary molars to be measured before they are shed.

Age 12: The permanent dentition is nearing completion. World wide compulsory schooling often finishes at around this age and it has become a standard measure for World Health Organisation (WHO) comparisons of dental health.

Age 15: This is the last age before many children leave school. For school-based projects the sample can often become distorted beyond age 15. It is a measure of the condition of the permanent dentition.

APPENDIX F

Comparison of Caries Prevalence at Baseline and Final Examinations

Author	Year	Age	Baseline exposed	Baseline control	Final exposed	Final control
Adriasola	1959	5	4.0	2.2	10.0	13.3
		8	7.6	4.2	0.8	2.4
		12	1.5	2.3	4.3	0.2
Alvarez-Ubilla	1959	5	4	2.2	10	13.3
Ast	1951	5	28.2	23.0	33.0	49.9
Beal	1971	5	16	29	24	41
Beal	1981	5	21	21	30	46
		8	35	41	44	69
		8	7	10	10	19
		12	7	27	7	22
Brown	1965	9-11	6.1	5.7	8.1	43.8
		12-14	0.6	1.2	2.3	18.7
DHSS England	1969	5	14	8	35	46
		8	22	20	37	53
		12	0	3	4	15
		14	6	0	5	4
Wales		5	7	10	14	31
		12	10	8	2	9
		14	6	5	1	3
Scotland		5	4.2	6.2	3.7	20.3
Gray	2000	5	74	60	64	76
Guo	1984	5	8.3	10.4	0.3	0.4
		8	79.6	70.9	29.9	85.3
		8	14.6	13.5	1.3	0.6
		12	56.5	51.3	16.8	40.1
		15	54.5	47.6	8.2	35.7
Kunzel	1997	5	22.7	33.6	32.2	52.5
		8	43.0	42.2	30.9	71.2
		8	5.2	4.8	5.7	24.7
		12	6.6	8.2	5.2	32.0
		15	5.8	5.9	2.5	12.1

A paired t-test was conducted to investigate whether there was any significant difference in caries experience at baseline between the exposed and control study areas. $t = 0.033$ on 29 degrees of freedom, 2-tailed p-value = 0.97, suggesting that there were no significant differences in baseline caries experience, as measured by the proportion of caries free children, between the two groups.

Caries experience in studies that examined dmft/DMFT or DMFS score

Author	Year	Age	Outcome	Baseline exposed	Baseline control	Final exposed	Final control
Alvarez-Ubilla	1959	5	dmft score	8.9	8.1	6.4	7.8
Arnold	1956	8	DMFT score	3.0	2.8	1.6	2.6
		12		8.1	8.7	5.9	7.7
		15		12.5	12.9	8.9	12.4
Ast	1951	8	DMFT rate per 100 erupted permanent teeth	17.1	17.3	9.9	17.2
		12		25.4	25.4	16.5	27.0
Beal	1981	5	dmft score	4.3	4.3	1.8	3.5
		8		5.0	5.4	3.4	5.0
		8	DMFT score	1.5	1.6	0.7	1.3
		12		3.5	4.3	2.7	4.1
Blayney	1960	8	DMFT score	2.5	2.2	0.9	2.4
		12		7.6	7.7	3.6	7.1
Brown	1965	9-11	DMFT score	4.1	4.2	1.5	3.7
		12-14		7.7	7.9	3.2	7.5
DHSS England	1969	5	dmft score	5.43	4.97	1.61	2.79
		8	DMFT score	2.4	2.4	1.08	1.85
		12		5.6	6.1	3.52	4.99
		14		8.4	7.9	5.77	6.74
Wales		5	dmft score	5.56	5.49	2.85	4.83
		12	DMFT score	4.65	3.95	4.38	6.16
		14		6.95	5.60	6.73	7.64
Scotland		5	dmft score	6.44	6.52	3.99	6.89
Guo	1984	5	dmft score	6.5	6.4	5.1	8.6
		8		4.2	3.5	2.5	6.2
		8	DMFT score	0.5	0.4	0.2	1.7
		12		1.1	0.9	1.9	4.3
		15		1.7	1.2	2.6	5.9
Hardwick	1982	12	DMFT score	4.3	4.4	4.6	4.3
		12	DMFS score	7.0	6.8	7.3	6.6
Kunzel	1997	5	dmft score	2.4	3.3	1.4	2.9
		8		4.9	4.9	2.8	4.9
		8	DMFT score	1.3	1.3	0.5	1.8
		12		3.6	3.5	2.0	4.8
		15		5.7	5.4	4.0	7.4
Loh	1996	7-9	DMFT score	2.9	1.9	2.0	3.1
		7-9		4.4	3.7	2.1	4.5

A paired t-test was conducted to investigate whether there was any significant difference in caries experience at baseline between the exposed and control study areas. t = 0.303 on 15 degrees of freedom, 2-tailed p-value = 0.77, suggesting that there were no significant differences in baseline caries experience, as measured by dmft/DMFT between the two groups.

APPENDIX G

Meta-regression for mean difference of dmft/DMFT – models not presented in main analysis

Model 1

This model was produced using a step-up regression analysis instead of a step-down analysis. The only difference compared to the model produced using the step-down method is that this model does not include temperature as an explanatory variable. The between study variance left in this model is greater than that remaining in the model presented in the main analysis suggesting that that model provides a better fit for the data.

Variable	Mean	Co-efficient	p-value	Variance
Constant		2.21 (0.21)	<0.001	0.583
Baseline DMFT/dmft *	3.6	0.26 (0.10)	0.011	
Validity score		-0.77 (0.43)	0.073	
Age (years)	9.5	0.13 (0.07)	0.050	
Study duration (years)	10.7	0.22 (0.08)	0.006	

Model 2

This is the model produced using a step-down regression analysis but study validity was not forced into this model. This model differs very little from the model presented in the main analysis; the coefficients, standard errors and p-values for the variables included in both models are almost identical.

Variable	Mean	Co-efficient	p-value	Variance
Constant		2.23 (0.17)	<0.001	0.393
Baseline DMFT/dmft *	3.6	0.37 (0.09)	<0.001	
Average temperature (^{o}C)	13.3	0.09 (0.03)	0.003	
Age (years)	9.5	0.16 (0.06)	0.005	
Study duration (years)	10.7	0.15 (0.08)	0.041	

APPENDIX H

Social class measures

A number of methods of measuring social class have been proposed, however no one measure is considered the gold standard. The Registrar General's classification is based on the occupation of the head of household. It is based therefore on individuals but may be inaccurate if another member of the family has a different level of occupation than that of the 'head of household'. There are a number of groups of people who cannot be classified e.g. students, unemployed. Townsend proposed an index of "material deprivation" based on electoral wards, that was constructed using four census variables (Table 1.0). Variations in health were shown to correspond closely with variations in material deprivation. The four variables chosen explained more variation in health than the Registrar General's indicators based on social class. The Jarman Index has been published widely, is readily available and has started to be used widely by health authorities for planning. It was originally designed as a method of identifying areas of high workload for general practitioners from routinely available census data. It was not designed for use as a measure of need within localities for either health care services or health promotion input and has not been validated adequately for these purposes (Campbell, 1991).

Table 1.0 Measures of social class or deprivation

Index	Description	Meaning of Score
Jarman (1983) *Social deprivation score*	Elderly living alone **Population aged under 5** One-parent families Lowest social class Unemployed Overcrowded Changed address within last year Ethnic minorities	Zero = population mean Negative score = less deprivation Positive score = more deprivation
Townsend et al. (1988) *Social deprivation score*	Economically active unemployed Households with no car Households not owner occupied Households overcrowded	Zero = population mean Negative score = less deprivation Positive score = more deprivation
Registrar Generals Classification of Occupation *Social class score*	Based on 'Head' of household	Class / Description I professional II managerial III skilled non-manual III skilled manual IV Partly skilled V Unskilled

APPENDIX I

Dental Fluorosis

Dental fluorosis is a hypocalcification of tooth enamel or dentine produced by the chronic ingestion of excessive amounts of fluoride during the period when teeth are developing. Clinically it varies in appearance from small white flecks on the enamel surface, visible only on very close inspection, to gross disturbances of the enamel structure.

The incorporation of fluoride into the hydroxyapatite, as proposed above as a mechanism for preventing caries, implies an age-related consequence for the development of fluorosis. Fluoride is incorporated into the tooth during its formation, hence, once the permanent teeth are formed the development of fluorosis is also complete.

A number of epidemiological indices for measuring the clinical manifestations of dental fluorosis have been developed. The most common indices are Dean's Index, Developmental Defects of Enamel and Modified Developmental Defects of Enamel, Thylstrup and Fejerskov Index, Tooth Surface Index of Fluorosis and Al-Alousi's Index. These are described in detail below.

Fluorosis Indices

Table I1 Dean's Index

Score	Classification	Criteria
0	Normal	Enamel represents the usual translucent semi-vitriform type of structure. Surface is smooth, glossy , and usually of a pale creamy white colour
0.5	Questionable	Enamel discloses slight aberration from the translucency of normal enamel ranging from few white flecks to occasional white spots. This classification is used in those instances where a definite diagnosis of the mildest form of fluorosis is not warranted and a classification of "normal" not justified.
1	Very mild	Small, opaque, paper white areas scattered irregularly over the tooth, but not involving as much as approximately 25% of the tooth surface. Frequently included in this classification are teeth showing nor more than about 1-2mm of white opacity at the tip of the summit of the cusps of the bicuspids or second molars
2	Mild	The white opaque areas in the enamel of the teeth are more extensive, but do not involve as much as 50% of the tooth
3	Moderate	All enamel surfaces of teeth are affected, and surfaces subject to attrition show wear. Brown stain is frequently a disfiguring feature
4	Severe	All enamel surfaces are affected and hypoplasia is so marked that the general form of the tooth may be affected. The major diagnostic sign of this classification is discrete or confluent pitting. Brown stains are widespread and teeth often present a corroded-like appearance

Table I2 a. Modified DDE Index for use in screening surveys

Score	Type of defect
0	All
1	Demarcated
2	Diffuse
3	Hypoplasia

Table I2 b. Modified DDE Index for use in general purpose epidemiological studies

Score	Type of defect
0	Normal
	Demarcated opacities:
1	White/cream
2	Yellow/brown
	Diffuse opacities:
3	Diffuse – lines
4	Diffuse – patchy
5	Diffuse –confluent
6	Diffuse/patchy + staining/loss of enamel
	Hypoplasia:
7	Pits
8	Missing enamel
9	Any other defects
	Extent of defect
0	Normal
1	<1/3
2	1/3 to 2/3
3	>2/3

Table I3 DDE Index

Score	Type of Defect
0	Normal
1	Demarcated opacity
2	Diffuse opacity
3	Hypoplasia
4	Hypoplasia pits
5	Hypoplasia grooves
6	Discoloration
7	Any other
	Sub-Type
1	White/cream
2	Yellow/Brown
	Diffuse opacity
1	Diffuse lines
2	Diffuse patchy
3	Diffuse confluent
4	Staining with codes 2 or 3
5	Pits< 2mm with codes 2 or 3
6	Pits> 2mm or loss of enamel with codes 2 or 3
	Extent (areas of surface affected) of Defect
1	Less than 1/3
2	At least 1/3 and less than 2/3
3	At least 2/3

Table I4 Thylstrup and Fejerskov Index

Score	Clinical appearance
0	Normal translucency of enamel remains after prolonged air drying
1	Narrow white lines located corresponding to the perikymata
2	*Smooth surfaces* More pronounced lines of opacity which follow the perikymata. Occasionally confluence of adjacent lines *Occlusal surfaces* Scattered areas of opacity <2mm in diameter and pronounced opacity of cuspal ridges
3	*Smooth surfaces* Merging and irregular cloudy areas of opacity. Accentuated drawing of perikymata often visible between opacities *Occlusal surfaces* Confluent areas of marked opacity. Worn areas appear almost normal but usually circumscribed by rim of opaque enamel
4	*Smooth surfaces* The entire surface exhibits marked opacity or appears chalky white. Parts of surface exposed to attrition appear less affected *Occlusal surface* Entire surface exhibits marked opacity. Attrition is often pronounced shortly after eruption
5	*Smooth and Occlusal surface* Entire surface displays marked opacity with focal loss of outermost enamel (pits)<2mm in diameter
6	*Smooth surfaces* Pits are regularly arranged in horizontal bands <2mm in vertical extension *Occlusal surfaces* Confluent areas <3mm in diameter exhibit loss of enamel
7	*Smooth surfaces* Loss of outermost enamel in irregular areas involving <1/2 of surface *Occlusal surfaces* Changes in morphology caused by merging pits and marked attrition
8	**Smooth and Occlusal surfaces** Loss of outermost enamel involving >1/2 of surface
9	*Smooth and Occlusal surfaces* Loss of main part of enamel with change in anatomic appearance of surface. Cervical rim of almost unaffected enamel is often noted

Table I5 Tooth Surface Index of Fluorosis

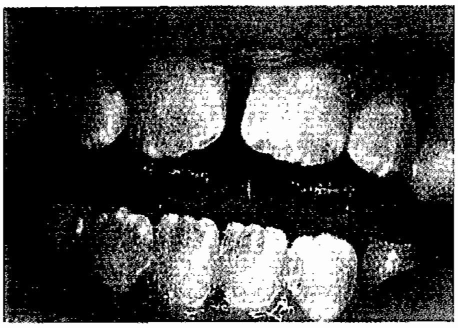
0	Enamel shows no evidence of fluorosis
1	Enamel shows definite evidence of fluorosis, areas with parchment-white colour that total less than one-third of the visible enamel surface. This category includes fluorosis confined only to incisal edges of anterior teeth and cusp tips of posterior teeth
2	Parchment-white fluorosis totals at least 1/3 of visible surface, but less than 2/3
3	Parchment white fluorosis totals at least 2/3 of visible surface
4	Enamel shows staining in conjunction with any of the preceding levels of fluorosis. Staining is defined as an areas of definite discoloration that may range from light to very dark brown
5	Discrete pitting of the enamel exists, unaccompanied by evidence of staining intact enamel. A pit is defined as a definite physical defect in the enamel surface with a rough floor that is surrounded by a wall of intact enamel. The pitted areas is usually stained or differences in colour from the surrounding enamel
6	Both discrete pitting and staining of the intact enamel exists
7	Confluent pitting of the enamel surface exists. Large areas of enamel may be missing and the anatomy of the tooth may be altered. Dark brown stain is usually present

Table I6 Al-Alousi's Index

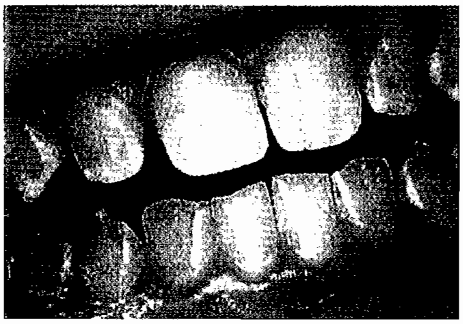
Type	Description
A	White areas less than 2 mm in diameter
B	White areas of or greater than 2 mm in diameter
C	Coloured (brown) areas less than 2 mm in diameter
D	Coloured (brown) areas of or greater than 2 mm in diameter
E	Horizontal white lines, irrespective of there being and white non-linear areas
F	Coloured (brown) or white areas or lines associated with pits or hyploplastic areas

Photgraphs of fluorosed teeth as classified by Dean's classification

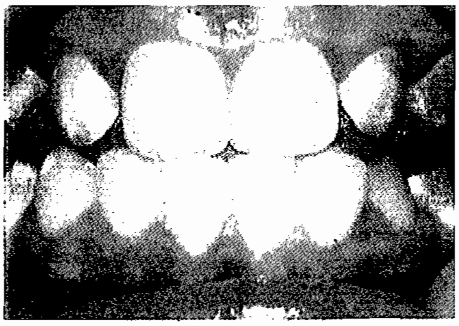
1. Normal (0).



2. Questionable (0.5).

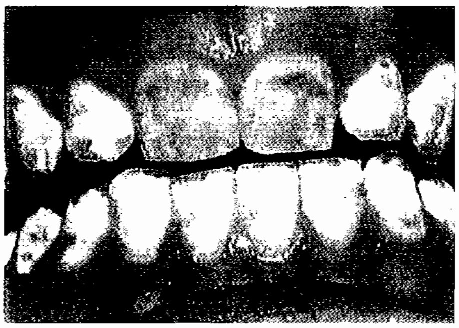


3. Very mild (1).



4. Mild (2).

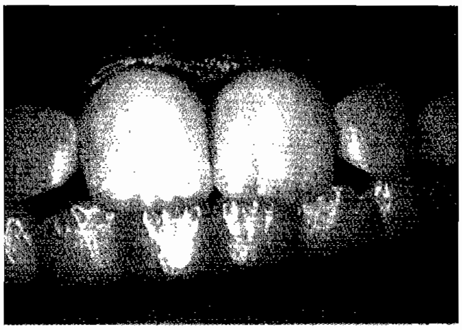
5. Moderate (3).



6. Severe (4).

Plates 1-6 Examples of Dean's classification system for dental fluorosis and assigned scores (From Driscoll *et al.*, 1983, by kind permission of the Authors and the *Journal of the American Dental Association*)

Photgraphs of fluorosed teeth as classified by the Thylstrup-Fejerskov index



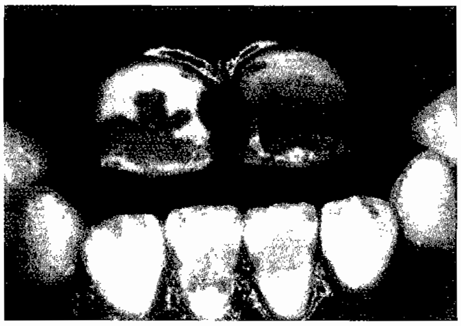
7. Tf score 1.
Fine lines across the entire tooth surface.

8. Tf score 2.
Fine lines frequently merge.

9. Tf score 3.
Irregular cloudy white areas.

10. Tf score 4 (right incisor) and score 5 (left incisor).

11. Tf score 7.



12. Tf scores 8 and 9.

Plates 7-12 Examples of the Thylstrup-Fejerskov index (By kind permission of Professor O. Fejerskov and Munksgaard Publishers. Copenhagen)

APPENDIX J

Algebraic form of univariate regression model for fluorosis analysis

For clarity, the algebraic form of the model fitted is provided below.

$$\ln(odds)_{ij} \sim N\left(a + b(fluoridelevel)_{ij} + u_j + v_j(fluoridelevel)_{ij}, \mathrm{var}_{ij}\right)$$

$$\begin{pmatrix} u_j \\ v_j \end{pmatrix} \sim MVN\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{u}^{2} & \sigma_{uv} \\ \sigma_{uv} & \sigma_{v}^{2} \end{bmatrix}\right),$$

Where i = 1 . . . . . I indicate the groups within the j = 1 . . . . . J studies. v_{ij} is the variance of the log odds of fluorosis for each group, a is the overall model intercept, b is the overall slope parameter, u_j is the deviance of the intercept away from a for the j^{th} study, and v_j is the deviance of the slope away from b for the j^{th} study. u_j and v_j are assumed to be dependent on each other and distributed multivariate normally.

APPENDIX K

Multiple regression analysis for fluorosis of aesthetic concern

This model builds on the mixed univariate model in Table 7.6. The groupings of cohorts of subjects within individual studies have been taken into account (separate intercept and slopes have been fitted to individual studies). Explanatory variables are included which explain a proportion of the variation between estimates. For this outcome, method of assessment, method of fluoridation (whether water was artificially or naturally fluoridated), and an interaction between level of fluoride and method of fluoridation are all highly statistically significant and included. The model parameters are summarized in the table below.

Variables	Parameter	P-value Individual Parameters	P-values Overall Variables	Coefficient	Variance	Odds (95% CI)
Fixed Effects						
Intercept	Intercept	0.02	NA	-3.003	1.392	0.050 (0.005 to 0.501)
Fluoride level (centred by subtracting 1.2565)	Fluoride level	0.06	0.0002	-4.457	5.072	0.012 (0.00 to 0.9058)
Method of assessment	Clinical	0.20	0.0001	-1.255	0.928	0.285 (0.043 to 1.885)
	Photograph	0.99		-0.012	2.555	0.989 (0.043 to 22.675)
	Both	0.0001		6.941	2.255	1033.530 (54.449 to 19618.13)
	Not Stated	.		0	.	.
Method of Fluoridation	Natural	0.005	0.0001	2.026	0.469	7.583 (1.980 to 29.042)
	Artificial	0.2713		-1.011	0.822	0.364 (0.062 to 2.152)
	Not Stated	.		0	.	.
Method of Fluoridation * Fluoride level (interaction term)	Natural * Fluoride level	0.02	0.0001	5.208	5.000	182.767 (2.283 to 14629.7)
	Artifical* Fluoride level	0.27		-2.861	6.539	0.057 (0.000 to 8.598)
	Not stated * Fluoride level	.	.	0	.	.
Random Effects						
Between study (intercept)					2.945	
Between study (fluoride level)					1.318	
Covariance of intercept and slope					1.297	

APPENDIX L

Meta-regression analyses with validity score forced into the model

Multivariate meta-regression analysis - dmft/DMFT score

Variable	Mean	Co-efficient	p-value	Variance
Constant		2.23 (0.18)	<0.001	0.393
Baseline dmft/DMFT	3.6	0.36 (0.10)	<0.001	
Age (years)	9.5	0.16 (0.06)	0.010	
Average temperature (°C)	13.3	0.08 (0.04)	0.042	
Study duration (years)	10.7	0.16 (0.08)	0.048	
Validity	5.3	-0.14 (0.49)	0.778	

Multivariate Analysis - % fluorosis

Variables	Parameter	P-value individual parameters	P-values Overall Variables	Coefficient	Variance	Odds (95% CI)
Fixed Effects						
Intercept	Intercept	0.9972		-0.069	0.273	0.93 (0.35, 2.85)
Fluoride level	Fluoride level (ppm)	0.0001		0.718	0.006	2.05 (1.76, 2.39)
Teeth type	Permanent	0.037	<0.001	-0.797	0.142	0.45 (0.21, 0.95)
	Both	0.001		-3.152	0.900	0.04 (0.001, 0.28)
	Primary	0.002		-5.234	2.631	0.01 (0.00, 0.13)
	Not Stated	.		0	.	.
Method of assessment	Clinical	0.75	<0.001	0.141	0.189	1.15 (0.49, 2.73)
	Photograph	0.12		1.196	0.593	3.31 (0.72, 15.18)
	Both	0.0002		2.612	0.450	13.63 (3.61, 51.49)
	Not Stated	.		0	.	.
Valditiy		0.8433		-0.028	1.150	0.97 (0.74, 1.28)
Random Effects						
Between study (intercept)					1.330	
Between study (fluoride level)					0.340	
Covariance of intercept & slope					-0.192	

Multivariate Analysis - fluorosis of aesthetic concern

Variables	Parameter	P-value individual parameters	P-values Overall Variables	Coefficient	Variance	Odds (95% CI)
Fixed Effects						
Intercept		0.0186		-3.221	1.681	0.04 (0.003, 0.56)
Fluoride level		0.052		-4.610	5.250	0.01 (0.00, 1.04)
Method of assessment	Clinical	0.2327	<0.001	-1.189	0.964	0.30 (0.04, 2.21)
	Photograph	0.9841		0.032	2.592	1.03 (0.04, 26.62)
	Both	0.0001		6.994	2.298	1090.2 (51.13, 23248.6)
	Not Stated	.				
Method of Fluoridation	Natural	0.0049	<0.001	2.069	0.485	7.92 (1.94, 32.28)
	Artificial	0.2821		-1.001	0.845	0.37 (0.06, 2.35)
	Not Stated	.		0		
Method of Fluoridation * Fluoride level (interaction term)	Natural * Fluoride level	0.0234	<0.001	5.349	5.170	210.45 (2.14, 20698.16)
	Artifical* Fluoride level	0.2743		-2.876	6.739	0.06 (0.00, 10.62)
	Not stated * Fluoride level	.		0		
Valditiy		0.8227		0.051	0.052	1.05 (0.67, 1.67)
Random Effects						
Between study (intercept)					3.111	
Between study (fluoride level)					1.395	
Covariance of intercept & slope					1.417	

Multivariate meta-regression analysis - bone fracture studies

Variable	Category	Co-efficient (95% CI)	p-value	Between study variance
Constant		1.06 (0.94, 1.18)	0.695	0.019
Study duration	<5 (17)			
	5-10 (19)	1.02 (0.88, 1.17)	0.813	
	>10 (4)	0.68 (0.55, 0.84)	<0.001	
	Not stated (15)	0.88 (0.73, 1.06)	0.170	
Validity	3.65	1.01 (0.96, 1.07)	0.695	

APPENDIX M

Protocol Changes

Changes to the protocol were made with the consultation of and agreement from the advisory panel. The changes to the original protocol were mainly to clarify or simplify the intent of the inclusion criteria. The range of analyses undertaken was broader than had been described in the protocol. Due to extremely limited evidence, the inclusion criteria for Objective 3 were expanded to include studies of level C evidence, and limited to studies from the UK.

1. The objectives of the review were re-phrased into questions
Objective 1:
Original: 1. Assessment of the effects of fluoridation of public water supplies in preventing caries (is a causal relationship likely?).
New: What are the effects of fluoridation of drinking water supplies on the incidence of caries?

Objective 2:
Original: If fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies (i.e. fluoridated toothpaste, educational programmes, and increased self awareness of health issues?).
New: If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

Objective 3:
Original: Determination of whether fluoridation results in a reduction of caries across social groups and between geographical locations.
New: Does water fluoridation result in a reduction of caries across social groups and between geographical locations, bringing equity?

Objective 4:
Original: Assessment of the negative health effects of fluoridation.
New: Does water fluoridation have negative effects?

Objective 5:
Original: Comparison of the effects of natural and artificial fluoridation to investigate any possible differences
New: Are there differences in the effects of natural and artificial water fluoridation?

Searching:
The protocol describes searching of electronic databases. In addition, other forms of searching were conducted, including searching the World Wide Web, hand searching, and a request for submissions on a web site dedicated to the review. Update searching was undertaken, which was also not described in the protocol.

Inclusion criteria (all changes are marked in Italics)
Changes to the quality inclusion criteria are shown below.

Level A (Highest quality of evidence, minimal risk of bias)
Original:

1. Prospective (planned) studies that started at either initiation or discontinuation of water fluoridation and have a follow up of at least two years for positive effects and at least 5 years for negative effects
2. Studies address at least three possible confounding factors and make corrections in the analysis where appropriate
3. Studies with the lowest bias where primary outcomes were blinded to examiners for fluoridation status of participants.

New:

- Prospective studies that started *within one year* of either initiation or discontinuation of water fluoridation and have a follow up of at least two years for positive effects and at least 5 years for negative effects.
- Studies *either randomised or* address at least three possible confounding factors and adjust for these in the analysis where appropriate.
- Studies where fluoridation status of participants was unknown to those assessing outcomes.

The major change in the definition of Level A evidence was to allow the start of the study up to a year before or after the change in fluoridation status of the study area. This was allowed because it was thought that no significant change would have occurred in one year, and to allow sufficient time for study procedures to be implemented.

Level B (Evidence of moderate quality, moderate risk of bias)
Original:

1. Studies that started less than one year after fluoridation was initiated or discontinued and had a prospective follow up of outcomes
2. Studies that measured and made corrections for less than three but at least one confounding factor
3. Studies that failed where primary outcomes were not blinded to examiners for fluoridation status, but made other provisions to prevent measurement bias

New:

- Studies that *started within 3 years of the* initiation or discontinuation of water fluoridation, with a prospective follow up for outcomes.
- Studies that measured and adjusted for less than three but at least one confounding factor.
- *Studies in which fluoridation status of participants was known to those assessing primary outcomes, but other provisions were made to prevent measurement bias.*

The main change to the definition of Level B evidence was to increase the allowed time period between change of fluoridation status of the study area and start of the study. It was felt that the original criteria of one year was too strict, in light of the change made to the definition of Level A evidence. The change in wording of the third point under Level B was to improve clarity, but not meaning.

Level C (Lowest quality of evidence, high risk of bias)
Original:

1. Studies of other designs (prospective or retrospective, concurrent or historical control) that meet other inclusion criteria
2. Studies that failed to account for confounding factors
3. Studies that did not prevent measurement bias

New:

- *Studies of other designs (e.g. cross-sectional), prospective or retrospective, using concurrent or historical controls, that meet other inclusion criteria.*
- Studies that failed to adjust for confounding factors.
- Studies that did not prevent measurement bias.

The major changes in the definition of Level C evidence were to improve clarity, but not meaning.

Objective Specific Criteria: (all changes are marked in Italics)
Objective 1
Original: Assessment of the effects of fluoridation of public water supplies in preventing caries
Participants:

1. Populations receiving fluoridated water (either naturally or artificially)
2. Populations receiving non fluoridated water

Intervention:
A defined fluoride -concentration present in drinking water, either controlled or naturally occurring
Outcomes:
Number of decayed, missing or filled teeth (DMFT, dmft, deft) and/or number of decayed, missing or filled surfaces (DMFS, dmfs) or percentage of caries free teeth or caries free subjects in those receiving fluoridated compared to non-fluoridated water
Study designs:
Prospective studies comparing two populations, one receiving fluoridated the other non-fluoridated water

New: Does fluoridation of drinking water supplies prevent caries?
Participants:
- Populations receiving fluoridated water (naturally or artificially)
- Populations receiving non-fluoridated water

Intervention:
- *A change in the level of fluoride in the water supply of at least one of the study areas, within three years of the baseline survey.*

Outcomes:
- *Any measure of dental decay*

Study designs:
Prospective studies comparing at least two populations, one receiving fluoridated the other non-fluoridated water, *with at least two points in time evaluated.*

The changes in the inclusion criteria for Objective 1 were changed as follows. Under intervention, the words were changed to indicate that there had to be a before and after fluoridation period studied. This is more specific than the original wording, and clarified the intent. The outcomes were changed to include any measure of dental decay that was presented by a study to allow for other measures. The study design wording was also changed to clarify that two points in time had to be studied.

Objective 2:
Original: If fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies
Participants:
1. Populations receiving fluoridated water (either naturally or artificially) who receive fluoride from other artificially supplemented sources (e.g. food, toothpaste, fluoride tablets, bottled drinks)
2. Populations receiving non fluoridated water who receive fluoride from other artificially supplemented sources

Intervention:
Fluoride at any concentration present in drinking water
Outcomes:
Number of decayed, missing or filled teeth (DMFT, dmft, deft) and/or number of decayed, missing or filled surfaces (DMFS, dmfs) or percentage of caries free teeth or caries free subjects in the four different participant groups
Study designs:
Prospective studies comparing the four populations outlined above, to investigate the differences in levels of tooth decay between the populations

New: If fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?
Participants:
- Populations receiving fluoridated water (naturally or artificially) *in addition to* other interventions.
- Populations receiving non-fluoridated water in *addition to other interventions*.

Intervention:
- *A change in the level of fluoride in the water supply of at least one of the study areas, within three years of the baseline survey.*

Outcomes:
- *Any measure of dental decay.*

Study designs:
- Prospective studies comparing at least two populations, to investigate the differences in levels of tooth decay between the populations *in the presence of other sources of fluoride, e.g. fluoridated toothpaste. Where specific information on the use of other sources of fluoride is not supplied, populations in studies conducted after 1975 in industrialised countries were assumed to have been exposed to fluoridated toothpaste.*

The population criteria were changed only to make it more clear that the effects of having fluoridated or non-fluoridated water in addition to other interventions were being studied. Intervention and Outcomes wording were changed as in objective 1, for clarification that two points in time, before and after fluoridation/discontinuation of fluoridation had to be studied. The study design criteria was altered to allow for the possibility that person-level use of fluoride was not adequately measured.

Objective 3
Original: Determination of whether fluoridation results in a reduction of caries across social groups and between geographical locations bringing equity
Participants:
1. Populations receiving fluoridated water (either naturally or artificially), from different social groups and geographic locations
2. Populations receiving non fluoridated water, from different social groups and geographic locations

Intervention:
Fluoride at any concentration present in drinking water, either controlled or naturally occurring
Outcomes:
Number of decayed, missing or filled teeth (DMFT, dmft, deft) and/or number of decayed, missing or filled surfaces (DMFS, dmfs), or percentage of caries free teeth or caries free subjects in those receiving fluoridated compared to non-fluoridated water compared between different social groups and geographic locations within the two participant groups
Study designs:
Prospective studies comparing two populations, one receiving fluoridated the other non-fluoridated water, across different social groups and geographic locations

New: Does fluoridation result in a reduction of caries across social groups and between geographical locations?
Participants:
- Populations from different social groups and geographic locations receiving fluoridated water (naturally or artificially).
- Populations from different social groups and geographic locations receiving non-fluoridated water.

Intervention:
- Fluoride at any concentration present in drinking water, either controlled or naturally occurring

Outcomes:
- *Any measure of dental decay.*

Study designs:
- *Any study design comparing two populations, one receiving fluoridated the other non-fluoridated water, across different social groups and geographic locations.*

The outcome measure criteria was altered as in other objectives. The study design was altered to allow for the lack of sufficient before-after study designs.

Objective 4:
Original: Assessment of the negative health effects of fluoridation
Participants:
1. Groups receiving fluoridated water (either naturally or artificially)
2. Groups receiving non fluoridated water

Intervention:
A defined fluoride -concentration present in drinking water, either controlled or naturally occurring
Outcomes:
Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other adverse effects reported in the literature compared between those receiving fluoridated compared to non-fluoridated water
Study designs:
1. Prospective study design which follows up 2 or more exposure groups with different levels of exposure to fluoride and continues for several years to allow comparison of possible adverse effects in the different groups
2. Retrospective study design comparing risks of adverse effects in two or more exposure groups
3. Retrospective design comparing odds of exposure to differing levels of fluoride in groups of people experiencing adverse effects which may be linked to water fluoridation compared to those without the condition under study
4. Geographical study comparing average exposure of the population to fluoride with the rate of the adverse effect for several populations to look for a relationship between the two

New: Does fluoridation have negative effects?
Participants:
- *Populations* receiving fluoridated water (either naturally or artificially).
- *Populations* receiving non-fluoridated water.

Intervention:
- *Fluoride at any concentration present in the water supply, either naturally occurring or artificially added.*

Outcomes:
- Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other *possible negative effects reported in the literature.*

Study designs:
- *Any study design comparing the incidence of any possible adverse effect between two populations, one with fluoridated water and the other with non-fluoridated water.*

Under participants, the word groups were changed to populations for clarity. The wording of the criteria for intervention and outcomes were changed for clarity. The wording of the study design criteria was simplified to allow any study design.

Objective 5:
Original: Comparison of the effects of natural and artificial fluoridation to investigate any possible differences
Participants:
1. Populations receiving artificially fluoridated water
2. Populations receiving naturally fluoridated water
3. Populations receiving non-fluoridated water

Intervention:
Fluoride at any concentration from a naturally and an artificially fluoridated water source
Outcomes:
Positive effects: Number of decayed, missing or filled teeth (DMFT, dmft, deft) and/or number of decayed, missing or filled surfaces (DMFS, dmfs), or percentage of caries free teeth or caries free subjects in those receiving artificially fluoridated compared to naturally fluoridated and non-fluoridated water
Negative effects: Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other adverse effects reported in the literature compared between those receiving artificially fluoridated compared to naturally fluoridated and non-fluoridated water
Study designs:
1. Prospective study design which follows up 2 or more exposure groups, at least one of which receives artificially fluoridated and another receives naturally fluoridated water,

with different levels of exposure to fluoride and continues for several years to allow comparison of possible adverse effects in the different groups

2. Retrospective study design comparing risks of adverse effects in two or more exposure groups, at least one of which receives artificially fluoridated and another receives naturally fluoridated water.
3. Retrospective design comparing odds of exposure to differing levels of fluoride, at least one of which receives artificially fluoridated and another receives naturally fluoridated water, in groups of people experiencing adverse effects which may be linked to water fluoridation compared to those without the condition under study
4. Geographical study comparing average exposure of the population to fluoride with the rate of the adverse effect for several populations to look for a relationship between the two

New: Are there differential effects of natural and artificial fluoridation?
Participants:
- Populations receiving artificially fluoridated water.
- Populations receiving naturally fluoridated water.
- Populations receiving non-fluoridated water.

Intervention:
- Fluoride at any concentration from a naturally or an artificially fluoridated water source.

Outcomes:
- Possible positive effects: *Any measure of dental decay.*
- Possible negative effects: Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and *any other possible negative effects reported in the literature.*

Study designs:
- *Any study design comparing populations exposed to different water fluoride concentrations, results obtained from areas using artificially and naturally fluoridated water supplies were compared to investigate any differences in effect.*

The outcomes for dental decay were changed as in the other criteria, the wording for outcomes of possible negative effects and study design were changed for clarity and simplicity, as in criteria for other objectives

Other changes to the protocol include:
The Review Manager software package was not used; other packages including StatsDirect, Stata and Microsoft Access were used instead. The protocol states that reasons for heterogeneity will be investigated and explanations provided. This was done using meta-regression as an exploratory analysis of heterogeneity, but had not been specified in the protocol. Cost- effectiveness is briefly mentioned in the protocol, as a part of a comparative analysis of positive and negative effects. Evaluating cost-effectiveness was not one of the identified objectives, and under advice from the advisory panel was not pursued. Publication bias was to have been evaluated using funnel plots and an assessment of studies appearing only as abstracts. However, the data were not suitable for producing funnel plots (e.g. too few studies of a given age group/outcome combination). The number of studies presented as abstracts but not as papers was negligible, and therefore not useful in estimating publication bias.