Public Health England

Protecting and improving the nation's health

Water Fluoridation

Health monitoring report for England 2018

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Glossary of acronyms

CI	Confidence Interval(s)
$d_3$mft	decayed (at dentinal level), missing or filled primary teeth
DWI	Drinking Water Inspectorate
EFSA	European Food Safety Authority
GA	General Anaesthesia
GIS	Geographic Information Systems
HES	Hospital Episode Statistics
HMR	Health Monitoring Report
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IRR	Incidence Rate Ratio
LQ	Lower Quartile
LSOA	Lower-layer Super Output Area
LTLA	Lower-tier Local Authority
MRC	Medical Research Council
MSOA	Middle-layer Super Output Area
MYPE	Mid-year population estimate
NCARDRS	National Congenital Anomaly and Rare Disease Registration Service
NHMRC	National Health and Medical Research Council
ONS	Office for National Statistics
OR	Odds Ratio
PCV	Prescribed Concentration Value
ppm	part per million
PPS	Probability Proportionate to the size
PSU	Primary Sampling Unit
QIMD	Quintile of Index of Multiple Deprivation
RR	Relative Risk
SD	Standard Deviation
STATA	Computer Statistical package – not an acronym
TF	Thylstrup-Fejerskov Index
UN	United Nations
UQ	Upper Quartile
US NRC	United States National Research Council
WSZ	Water Supply Zone

Short lay summary

Background

Tooth decay (dental caries), caused by regularly eating and drinking sugary foods and drinks, is a significant problem for adults and children in England. A quarter of five-year-olds experience tooth decay and around 40,000 children and young people have teeth removed (due to decay) in hospital each year. Fluoride is naturally occurring and likely to be found in drinking water and many foods in varying amounts. It is also added to toothpaste. Less severe tooth decay has been observed in populations whose drinking water contains greater concentrations of fluoride than in populations with low drinking water fluoride concentrations. For this reason, water fluoridation schemes adjust fluoride levels in water supplies in some parts of England in an effort to reduce dental decay. This Public Health England monitoring report, on behalf of the Secretary of State for Health and Social Care, compared data on the health of people living in areas of England with differing concentrations of fluoride in their drinking water supply.

Dental health

- Five-year-olds in areas with water fluoridation schemes were much less likely to experience tooth decay, and less likely to experience more severe decay than in areas without schemes.
- The chances of having a tooth/teeth removed in hospital because of decay were also much lower in areas with water fluoridation schemes.
- Children from both affluent and deprived areas benefitted from fluoridation, but children from relatively deprived areas benefitted the most.
- Dental fluorosis[1], at a level that may effect the appearance of teeth, was observed in 10% of children/young people examined in 2 fluoridated cities[2]. However, there was no difference between children and young people surveyed in fluoridated and non-fluoridated cities when asked about their opinion on the appearance of their teeth, taking into account concerns which have resulted from any cause (eg poor alignment, decay, trauma or fluorosis).

Non-dental health outcomes

Taken alongside the existing wider research, our results **do not** provide convincing evidence of higher rates of hip fracture, Down's syndrome, kidney stones, bladder cancer, or osteosarcoma (a cancer of the bone) due to fluoridation schemes.

[1] mottling of the teeth as a result of exposure to fluoride, of which fluoridation schemes may contribute
[2] Children were surveyed in fluoridated cities (Birmingham, Newcastle) and non-fluoridated cities (Manchester, Liverpool)

Conclusion

The findings of this report agree with the view that water fluoridation is an effective and safe public health measure to reduce the frequency and severity of dental decay, and narrow differences in dental health between more and less deprived children and young people.

Executive summary

Background

Dental caries (tooth decay) is largely preventable. Those with dental caries can suffer pain and infection and often have difficulties eating, sleeping and socialising. It is a significant public health problem internationally and in England with 12% of three-year-olds having caries in their primary teeth and 25% of five-year-olds, rising up to half of surveyed five-year-olds in the worst affected local authority areas[1, 2]. Sizeable inequalities in the prevalence of caries exist between affluent and deprived communities, and it is a common cause of hospital admissions in children[3].

Fluoride is naturally occurring and likely to be found in sources of drinking water, in varying amounts. It is also present in some foods and drinks, and in the majority of toothpastes. During the early 20th century, lower levels of dental caries were found to be associated with certain fluoride levels in drinking water. This observation led ultimately to water fluoridation schemes that adjust fluoride levels in community water supplies in an effort to reduce dental caries. In some parts of England the level of fluoride in the public water supply already reaches the target concentration of water fluoridation schemes (one milligram per litre (1mg/l), sometimes expressed as one part per million (1ppm)), as a result of the geology of the area. In other areas the fluoride concentration has been adjusted to reach this level as part of a fluoridation scheme. Currently, around 6 million people in England live in areas with fluoridation schemes. Many schemes have been operating for over 50 years. In ‘Local authorities improving oral health: commissioning better oral health for children and young people’[4], Public Health England recommends water fluoridation as one of 9 evidence based community interventions and is satisfied that fluoridation is an effective community-wide public health intervention.

PHE monitoring role

PHE, on behalf of the Secretary of State for Health and Social Care, is required by legislation to monitor the effects of water fluoridation schemes on the health of people living in the areas covered by these arrangements, and to produce reports at no greater than four-yearly intervals. This report fulfils this requirement and we will consult with local authorities prior to publication of a further report within the next 4 years.

Methods

Firstly, we described the size of populations receiving different fluoride concentrations in their water supply and the source of this fluoride (ie whether adjusted by a scheme or

from the surrounding geology). Though it should be noted that, in terms of chemistry and bioavailability it is likely there is no important difference between added and "natural" fluoride[5, 6].

We then compared the frequency of specified health effects across populations in receipt of public water supplies within different concentration categories of fluoride (<0.1mg/l, 0.1mg/l-<0.2mg/l, 0.2mg/l-<0.4mg/l, 0.4-<0.7mg/l, ≥0.7mg/l). Non-dental health outcomes were chosen by the PHE fluoridation working group after considering the toxicological and epidemiological evidence for previously suggested health risks of fluoride exposure, and the availability for analysis of data relevant to these health outcomes. To fulfil the requirement to monitor health effects in areas with water supplies fluoridated with a scheme (rather than fluoride deriving from the geology of the area), we additionally performed comparisons for the following subgroups:

- for non-dental health effects we compared populations in receipt of public water supplies with a fluoridation scheme where the fluoride concentration averaged ≥0.2mg/l, versus populations where the fluoride concentration averaged <0.2mg/l (a level considered as 'not fluoridated' (from any source) for this analysis). Selection of this concentration, lower than typically achieved by fluoridation schemes with a 1mg/l target, was chosen as it would be sensitive to the detection of adverse effects occurring even at relatively low fluoride concentrations (ie 0.2-0.7mg/l).
- for dental health effects we compared populations in receipt of public water supplies with a fluoridation scheme where the fluoride concentration averaged ≥0.7mg/l, versus populations where fluoride concentration averaged <0.2mg/l. We used the higher 0.7mg/l value here as we were monitoring the beneficial rather than adverse health effect of fluoridation. This change allowed us to quantify the likely public health impact of fluoridation schemes on caries and caries-related extractions. International research evidence suggested that beneficial dental health effects were more likely to be observed above 0.7mg/l than at lower values, hence we selected this higher value to better quantify the dental health benefits of fluoridation schemes achieving concentrations likely to be most effective for dental health

We used statistical models adjusted for factors, other than water supply fluoride concentrations, that could explain differences in rates of health outcomes between areas.

The most recent reporting of fluorosis prevalence and severity in England was measured in research commissioned by PHE to inform this health monitoring report. The population under examination was drawn from 4 cities; Newcastle upon Tyne (fluoridated), Birmingham (fluoridated), Liverpool (non-fluoridated) and Manchester (non-fluoridated). The results of this study were reported by Pretty et al [7].

Results and discussion

Fluoride concentration in public water supply in England

Almost all (97%) of the England annual fluoride concentration monitoring observations were linked to fluoride water supply mapping data for 2005 to 2015. On average, between 2005 to 2015, 72% of the population received a water supply with a low concentration of fluoride (less than 0.2mg/l). Ten per cent of the population received a water supply reaching a fluoride concentration of at least 0.7mg/l. Of these, almost all (92%) lived in an area where the fluoride concentration was adjusted by a fluoridation scheme; the remainder (some 400,000 people) lived in areas where fluoride was elevated due to the surrounding geology.

Dental health of five-year-olds

The analyses in this report show water fluoridation was associated with a reduction in the number of five-year-olds who experience caries and with a decrease in caries severity. At all levels of deprivation, the odds[3] of having experience of caries were lower in five-year-old children living in areas with the highest compared to the lowest fluoride concentrations. The higher the concentration of fluoride, the greater the protective effect observed. The odds of experiencing caries were reduced by 23% (95% confidence interval (CI) 9%-39%) for five-year-olds living in the least deprived areas and 52% (95% CI 47%-56%) for five-year-olds living in the most deprived areas at concentrations of ≥0.7mg/l, compared to the lowest fluoride concentration of <0.1mg/l. These are significant reductions from a public health perspective. As the greatest reductions in the odds of having caries experience were observed in children in the most deprived areas, fluoridation narrowed differences in dental health between more and less deprived children.

If all five-year-olds with drinking water with <0.2mg/l fluoride instead received at least 0.7mg/l from a fluoridation scheme, then the number experiencing caries would be lower. The fall would be 17% in the least deprived areas, rising to 28% in the most deprived areas. Given that 70% of the population of five-year-olds received water supplies where fluoride concentrations were less than 0.2mg/l, potentially many children could benefit from fluoridation.

3 The odds of an event occurring is the probability that this event will occur divided by the probability that the event will not occur

Hospital admissions of children and young people aged 0-19 years

Hospital admissions for caries-related tooth extractions, as recorded in hospital statistics, were common, averaging approximately 40,000 per year. Admissions were 59% lower (95% CI 33% to 76%) in areas with fluoride of ≥0.7mg/l, compared to areas with <0.1mg/l. The higher the concentration of fluoride, the greater the protective effect observed. This is likely to have noticeable effects on the relative costs of dental service provision due to the high costs associated with treatment in hospital. The greatest absolute reduction in admissions was seen for the most deprived children, which would narrow dental health inequalities.

If all children and young people with drinking water with <0.2mg/l fluoride instead received at least 0.7mg/l from a fluoridation scheme, then the number with hospital admissions for tooth extraction would be lower by 45 to 68%. Given that 70% of the population of children and young people lived in areas where fluoride concentrations are less than 0.2mg/l, potentially many children could benefit from fluoridation. These results should be interpreted with caution due to limitations in data quality of hospital statistics, but are in keeping with the wider supporting evidence.

Dental fluorosis (mottles or flecks on teeth caused by fluoride)

The number of surveyed 11 to 14-year-olds with any positive score on examination for fluorosis was greater in the fluoridated cities (Newcastle and Birmingham 61%) compared to the non-fluoridated cities (Manchester and Liverpool, 37%). Fluorosis found on examination to be of a level corresponding to what would typically be considered to cause at least mild aesthetic concern, was 10.3% in the 2 fluoridated cities and 2.2% in the non-fluoridated cities. However, there was no significant difference in the mean aesthetic score[4] between respondents from fluoridated and non-fluoridated cities (p=0.572), suggesting that, in the age group considered, the presence of fluorosis does not appear to cause aesthetic concern or, where it does cause concern there is an equal level of dissatisfaction due to other factors eg trauma, orthodontic malalignment or caries.

Hip fracture admission

No clear pattern of association was observed for the 50 to 64 or 65 to 79 age groups. In the younger age group 0 to 49, there was statistical evidence that fluoride concentrations greater than 0.1 mg/l were associated with lower risk of hip fracture admission, whereas in older adults (80+), fluoride concentrations of at least 0.1mg/l were generally associated with a small increase in hip fracture admission risk.

[4] Based on the response of the surveyed participants to a question asking them to rate their satisfaction with the aesthetic appearance of their teeth

However, there was no consistent change in hip fracture admission risk within the age groups as the concentration of fluoride increased. These inconsistencies by fluoride concentration/age, taken together with the overall existing evidence from published epidemiological and toxicological studies, do not provide convincing evidence for a causal association.

Kidney stones

The rate of hospital admissions for kidney stones was 10% lower (95% CI 2%-18%) in areas with a fluoridation scheme. However, when the association between admissions and fluoride concentration categories was examined, an increase in admissions was seen at some fluoride concentrations, whilst no increased risk was observed at others. There was no consistent change in kidney stone admission risk as the concentration of fluoride increased. These inconsistencies by fluoride concentration, the lack of wider evidence supporting a reliably demonstrated relationship, and concerns about data quality, do not provide convincing evidence for a causal association.

Down's syndrome

In areas with a fluoridation scheme the rate of Down's syndrome was 8% lower than in areas without a scheme, but the 95% confidence interval overlapped one (95% CI 0.84-1.02), indicating very limited statistical evidence for such an association. However, when the association between Down's syndrome and fluoride concentration categories was examined, an increase in cases was seen at some fluoride concentrations whilst no increase was observed at others. There was no consistent change in risk of Down's syndrome as the concentration of fluoride increased. These inconsistencies by fluoride concentration, and the lack of wider evidence supporting a reliably demonstrated association, do not provide convincing evidence for a causal association.

Bladder cancer

In areas with a fluoridation scheme the rate of bladder cancer was 6% lower (95% CI 2%-10%). A similar reduction was observed in populations with the highest compared to lowest fluoride concentration categories. However, there was no consistent decrease in risk as the concentration of fluoride increased. There was very little wider evidence supporting a protective effect of fluoride exposure on bladder cancer occurrence. These inconsistencies by fluoride concentration and the lack of wider supportive evidence do not provide convincing evidence for a protective relationship.

Osteosarcoma (a form of bone cancer) among people aged less than 50

There was no evidence of an association between fluoridation and osteosarcoma in 0 to 49-year-olds.

Conclusion

The findings of this report are consistent with the view that water fluoridation is an effective and safe public health measure to reduce the prevalence and severity of dental caries, and reduce dental health inequalities.

This 2018 monitoring report has provided a more detailed description of the size of populations receiving different concentrations of fluoride in their water supply and consequently a more in-depth examination of the association between fluoridation and health outcomes than the 2014 report.

The reduction in the number of five-year-olds experiencing caries and the decrease in the severity of this dental disease was significant in those receiving a fluoridated water supply, and most clearly so in more deprived areas, narrowing differences in dental health between more and less deprived children. The effect of fluoridation on admission for tooth extraction was also substantial. A larger number of the most deprived children and young people benefited, again lessening differences in dental health between more and less deprived children and young people.

We have also been able to explore associations with potential adverse health effects in more detail: despite some suggestion of associations between water fluoridation and certain health effects, the overall results of our analysis, and weight of wider evidence means causal associations are unlikely.

The ecological design of this report has some limitations. We can estimate the potential exposure to fluoride in water using the concentration as a proxy, but we do not know how much people drink or whether they have other sources of fluoride. Additionally, the adjustment for factors other than fluoride/fluoridation that may influence the health outcomes studied can only be done on the basis of area averages, which may incompletely adjust for these factors. Therefore, this report alone does not allow conclusions to be drawn regarding any causative or protective role of fluoride; similarly, the absence of any associations does not provide definitive evidence for a lack of a relationship. This is particularly the case for non-dental health outcomes, where the weight of wider epidemiological evidence for a causal relationship at drinking water fluoride concentrations typical of those in England, and toxicological evidence for a biological mechanism of action, is generally much more limited. It may be beneficial to further evaluate outcomes in other populations, with contrasting fluoride levels, and alternative study designs, to assess if these findings can be replicated.
PHE continues to keep the wider evidence under review and will consult with local authorities prior to publication of a further report within the next 4 years.

Background

PHE, on behalf of the Secretary of State for Health and Social Care, is required by legislation to monitor the effects of water fluoridation schemes on the health of people living in areas covered by these arrangements and to produce reports at no greater than four-yearly intervals. This report, the second in the series, fulfils this requirement and we will consult with local authorities prior to publication of a further report within the next 4 years.

Dental caries, also known as dental decay or tooth decay, is a disease that affects people at all life stages and affects both primary (baby) and permanent (adult) teeth. Dental caries is caused by multifactorial and complex interactions. It occurs when oral bacteria produce acids that demineralise the tooth surface, allowing the bacteria to progressively invade the tooth[8]. Eating and drinking sugary food and drink fuels acid formation by the bacteria. The buffering action of saliva can change the process to remineralisation, a process for which fluoride acts as a catalyst[9].

Dental caries is largely preventable, however, it is a significant public health problem internationally. Those with dental caries can suffer pain and infection and often have difficulties eating, sleeping and socialising[10]. In children, this can mean taking time off school to attend the dentist and/or hospital, and if this experience is a child's first introduction to dental care it can lead to fear and anxiety with lifetime consequences. Despite reductions in prevalence since the 1970s, caries remains a significant problem in England with 12% of three-year-olds and 25% of five-year-olds having caries in their primary teeth, rising up to half of surveyed five-year-olds in the worst affected local authorities[1-3]. Dental caries is one of the most common causes of hospital admission in children, often for extraction of multiple decayed teeth under general anaesthetic[3]. Sizeable inequalities in caries prevalence still exist, with better dental health seen in affluent compared to deprived communities [3].

Fluoride is naturally occurring and present in drinking water sources in varying amounts. It is also present in certain foods. In the early 20th century, lower levels of dental caries were found to be associated with certain fluoride levels in drinking water. These observations ultimately led to the introduction of water fluoridation schemes to adjust fluoride levels in community water supplies, in an effort to reduce levels of dental caries in the populations they serve. More recently, fluoride has also been included in toothpaste and dental products such as gels and varnishes, use of which depends upon individual action and on intervention by dental professionals.

Economic evaluation has shown water fluoridation to offer a high return on investment. A return on investment tool, commissioned from the York Health Economics Consortium in 2016 and developed in partnership with PHE, estimates the economic

benefits associated with reducing dental caries in five-year-old children. This includes monetised savings to the local authority and the NHS. Based on a cohort of five-year-old children and the average decayed, missing and filled teeth as a result of dental caries (dmft) for England of 0.8 the estimated return for £1 investment into a water fluoridation scheme would be £12.71 after 5 years and £21.98 after 10 years. In areas of high deprivation where dmft is greater than the average for England, the return on investment will be greater [(11)].

Water fluoridation schemes

The first water fluoridation scheme was introduced in the US in 1945, in the city of Grand Rapids, Michigan and there is now extensive coverage of the US by similar schemes, with over 200 million US citizens having a public water supply in which the level of fluoride is adjusted. Following pilot schemes in the UK, the first substantive water fluoridation scheme was for Birmingham in 1964. Further schemes were progressively introduced that now cover around 6 million people, approximately 10% of the population of England. Over two-thirds of the population of the West Midlands live in an area where the level of fluoride is adjusted. Smaller schemes operate in parts of the North East, the East Midlands, Eastern England, the North West, and Yorkshire and the Humber. Water companies publish details of the levels of fluoride in their supplies and this information is normally available on their websites. Information is also available via the PHE Water Fluoridation Toolkit 2016 for local authorities[(12)], with details on schemes and the scientific evidence regarding water fluoridation[5].

The adjustment of fluoride levels in drinking water supplies in England is expressly permitted by Parliament, the relevant legislation being contained within the Water Industry Act 1991, as amended. The legislation sets out the circumstances in which a water company can be required to operate a fluoridation scheme. The power to make decisions regarding fluoridation schemes has resided with local authorities since 2013. Water fluoridation schemes aim to achieve a level of one part of fluoride per million parts of water (1ppm or 1milligram of fluoride per litre of water). The maximum amount of fluoride in public water supplies, permitted by water quality standards, is 1.5 mg fluoride per litre of water. Some water supplies in England, serving around a third of a million people, contain levels of fluoride that, without any adjustment, are close to those that fluoridation schemes seek to achieve. Water companies that operate schemes must comply with the requirements of the Code of Practice[(13)] published by the Drinking Water Inspectorate (DWI), the water quality regulator for England and Wales. This includes systems to monitor and control equipment used to add fluoride to water supplies.

[5] https://www.gov.uk/government/publications/improving-oral-health-community-water-fluoridation-toolkit

Public water supplies are delivered through a system of defined zones known as water supply zones (WSZs). Each WSZ is defined by either a single point of water supply, or where there are multiple supply sources of water of a similar nature and treatment, to permanent resident populations of 100,000 or fewer[14]. Water companies in England have a duty to monitor the fluoride concentration of public water supplies in the WSZs they supply, and provide these monitoring data to the DWI.

Sampling is performed to verify water quality, ensuring fluoride concentrations do not exceed the prescribed concentration value (PCV) of 1.5mg/L, and in fluoridated areas, are reaching the target level of 1.0mg/L[13]. Fluoride concentrations within the WSZs are sampled from randomly chosen sampling points (typically consumers' taps), that must be representative of the WSZ as a whole[14]. Samples may also be taken from 'water supply points', which may be treatment works outlets, service reservoir outlets, or blending points, and may supply more than one zone, provided it can be demonstrated that there is no material difference in the concentration between the supply point and the consumers' taps in the zone[13]. Sampling frequency depends on local factors such as population size and daily volume of water supplied (for supply point samples)[14]. Concentration testing must meet minimum standards for accuracy and precision [15].

It is possible that disruption to the supply of fluoridated water can occur in areas that are subject to water fluoridation arrangements if, for example, maintenance work becomes necessary at a particular water treatment works or technical problems prevent operation of the scheme. In such circumstances, water may need to be routed from an alternative water treatment works which does not operate a water fluoridation scheme in order to maintain supplies. This can result in the water supply reaching sub-optimal levels of fluoride or fluoridation ceasing for a period, depending upon the nature of the issue.

Use of monitoring data to inform fluoride/fluoridation exposure models is limited by constraints in data availability, meaning assumptions have had to be made about exposure in areas or time periods for which data are unavailable. Since 2004 the DWI have collated detailed maps of WSZ boundaries (used to link fluoride concentration to a geography, and then with health data). PHE obtained WSZ map data from 2004 onwards from the DWI, and were able to prepare map data from 2005 to 2015 to link to fluoride concentration monitoring data and health data for analysis. Therefore, the most reliable exposure assessment is for 2005 to 2015. However, considering fluoride concentration data from earlier years is important for health outcomes with a long induction period, such as cancers. PHE therefore also obtained fluoride monitoring data from the DWI for 1995 to 2004. Even though these data could not be mapped and therefore linked to health data, by describing and comparing fluoride concentration data from 2005 onwards with earlier data from 1995 to 2004, it has been possible to

consider whether fluoride concentrations during the later period were stable enough to be able to assume that exposure in this period was representative of prior exposure.

Rationale for monitoring the health effects of fluoridation schemes

Section 90A of the Water Industry Act 1991 requires a “relevant authority”, that has entered into fluoridation arrangements, to monitor the effects of the arrangements on the health of persons living in the area specified in the arrangements. It also requires that such an authority publishes reports containing an analysis of those effects, making available any information, or summaries of information, collected by it for these purposes.

As of 1 April 2013, the Secretary of State for Health and Social care is the "relevant authority" in England for the purposes of the fluoridation provisions in the Water Industry Act 1991, including in relation to fluoridation arrangements that had effect prior to 1 April 2013. In practice, the secretary of state's fluoridation functions are exercised by PHE. The first PHE report monitoring the health effects of these arrangements was published on 25 March 2014, and further reports are required at no greater than four-yearly intervals, beginning with the date on which the last report was published, unless the schemes in question are terminated. This report, the second produced by PHE, is designed to satisfy these requirements with respect to the current water fluoridation schemes in England.

The protective effect of community water fluoridation on caries is established, but secular changes in diet and oral hygiene (that may also result in exposure to fluoride from sources other than water, eg toothpaste) may also affect caries risk[16]. Additionally, the evidence for water fluoridation’s effect on dental health inequalities is less certain than that for overall impact, making re-assessment important. For other non-dental health outcomes, this report will add to the evidence base regarding possible associations. This information will contribute to an assessment of whether the addition of fluoride to public water supplies in England is safe, effective, and where implemented, an equitable public health intervention.

Selection of health indicators

There are 2 evidence-based dental effects of fluoridation: on levels of dental caries and on levels of dental fluorosis. This report therefore considers these 2 effects.

The selection of indicators for possible non-dental effects is more complex. Even without adjustment, people in some parts of England have been exposed for generations to levels of fluoride that are the same as or close to levels achieved by fluoridation schemes; others were, before the implementation of specific water quality standards, exposed to levels far in excess of the current regulatory limit of 1.5mg/l. The schemes themselves have been in existence in England for over fifty years in some areas[12], and now cover some 6 million people. Internationally it is estimated that

around 370 million people in numerous countries drink fluoridated water including over 200 million people in the US[17]. Despite the extent and duration of schemes, no adverse health effects have been proven from water fluoridation schemes, other than an increase in mild dental fluorosis (mottling).

The range of health conditions that have been alleged as a consequence of water fluoridation is substantial, but the scientific basis is inconclusive. Additionally, the theoretical plausibility of claims of adverse health effects is variable. A monitoring regime which included all conditions claimed to arise from exposure to drinking water would be very extensive, resource-intensive, and disproportionate to the quality of science underpinning each particular assertion. Given those considerations, PHE has decided that the content of this report should aim to address a defined number of health risks and should reflect the practicalities of the availability and robustness of data. PHE is committed to keeping the evidence base for fluoridation under review and has consulted with local authorities that have fluoridation schemes within their geographies when determining which non-dental health outcomes to examine in this report. Consultation with relevant local authorities will also be undertaken before determining the content of any subsequent health monitoring reports.

The effects of fluoride in water have been extensively studied and reviewed over the last 50 years. Other than the 2014 PHE monitoring report[18], the most recent publication in the UK was the Cochrane Database Systematic Review: Water Fluoridation for the Prevention of Dental Caries, 2015[19]. Other important evaluations that we have drawn on include those by the Australian Government National Health and Medical Review Council 2017[20, 21], the Irish Health Research Board Review 2015[22], the US Public Health Service Recommendation for Fluoride Concentration in Drinking Water 2015[23], the Royal Society of New Zealand 2014[24], the US Community Preventive Services Task Force 2013[25], the Australian National Health and Medical Research Council 2007[26], the US National Research Council 2006[27], the Medical Research Council 2002[28] , and the NHS Centre for Reviews and Dissemination 2000[29, 30]. Additionally, the European Food Safety Authority 2005[31], and the European Commission Scientific Committee on Health and Environmental Risks 2011[32] were considered.

The PHE fluoridation and health working group drew on these authoritative sources in selecting a number of indicators of health conditions for inclusion in this health monitoring report (HMR). The chosen indicators of various health conditions have been selected based on toxicological evidence, previously suggested health effects, the epidemiological evidence base, potential impact on population health, the quality and availability of data, and the validity of the indicator, as assessed by a PHE working group. The selected indicators will be reviewed for future reports in the light of emerging evidence. The indicators that have been selected are summarised in Table 1, below.

Table 1. Selected indicators for fluoridation health effects monitoring programme

Health outcome	**Indicator selected following assessment of the evidence base**	**Rationale for inclusion**
Dental outcomes: Dental caries	Decayed, missing and filled teeth ($d_3$mft[6]) as mean $d_3$mft score and prevalence of $d_3$mft>0 in five-year-old children Incidence of hospital admission of children (aged 0 to 19 years) for extraction of teeth due to dental caries	Evidence of reduction in dental caries in areas where water fluoride levels are adjusted to 1mg/l. Survey of five-year-olds (2014 to 2015) used as it provided the most recent epidemiological data.
Dental fluorosis	TF index[7]	Evidence for dental fluorosis associated with fluoride intake
Non-dental outcomes: Bone health	Hip fracture Incidence of emergency hospital admissions where a diagnosis of hip fracture was made.	Fluoride in drinking water is an important source of population exposure to fluoride[(32)], therefore fluoridation would be expected to significantly increase fluoride intake. About half of the fluoride ingested is taken up by bone[(33)] with theoretically plausible implications for its mechanical properties. An effect of fluoridation on the risk of fracture, adverse or beneficial is theoretically plausible.

[6] The subscript '3' refers to decay into the dentine of the tooth. This threshold is widely accepted in the literature as a standard method for identifying more severe carious lesions, but it provides an underestimate of the true prevalence of disease.

[7] Thylstrup and Fejerskov index, an index for reporting severity of dental fluorosis

Health outcome	**Indicator selected following assessment of the evidence base**	**Rationale for inclusion**
		Hip fracture is a common and serious condition. The MRC report (2002)[28] suggested a worst case relative risk estimate of 1.2 for hip fractures but stated that it was most likely that fluoride had no impact on risk and there could even be a protective effect.
Renal effects	Incidence of emergency hospital admissions where a diagnosis of kidney stones was made	Fluoride ingestion is asserted to be a risk factor for kidney stones. Most ingested fluoride is excreted via the kidney, which is therefore exposed to relatively high fluoride concentrations.
Congenital anomaly	Incidence of Down's syndrome	Down's syndrome is due to the nondisjunction of chromosome 21, most often in the oocyte[34]. The York Review, a systematic review of the literature, and the MRC report concluded that the evidence for the association with exposure to fluoride was insufficient and inconclusive[28, 29].
Cancer outcomes: Cancer	Bladder cancer incidence	Theoretical plausibility arises because fluoride is excreted in the urine and the bladder lining is therefore exposed to relatively high concentrations.
	Primary osteosarcoma incidence (aged <50 years)	Theoretical plausibility arises from deposition of fluoride in bone and a mitogenic effect on osteoblasts. A 2006 exploratory analysis found an association between fluoride exposure in drinking water during childhood and the incidence of osteosarcoma among males[35]. Those aged >50 years have not been considered in this analysis as osteosarcoma in this group is likely to be secondary to Paget's disease[36]. The International Agency for Research on Cancer (IARC) 1987

Health outcome	Indicator selected following assessment of the evidence base	Rationale for inclusion
		monograph concluded that there was inadequate evidence of carcinogenicity by inorganic fluorides used in drinking water, and that available studies were 'mutually consistent in not showing a positive association between exposure to fluoride and overall cancer rates or rates of different cancers'[37]. The MRC report (2002) concluded that the evidence available has not established that fluoride is genotoxic to humans and most of the studies suggest that it is not, but the possibility of some genotoxic effect cannot be excluded[28].

Certain outcomes were considered but then not included in the report. These outcomes and the rationale for exclusion are detailed in Table 2.

Table 2. Outcomes considered but not included for this health monitoring report

Outcome	Rationale for exclusion from report
Hypothyroidism	An association between exposure to fluoride in public water supplies and hypothyroidism was reported by Peckham et al [38], though there were concerns recorded about the methods used and interpretation of results from analysis of routine data with several important limitations [39-42]. No new routine data source without such limitations was available, so the working group could not address this outcome. However, as part of its commitment to continually reviewing and developing the evidence around fluoridation, PHE, with direction from the working group, is exploring whether primary care datasets can be used to investigate a potential relationship between fluoride concentration and hypothyroidism.
Intelligence Quotient (IQ)	At the time the PHE working group were considering health outcomes, the evidence for an association between lower IQ and fluoride in water was considered weak[22, 24], and there were no quality routine datasets available for analysis. Therefore IQ was not considered a priority health outcome for inclusion.
All-cause mortality, all fracture, all cancers	The evidence for an effect of fluoride exposure at levels typically seen in England on these outcomes is weak and inconsistent [22, 24, 28]. The 2014 PHE fluoridation and health monitoring report detected a weak, negative ('protective') association between fluoridation scheme exposure and all-cause mortality, and no association with all cancers, and did not investigate all fractures[18]. The working group for this 2018 report considered the monitoring of more specific outcomes a higher priority.

Aims and objectives

Aims

The overall aim of this report is to determine the association between concentration of fluoride in public water supplies in England and selected dental and non-dental health outcomes, in order to monitor the effects of water fluoridation arrangements.

Specific objectives

- Describe water supply zone fluoride concentrations for the public water supply serving the population of England from 1995 to 2015, and compare fluoride concentration data from 2005 to 2015 with earlier data from 1995 to 2004
- Describe the size of populations in England receiving water containing various categories of fluoride concentration, sub-grouped by the source of fluoride, during 2005 to 2015.
- Determine the association between concentration of fluoride in public water supplies in England and selected dental and non-dental health outcomes.
- Determine the association between exposure to a scheme and selected dental and non-dental health outcomes.
- Determine whether socioeconomic status is an effect modifier of the fluoride-outcome association, for dental caries and hospital extraction outcomes.

Methods

High level summary of methods

Exposures assigned

We first described population level exposure to fluoride in public water supplies, and fluoridation schemes. We then examined specified health effects across populations in receipt of public water supplies at different concentrations of fluoride (<0.1mg/l, 0.1mg/l-<0.2mg/l, 0.2mg/l-<0.4mg/l, 0.4-<0.7mg/l, ≥0.7mg/l), irrespective of the source. Then, to fulfil the requirement to monitor health effects of water supplies fluoridated with a scheme (rather than fluoride deriving solely from the geology of the water supply), we analysed the same data for the following subgroups:

- for non-dental health effects we compared populations in receipt of public water supplies with a fluoridation scheme where the fluoride concentration averaged ≥0.2mg/l, versus populations where the fluoride concentration averaged <0.2mg/l (a

level considered as 'not fluoridated' (from any source) for this analysis). Selection of this concentration, lower than typically achieved by fluoridation schemes with a 1mg/l target, was chosen as it would be sensitive to the detection of adverse effects occurring even at relatively low fluoride concentrations (ie 0.2-0.7mg/l).

- for dental health effects we compared populations in receipt of public water supplies with a fluoridation scheme where the fluoride concentration averaged ≥0.7mg/l, versus populations where fluoride concentration averaged <0.2mg/l. We used the higher 0.7mg/l value here as we were monitoring the beneficial rather than adverse health effect of fluoridation. This change allowed us to quantify the likely public health impact of fluoridation schemes on caries and caries-related extractions. International research evidence suggested that beneficial dental health effects were more likely to be observed above 0.7mg/l than at lower values [23], hence we selected this higher value to better quantify the dental health benefits of fluoridation schemes achieving concentrations likely to be most effective for dental health.

Available evidence, though limited in extent, strongly suggests, in terms of chemistry and bioavailability there is no important difference between added and "natural" fluoride[5, 6]. The 2 tier method of analysis was implemented to fulfil the requirement to moinitor health effects of water supplies fluoridated with a scheme.

All fluoride concentration categories to be used for analysis were determined *a priori*.

Study population

England residents were eligible for analysis[8]. The age of the eligible population and study period varied by the outcome studied.

Study design

We used an ecological study design ie the exposure, potential confounders, and outcomes of interest were measured and analysed at area level, rather than individual level.

[8] It is estimated 1% of the population receive water supplies from private sources. It was impractical to exclude this group from analyses of health outcomes. This is unlikely to significantly affect the findings.

Exposure indicator

Rationale for exposure model

Although fluoride in drinking water is not the only source of fluoride, drinking water with more than 0.3 mg/L of fluoride is amongst the main sources in human total fluoride intakes, particularly at higher fluoride concentrations (eg >0.7mg/l) typically seen in fluoridated supplies[32]. At water fluoride concentrations <0.3mg/l, therefore, other sources may be more important. Fluoride is readily and predictably absorbed into the body via the gastrointestinal tract, and this is the main mode of absorption[43]. Thus, fluoride in drinking-water is generally bioavailable. This is unlikely to be affected by water hardness at concentrations of around 1mg/l[5].

Fluoride intake from water depends on both the concentration and the volume of water consumed (which varies from person to person). While it would be informative to know frequency and quantity of consumption, such data, for example from surveys of drinking water consumption, were only available at a regional level in England, too large a population level to usefully add to this report's exposure assessment. Exposure duration data would also have been useful, but would have required individual residential histories, which were not available and therefore could not be included.

Other fluoride sources include diet, fluoride-containing dentifrices, and professionally applied dental fluoride treatments. It would be interesting to link health effects to a measure of the total daily fluoride intake from all sources or the total dose of fluoride absorbed by each person. This can be estimated by biological monitoring using biological samples for example urine. However, again such total fluoride intake data were not available at a population level. To study the effect of fluoride the exposure assessment has focussed on concentration of fluoride in the water supply. This is the one of the main determinants of how much fluoride people absorb, although we recognise that total intake also depends on factors for which we have no data.

Fluoride exposure indices based on concentration and fluoridation scheme flagging data

The information most relevant to the exposure of interest was the fluoride concentration of water from public water supplies for residents of England. Exposure indicators were estimated by combining fluoride concentration obtained from routine fluoride monitoring data from 1995 to 2015, provided by the Drinking Water Inspectorate (DWI), and population data obtained from the Census and related mid-year estimates computed by the Office for National Statistics (ONS).

Since 2006, the DWI has retained annual records that identify, via a flag, those WSZs that have fluoridation schemes. As no new fluoridation schemes have been initiated

since 1995, flagged WSZs were considered to have been fluoridated from at least 1995 continuously to 2015, unless there was known to be significant operational disruption in those zones (see exposure indicator descriptive analysis, and data management in methods section, for more information).

Water Supply Zone boundary data used to define exposure geography

The DWI supplied copies of water company WSZ boundary files in digital format from 2004 to 2015, of which we were able to prepare 2005 to 2015 for analyses.

Allocating fluoride exposure to statistical and administrative areas in England

It is important to perform analyses using the smallest sized geography available as the unit of analysis, in order to maximise statistical power and to allocate the data that best describes the attributes and exposure of the population of interest, but at a large enough geography such that the statistical models used are capable of achieving a reasonable fit to the data. The smallest geographical unit of analysis was the Lower layer Super Output Area (LSOA), and analyses at larger geographical areas were performed by using LSOA level fluoride, health and population data as 'building blocks', aggregated to form their larger 'parent' Middle layer Super Output Area (MSOA) and Lower Tier Local Authority (LTLA) areas (with which their borders match). See appendix 1 for more information on these geographic units of analysis. We used Geographic Information Systems (GIS) point-in-polygon (PIP) methods to assign fluoride concentration data to statistical areas using the population weighted centroid of each LSOA. The population weighted centroid of each LSOA ('point'), which assigns a single geographic point to each LSOA based on the largest aggregation of its population, was overlaid onto WSZs ('polygons'), thereby allocating a fluoride concentration from a WSZ to an LSOA (and their populations).

The geographic footprints of WSZs are not fixed over time. WSZs may be aggregated or dis-aggregated to ensure continuity of supplies, hence the number and geographic boundaries of zones may change, making tracking of fluoride concentration data from individual WSZs over time challenging. Each water company gives each WSZ a site reference code but these codes may not be unique across all water companies in England. Similarly water companies have merged or ceased to operate at various points in time so WSZs are not perpetual. To overcome the issue of WSZs changing shape and size over time, point-in-polygon analysis was repeated for each year of available (mapped) WSZ data (2005-2015). The linked LSOA-WSZ pairs were then merged with the DWI fluoride concentration and fluoridation scheme flagging dataset, using concatenated site reference and water company coding (ie creating a unique identifier by conjoining the site reference and water company acronym) by year to identify common WSZ years. Arithmetic mean period fluoride concentrations for the

exposure period of interest were then aggregated from LSOA to higher geographic levels, weighted by the exposed population.

Categorising water supplies by fluoride concentration

Health outcomes were compared between populations receiving different categories of fluoride concentration in their water supply. Fluoride concentration in water supply, regardless of source, was categorised into:
0.0-<0.1mg/l, 0.1-<0.2mg/l, 0.2-<0.4mg/l, 0.4-<0.7mg/l, ≥0.7mg/l

These categories were selected because:

- from international evidence, the association between fluoride concentration and decreasing caries prevalence was thought to increase linearly with increasing fluoride concentration, with reductions in dental caries plateauing above 0.7mg/l[(23)]
- from pilot work to assess the population exposed to different categories of fluoride concentration, the population within each fluoride concentration category varied, resulting in the large majority of the population receiving a water supply with a low fluoride concentration (<0.4mg/l). Therefore, the number of health outcomes were likely to still be high enough to allow categorising fluoride concentration below this level into several groups, allowing potential detection of a dose-response and/or threshold effect between fluoride exposure and health outcome
- further categorising the fluoride concentration of the population receiving water supplies with fluoride >0.4mg/l would give the ability to detect a dose-response, plateau, and threshold effect at higher fluoride levels. Detection of a dose response is important when considering evidence for causality of any potential association with an outcome
- given the relatively low water fluoride concentrations in England, the population receiving supplies at concentrations >0.4mg/l was thought unlikely to be large enough for division into more than 2 further categories and still allow meaningful examination of associations with less common health outcomes

Data management for exposure data descriptive analysis

Data cleaning, management and analysis were executed in Excel and STATA.

Exposure data (fluoride concentration monitoring data) were processed in Excel to produce a dataset containing data points for 1995 to 2003 and 2004 to 2015[9] in 2

[9] The DWI provided disaggregated fluoride monitoring data for 2004-2015 for England and Wales, and summary data for 1995-2003 for England and Wales

single sheets. These were then imported into STATA to be appended into a single dataset for further processing as described below:

- recoding: a unique identifier for each water supply zone was created by concatenating the water company and site reference variables
- collapsing of raw monitoring data for 2004 to 2015 data (as pre-2004 data were provided as already collapsed/summary data): data points for each individual fluoride concentration measurement for each zone were collapsed by grouping on supply zone and year using the newly coded unique identifier. Data were collapsed in this way to avoid weighting by zones/years with more measurements taken. Variables expressing summary statistics for each water supply zone (by year) were created in this process
- the 2004 to 2015 summary dataset was then appended onto the pre-2004 summary dataset
- fluoride flagging from 2006 was used to assign presence or absence of fluoridation scheme, after checking for inconsistencies in flagging over time
- as fluoride monitoring data were not specific to England, we created a variable to flag WSZs that supplied an England LSOA during 2005 to 2015 (which was also assigned to their matched pre-2005 zones). We then dropped from the analyses WSZs that only supplied LSOAs in Wales

Missing data, outliers and unexpected values (eg high fluoride concentrations in zones not flagged as fluoridated, and vice versa) were investigated. As there have been no new fluoridation schemes initiated since 1995, we assumed all zones ever fluoridated should have consistent fluoride flagging. Where this was not the case, we asked the DWI to check their supporting databases as to whether the zone was truly fluoridated or not, and whether inconsistent flagging may have been the result of disruption in operation of fluoride plant. If there was known significant disruption, then the zone was re-flagged as being not fluoridated for the years during which fluoridation was disrupted.

Exposure indicator descriptive analysis

The number of water supply zones, number of samples, and average number of years of monitoring data per WSZ were described from 1995 to 2015 stratified by time period (1995 to 2004 or 2005 to 2015), reflecting the variation in availability of WSZ mapping data, and approach to fluoridation and its monitoring over different time periods. We then described the annual mean fluoride concentrations in each zone for these 2 time periods, stratified by presence of a fluoridation scheme, using histograms and box-plots.

Stability of fluoride concentrations within unique zones was further described by creating scatter plots and calculating Spearman Rank coefficients (stratified by

presence or absence of a fluoridation scheme) for the WSZ-level period mean fluoride concentrations from1995 to 2004 compared to 2005 to 2015. Spearman Rank coefficients were calculated given the non-parametric distribution of the data in fluoridated areas. Fluoridation schemes known to have significant disruption to operation were excluded from the creation of scatter plots, and correlation analysis.

MSOA-level public water supply grand mean (of the annual means) fluoride concentrations for 2005 to 2015, and location of fluoridation schemes, were then described spatially by mapping the 2005 to 2015 grand mean fluoride concentrations and the distribution of fluoridation schemes onto 2011 MSOA boundaries. In order to map grand mean fluoride concentrations onto MSOA boundaries, we first calculated the grand mean fluoride concentrations for each LSOA, and then aggregated to MSOA level by weighting the means of each constituent LSOA by its 2005 to 2015 population, using ONS mid-year population estimates. We then tabulated the MSOA-level count of population supplied (taking the period average), for categorised levels of fluoride concentration in mg/L.

Health outcomes and potential confounders

Outcome indicators used, and data sources

Table 3 presents the list of the health outcomes investigated in this report, and for each: the source of data, indicator measure, geographical level, time-period studied, numerator, denominator and indicator calculation, case definition criteria and *a priori* confounding variables available for analyses are presented.

The time period studied for each outcome was decided *a priori*, based on:

- data quality (hospital episode data were obtained from 2007 to coincide with full introduction of the Payments By Results method for secondary care organisations to submit activity data to calculate payment return, with a resulting increase in recording and coverage of such statistical returns[(44)])
- availability of data (data on osteosarcoma and bladder cancer incidence, and Down's syndrome incidence was limited to the periods included in Table 3)
- expected incidence to provide adequate statistical power (for outcomes with sparse events, all years available were selected)
- a sufficient induction period for initiation of pathology from the initiation of fluoridation schemes

Potential confounders used, and data sources

All health outcomes were studied by aggregating data for each concentration category of exposure to fluoride in the water supply. Risk of illness is highly dependent on

factors that vary between different areas of England, including age- and gender-distribution, deprivation and ethnicity. We therefore attempted to account for these potentially confounding factors by using adjusted comparisons when evaluating the effects of fluoridation.

Confounders were selected according to:

- likely effect on direction and size of exposure-outcome association
- availability of data at same geographic level of outcome

Several potential confounders are likely to have an important influence on exposure-outcome association but are not measured at a geographic level to facilitate analysis. In this case, other variables that are measured at a usable geographic level may correlate with the confounding variable, allowing a degree of indirect adjustment for the confounder on multivariable analysis. Area-level deprivations status (as measured by the Index of Multiple Deprivation (IMD)) is an ecological measure (produced using LSOA level data) used for examining socio-economic indicators according to small geographic area. It has been documented to show a degree of correlation with the following potential confounders:

- smoking[45]
- low fruit/vegetable diet and/or high non-milk sugar dietary intake in adults and children[46, 47]
- obesity[48]
- tooth brushing in children[47]
- alcohol intake[49]
- bone mineral density[50]

The latest IMD dataset was released in 2015. In order to aggregate to higher geographies, average scores were calculated from population weighted averages of their constituent LSOA scores, following guidance in appendix A of the research report released with the English indices of deprivation 2015[51].

For more detailed information on potential confounders, see Table A2 in the appendix.

Table 3. Health outcomes; source of data; outcome indicator; geographical level; time period studied; population denominator; case definition criteria; *a priori* potential confounders

Health outcome	Source of data	Outcome indicator	Geographical level of outcome data for analysis	Time period	Numerator, denominator, and indicator calculation	Case definition criteria	A priori potential confounders
Dental Caries	National Dental Epidemioloy Programme for England. Survey Sample data.	Presence of caries experience at 5-years old as *mean* $d_3$mft score and prevalence of any $d_3$mft>0	LSOA	2014 to 2015 (five-year-olds)	***mean* $d_3$mft:** grand mean of number of teeth with caries experience per child[10]/number of children examined in the same geography; **prevalence of any $d_3$mft>0**: number of children with caries experience ($d_3$mft>0)	*mean* $d_3$mft *score* and *prevalence of any* $d_3$mft>0	Deprivation†, ethnicity

[10] Children had all teeth examined

Health outcome	Source of data	Outcome indicator	Geographical level of outcome data for analysis	Time period	Numerator, denominator, and indicator calculation	Case definition criteria	A priori potential confounders
					divided by number of children examined in the same geography		
Admissions for extraction due to dental caries age 0-19	Dental Public Health Intelligence Programme (using HES)[11]	Incidence of Hospital admission of children (aged 0 to 19 years) for extraction of one or more primary or permanent teeth – due to caries	MSOA	2007 to 2015	Count of cases divided by ONS mid-year population estimates for relevant age and year	HES code F09 and diagnostic codes K021, K028, K029, K045, K047 De-duplication not required.	Age, gender, deprivation†, ethnicity

[11] http://www.nwph.net/dentalhealth/extractions.aspx

Health outcome	Source of data	Outcome indicator	Geographical level of outcome data for analysis	Time period	Numerator, denominator, and indicator calculation	Case definition criteria	A priori potential confounders
Dental fluorosis	Pretty et al 2016[7]	Thylstrup and Fejerskov (TF) index	City of residence (limited to 4 cities)	2015	Count of cases divided by study population	TF index>0	None
Down's Syndrome	The National Congenital Anomaly and Rare Disease Registration Service	Incidence proportion[12] of Down's Syndrome	LTLA	2012 to 2014	Count of cases, stratified by maternal year of age, divided by ONS live births per year stratified by maternal year of age for 2012 to 2014	All cases: live births, stillbirths (at least 24 weeks' gestation), late miscarriages (20 to 23 weeks' gestation), and terminations of pregnancy with fetal anomaly	Maternal age

[12] We have used the term "incidence proportion" to align the nomenclature used across the indicators in this report. However, conventionally congenital anomaly registers would report prevalence estimates when analysing counts of new cases of congenital anomaly. This is because it is not possible to ascertain all "new" cases of any particular anomaly, as a proportion of pregnancies affected will miscarry spontaneously before being diagnosed.

Health outcome	Source of data	Outcome indicator	Geographical level of outcome data for analysis	Time period	Numerator, denominator, and indicator calculation	Case definition criteria	A priori potential confounders
Hip fracture	HES	Incidence of emergency admissions; 1st or 2nd diagnosis	MSOA	2007 to 2015	Count of cases divided by ONS mid-year population estimate for 2007-2015	HES code S72.0 to S72.2. Duplicates in each 12 month period, as evaluated by the unique HES identification number, to be removed	Gender will be stratified, so adjust for age[Ω], deprivation, ethnicity
Kidney stone	HES	Incidence of emergency admissions; 1st or 2nd diagnosis	MSOA	2007 to 2015	Count of cases divided by ONS mid-year population estimate for 2007-2015	HES codes N20.0 to N20.2; N20.9. Duplicates in each 12 month period, as evaluated by the unique HES identification number, to be removed	Age, gender, deprivation, ethnicity

Health outcome	Source of data	Outcome indicator	Geographical level of outcome data for analysis	Time period	Numerator, denominator, and indicator calculation	Case definition criteria	A priori potential confounders
Bladder carcinoma	English Cancer Registration	Incidence of primary invasive bladder cancer	MSOA	2000 to 2015	Count of cases divided by ONS mid-year population estimates 2000 to 2015	ICD-10 C67	Age, gender, deprivation, ethnicity
Primary osteosarcoma (age <50 years)	English Cancer registration	Incidence of primary osteosarcoma	LTLA	1995 to 2015	Count of cases divided by ONS mid-year population estimates 1995 -2015	ICD-10 9180-9195 suffix 3	Age, gender, deprivation, ethnicity

†An interaction term for area level IMD was fitted to investigate *a priori* specified potential interaction between fluoride and IMD on caries

Ω Analysis was stratified by gender, and an interaction term by age band introduced to investigate *a priori* specified potential interaction between fluoride and age/gender

LSOA – Lower layer Super Output Area; MSOA – Middle layer Super Output Area; LTLA – Lower Tier Local Authority; TF– Thylstrup and Fejerskov

Dental indicators

Dental caries

Dental caries data were obtained from the most recent survey of five-year old children (2014/15) undertaken for the National Dental Epidemiology Programme for England[(1)]. This survey involved visual examination of children's teeth by trained and calibrated examiners who followed a nationally agreed protocol, providing comparable data that was reported by lower tier local authority.

Prevalence is typically reported as the percentage of children with caries experience (ie with one or more obviously decayed, missing or filled primary teeth, due to caries, denoted as %$d_3$mft>0). In this survey dental caries is reported as being present only if there is obvious decay affecting the inner tooth tissue, called dentine. The subscript 3 indicates this level of detection.

Mean severity of dental caries is typically reported as the mean number of teeth showing signs of having been affected by caries when the child was examined – whether the teeth are actively decayed at the time or have previously been filled or extracted – decayed/missing/filled teeth ($d_3$mft).

Aggregate counts of affected children, and mean number of teeth affected per child, were extracted at LSOA level from the survey dataset. Children attending mainstream schools in England formed the sampling frame for this survey, stratified at the level of lower tier local authorities. At this local authority level, cluster sampling was used to select mainstream schools, the Primary Sampling Unit (PSU). PSUs were selected with probability proportionate to the size (PPS) of the school. In larger schools random samples of children were taken, whereas all children were sampled in smaller schools [(1)]. Once a child had been selected within the sampling frame, examination of the child's teeth was only conducted when consent had been received from the child's parent/carer. Published survey results at LTLA level did not account for clustering of children within PSU, and therefore did not calculate a design effect (G. Davies 2017, private communication).

For other dental outcome and non-dental outcomes we aimed to analyse data on all cases, not a sample.

Dental admissions

The data presented on incidence of hospital admission of children and young people, aged 0 to 19 years, for extraction of one or more primary or permanent teeth due to dental caries, are from the Dental Public Health Intelligence Programme (2007 to 2015) using hospital episode statistics (HES). Incidence was calculated by dividing the

number of episodes by Office of National Statistics (ONS) mid-year population estimates for the relevant age and year. It was decided that de-duplication of episodes within each 12 month period (as performed for hip fracture and kidney stone analyses) was not required. This was because many hospital dental services elect to follow a more radical treatment plan (ie extraction of all teeth that are carious, even if the teeth are not giving symptoms, within one episode of care), if a child is undergoing a GA for dental treatment aiming to avoid a repeat anaesthetic for further dental extractions. Dental extractions in children are simple surgical procedures and nearly all completed in one anaesthetic session. Therefore, repeat admission for surgery within 12 months was thought to be uncommon, and unlikely to impact on our analysis.

Dental fluorosis

There is a range of clinical indices for reporting dental fluorosis. The Thylstrup and Fejerskov (TF) index is commonly used in Europe and Asia and has been validated histologically[52].

The most recent reporting of fluorosis prevalence and severity in England was measured using primarily the TF index in research commissioned by PHE to inform this health monitoring report. The population under examination was drawn from 4 cities; Newcastle upon Tyne (fluoridated), Birmingham (fluoridated), Liverpool (non-fluoridated) and Manchester (non-fluoridated). The results of this study were reported by Pretty et al [7].

To mitigate dental examiner bias and assist differential diagnoses, fluorosis evaluations were undertaken remotely by examiners unaware of where the participant was resident, viewing high quality, polarised images of the maxillary anterior teeth produced using standardised cameras under standardised lighting conditions. This methodology afforded a valid detection and diagnosis of fluorosis.

Non-dental, non-cancer health indicators

Hip fracture

The indicator studied was the number of hip fracture in-patient consultant episodes per MSOA in England, recorded in HES according to the following case definition; admission date between April 2007 and March 2016; coded as S 72.0; S72.1; S72.2; occurring as the first or second diagnosis; emergency admission. Duplicates, as evaluated by the unique HES identification number within each financial year of data extracted, were removed. *A priori* confounding variables/effect modifiers examined were age, gender, deprivation – measured by IMD 2015; ethnicity – gender-specific proportion of the population recorded as white, in 0 to 24, 25 to 49, 50 to 64, and 65+

age groups, from ONS 2011 census data, obtained at 2011 LSOA level and aggregated to MSOA level.

Kidney stones

The indicator studied was the number of kidney stones in-patient consultant episodes per MSOA in England recorded in HES according to the following case definition; admission date between April 2007 and March 2016; coded as N 20.0; N20.1; N20.2; N20.9; occurring as first or second diagnosis; emergency admission. Duplicates, as evaluated by the unique HES identification number within each financial year of data extracted, were removed. *A priori* confounding variables examined were age, gender, deprivation – measured by IMD 2015, ethnicity gender-specific proportion of the white population, in 0 to 24, 25 to 49, 50 to 64, and 65+ age groups, from ONS 2011 census data, obtained at 2011 LSOA level and aggregated to MSOA level.

Down's syndrome

Counts of cases of Down's syndrome, aggregated by individual year of maternal age (at diagnosis) at LSOA level, were obtained from the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). The case definition included all cases of Down's syndrome in England, including: live births; stillbirths (24+ weeks' gestation); late miscarriages (20 to 23 weeks' gestation); terminations of pregnancy with fetal anomaly; 2012 to 2014 inclusive.

Almost every baby with clinical features suggesting Down's syndrome, as well as any antenatal diagnostic sample from a pregnancy suspected to have Down's syndrome, receives a cytogenetic examination, since the definitive test for the syndrome is detection of an extra chromosome 21 (trisomy 21). All clinical cytogenetic laboratories in England submit information for each such diagnosis and its variants to NCARDRS. NCARDRS incorporated the old National Cytogenetic and Down's syndrome Register. Since its inception the register has captured data for an estimated 93% of all diagnosed births and pregnancy terminations to residents of England [(53)]. Cases of Down's syndrome were categorised according to year of diagnosis for live births, stillbirths (24+ weeks' gestation), late miscarriages (20 to 23 weeks' gestation) and terminations of pregnancy with fetal anomaly. Maternal age-specific case counts were then aggregated to LTLA level.

The risk of a Down's syndrome birth is highly associated with maternal age[(54)], therefore this variable was considered as an *a priori* confounder. Counts of live births by individual year of maternal age and postcode of residence were obtained from ONS data held by PHE. These maternal age-specific birth counts were then aggregated to LTLA level, using postcode to allocate LTLA.

Cancer indicators

Cancer data were extracted from the cancer registry by the National Cancer Registration and Analysis Service.

Bladder cancer

The case definition for bladder cancer was; all primary invasive bladder cancer in England recorded in the cancer registry with date of diagnosis between 2000 and 2015 inclusive; ICD-10 code C67. *A priori* confounding variables examined were age, gender, deprivation – as measured by IMD 2015, and gender-specific ethnicity – obtained from 2011 census at 2011 LSOA level, aggregated to MSOA level. Age and gender-specific case counts were aggregated to MSOA level for analysis.

Osteosarcoma

Osteosarcoma was considered as an indicator separately for those aged less than 50 years, to reflect the aetiology of osteosarcomas in the over 50s more commonly resulting from Paget's disease and prior radiotherapy[36]. The case definition for osteosarcoma was all cases in England recorded in the cancer registry with date of diagnosis between 1995 and 2015 aged less than 50 years at the time of diagnosis; ICD-10 codes 9180 to 9195, suffix 3; ICD-10 codes were chosen on advice of the National Cancer Registration and Analysis Service Site Specific Reference Group for Bone and Soft Tissue Sarcoma experts. The time-periods chosen were a balance between being sufficiently long to provide statistical power and allowing an approximate lag period of at least 10 years after the introduction of the majority of fluoridation schemes. *A priori* confounding variables examined were: age, gender, deprivation – IMD 2015, and ethnicity – obtained from 2011 census at 2011 LSOA level and aggregated to LTLA level. Age and gender-specific case counts were aggregated to LTLA level for analysis.

Time period of exposure

The exposure time period of interest varied by the induction period of the health outcome being considered (see Table 4.)

Table 4. Water fluoridation exposure periods of interest

Outcome of interest and data period	Period for exposure assessment	Exposure period notes
Dental Caries in five-year-olds (2014 to 2015 school year)	For children aged 5 in 2014 to 2015: mean fluoride concentration January 2009 to December 2015	Incorporation of fluoride into developing tooth tissue and after tooth eruption are both likely to play a role in modifying caries risk [55-57]. The development of caries severe enough to result in detection on dental survey, or extraction, will potentially be affected by exposure to fluoride during the pre-eruptive and post-eruptive periods of tooth development. As the pre-eruptive period begins during fetal development, and it is thought that fluoride can cross the placenta[33, 58] (though the relationship between maternal and fetal exposure is less clear and the placenta may act as a partial barrier[59]), the induction period should include fluoride exposure in utero.
Hospital admissions for dental extractions due to dental caries in children and young people aged 0 to 19 years 2007 to 2015	Hospital admissions for dental extractions due to dental caries in 0 to 19 year olds: mean fluoride concentration in 2007 to 2015	Given the mixed age groups for caries extraction data, such specificity is not required, hence the period exposure chosen.
Dental fluorosis in 11 to 14 year-olds 2015	Reported lifetime residence in a fluoridated/non-fluoridated city	Data collection and analysis was undertaken before data on fluoride levels became available. The study was limited to children who self-reported lifetime

Outcome of interest and data period	Period for exposure assessment	Exposure period notes
		residence in the study city. There may have consequently been some mis-classification (Pretty et. al 2016[7]).
Non-dental, non-cancer Hip fracture 2007 to 2015	Mean fluoride concentration 2005 to 2015	The induction period is expected to be relevant to a chronic exposure over at least 10 years, ie from at least 1997. Accurate data on exposure prior to 2005 is not available, therefore the concentrations during 2005 to 2015 were used as a proxy for likely prior exposure. Given the last fluoridation scheme was initiated in 1991 (and the majority before the early 1980s), the time periods selected give an adequate minimum induction period.
Kidney stone 2007 to 2015	Mean fluoride concentration 2005 to 2015	Kidney stones are likely to develop over several years[60], but may also develop more rapidly (several months) in environments conducive to their formation[61].
Non-dental, cancer Bladder cancer 2000 to 2015 Primary osteosarcoma 1995 to 2015	Mean fluoride concentration 2005 to 2015	The induction period for cancers is expected to be at least 10 years. See notes on hip fracture above. A small number of osteosarcoma cases may have been exposed to fluoride for less than 10 years in areas with schemes that imitated after 1985.

Outcome of interest and data period	Period for exposure assessment	Exposure period notes
Congenital Down's syndrome 2012 to 2014	Mean fluoride concentration 2011 to 2014	Down's syndrome is due to the nondisjunction of chromosome 21, most often in the oocyte. The most likely time in the woman's lifecycle at which this may occur is not firmly known, and may occur prenatally in the mother of the case (ie before the mother herself was born) and then during her lifetime until after fertilisation[34]. The exposure period of interest for this study therefore included the time of ovulation and conception, but we could not include other lifetime exposure due to the mixed age groups studied.

Data management for health outcomes analysis

Data acquisition

Data cleaning, management and analysis were conducted in Excel and STATA.

Population level denominator and confounder data were obtained from the Office for National Statistics (2011 census ethnicity data), PHE population databases (age- and gender-specific population counts), and Department for Communities and Local Government (index of multiple deprivation data). Water company WSZ digitized boundaries, and public water supply fluoride concentration and fluoridation flagging exposure data were collected from the DWI.

Data re-coding

Outcome counts and population denominators (and ethnicity counts) at LSOA level, from separate years were aggregated for all years combined, into age-gender specific groups specified for analysis. Age was coded into a categorical variable, with the youngest groups as base reference age band. Gender was coded into a binary variable. Gender-specific ethnicity counts of individuals of white ethnicity, and total population by age-band (available in bands of 0 to 24 years, 25 to 49 years, 50 to 64 years, 65 years and over), were used to generate the percentage, as a continuous variable, of the white population out of the total area age-specific population, using 2011 census data. Using IMD 2015 scores, area-level deprivation status was ranked and coded into quintiles as an ordered categorical variable.

Outcome data were linked to exposure and confounder data (using STATA *merge* function on geographic area ID at LSOA level). Data were checked for missing and outlying values, and discrepancies verified with the data-custodian.

Aggregation to MSOA and LTLA level from LSOA level

LSOA level data were aggregated to age-gender specific MSOA or LTLA level using an LSOA 2011 to MSOA 2011/LTLA 2011 level lookup code, downloaded from the gov.uk Open Geography portal, using the STATA merge function to assign an MSOA/LTLA code to each LSOA, and the collapse function to sum the MSOA/LTLA level outcome counts and population counts. A weighted MSOA/LTLA level average fluoride concentration and deprivation score was produced by averaging the LSOA level concentrations/scores, weighting by the MSOA/LTLA level exposed population.

Analysis of the association between fluoride concentration and health outcomes

Statistical analysis was performed using Stata 14 (Stata Corp, College Station, TX, US)

Descriptive epidemiology

Dental caries prevalence and severity

We calculated summary statistics (proportion of children with $d_3$mft>0, and sample-weighted grand mean of $d_3$mft) for each category of fluoride exposure status. Summary crude statistics were not weighted by inverse inclusion probability weights (the inverse of the probability of subject selection), to take account of varying selection probabilities between survey strata) because of unknown selection probabilities of the surveyed five-year-old children. As such, the prevalence estimates are valid only for the children surveyed, and can be extrapolated only after determining how representative the surveyed children are of the wider population. We therefore calculated the proportion of surveyed five-year-olds within each fluoride concentration category, deprivation quintile, and of white ethnicity, and repeated this for all five-year-olds in England (using mid-year population estimates for 2014), to compare the characteristics of the 2 groups. For proportion of white ethnicity surveyed and in the general five-year-old population, this was estimated by multiplying the proportion of 0 to 25-year-olds of white ethnicity in each LSOA on census 2011, by the count of five-year-olds surveyed, and the mid-year estimate of five-year-olds, respectively. The 0 to 25 year age band was the closest available age grouping by ethnicity at LSOA level.

Hospital episodes for dental extractions for caries reasons

Case counts were aggregated by fluoridation status to calculate a crude incidence (density) rate per category of fluoridation exposure, by dividing the episode count by the total persons at risk in 2007 to 2015.

Hip fracture, kidney stone, bladder cancer, and osteosarcoma

Case counts were aggregated by fluoridation status. A crude annual incidence (density) rate was calculated per category of fluoridation exposure by dividing the case count by the total person years at risk (the sum of the annual denominators).

Down's syndrome

Counts were aggregated by fluoridation status. A crude annual incidence proportion was calculated per category of fluoridation exposure by dividing the case count by the total number of live births per year[13].

Analytic epidemiology

General approach

We used univariate regression to determine crude regression coefficients of the outcome for each category increase of fluoridation exposure. Multivariable models were then constructed to determine regression coefficients and their 95% confidence intervals, adjusted for all *a priori* selected potential confounders. A p value was calculated using a *z* test to indicate the strength of the evidence against the null hypothesis that the regression coefficient did not vary by exposure to fluoride/fluoridation. The regression technique chosen depended on the underlying distribution of the dependent variable data. The distributions of count data were inspected using a histogram. If the data appeared to fit a Poisson distribution, a Poisson model was fitted to the data aggregated at that geographic level of analysis. If performing the regression in this combination of geographic level of analysis and age groupings was considered likely to give a poor model fit, due to a high proportion of zero values relative to non-zero values eg >40%, outcome data were further aggregated to give fewer zero counts, either by aggregating age groups (age bandings to aggregate to were defined *a priori)*, or if necessary aggregating the unit of analysis to the next highest geographic level. If multivariable Poisson modelling revealed over-dispersion (deviance/degrees of freedom>2.0), a negative binomial model was instead adopted for both univariate and multivariable models. See the section below for details of methods used for the dental caries survey data analyses. Regression coefficients were converted to odds ratios (following logit-Binomial regression) or risk ratios (following Poisson regression or Negative Binomial regression) using STATA's '*eform'* option.

A backward stepwise procedure was used to fit the most parsimonious model, using the Wald test to determine whether the coefficient(s) of the independent variable was significantly different from zero (and therefore were assumed likely to improve the model fit to the data), taking a significance level of $p<0.10$. However, certain variables were identified *a priori* as likely important potential confounders, and were therefore not assessed for removal from the model (see Table A2).

[13] The denominator would ideally be total number of pregnancies, but these are very difficult to measure with precision, therefore live births were used as a proxy.

For all outcomes other than Down's syndrome, osteosarcoma, and dental caries survey data outcomes, a fixed effects model with a cluster option (using the 'parent' LTLA of the LSOA/MSOA unit of analysis) was adopted to inflate the standard error to account for likely non-independence between the values of the outcome variable for LSOAs/MSOAs within the same LTLA. The Down's syndrome and osteosarcoma models adopted usual standard errors, because age (or maternal age for Down's syndrome) is the overwhelming risk factor, and non-independence within regions was thought unlikely. Dental caries prevalence data modelling is discussed further below.

We then modelled the categorical fluoride exposure variable as a linear term, in order to determine whether there was a linear trend in the regression coefficient with each increase in fluoride concentration category. Evidence of a linear trend may indicate a dose response, but must be carefully interpreted alongside the coefficients from the aforementioned multi-categorical analysis to assess whether a truly linear relationship is apparent.

An interaction term was fitted between fluoride concentration category and *a priori* specified potential effect modifiers, and the resulting joint term tested for statistically significant evidence of interaction ($p<0.10$) using a Wald test. If a statistical interaction was present, the stratum specific estimates of the effect modifier were presented.

All confounders, other than ethnicity, were modelled as categorical variables. Post-estimation, the assumed linear relationship between ethnicity (modelled as a continuous covariate) and the outcome was checked by confirmation that when ethnicity was successively modelled as a quadratic and cubic function, their coefficients were not significantly different from zero (using a Wald test p value of <0.05). If a non-linear term resulted in superior model fit, then ethnicity was instead categorised into quintiles and modelled as a categorical variable.

Prevalence of caries experience, and mean caries severity

Proportion data were analysed using a Binomial model with logit link, using sample size as the number of 'trials' per LSOA. We calculated unadjusted odds ratios (for prevalence of caries experience), for each category increase of fluoridation exposure, at LSOA level.

The mean $d_3$mft data distribution was severely skewed. Log transformation was inappropriate due to zero values[62]. Therefore an ordered logistic regression approach was taken, by splitting the outcome into ordered categories of '0' for zero values, and then 3 further categories ('1', '2' and '3'), formed from equal tertiles of the remaining outcome data. The proportional odds assumption was tested across response categories using an approximate likelihood ratio test, a p value of <0.05 being the cut-off used to reject proportionality of odds. This being the case, data were modelled using

gologit2 user-written STATA command, which is appropriate for fitting models where the proportional odds assumption is violated[63].

For all dental outcomes, an *a priori* interaction between deprivation status (measured by quintile of index of multiple deprivation) and fluoridation status was tested using the methods outlined above. When an interaction was confirmed, deprivation quintile stratum-specific regression coefficients, adjusted for covariates, are presented.

Robust standard errors were adopted to adjust the standard error for PSU level clustering not accounted for in the primary survey analysis. Note, inverse inclusion probability weights were not used in regression analyses, as the relationship between the exposure and outcome at the unit of analysis level was of interest, rather than the prevalence of caries itself. Therefore, an unweighted model-based estimate is appropriate and unbiased[64].

Public health impact measures

The preventive fraction (as a percentage) in children exposed to fluoride was calculated to indicate the percentage of prevalent cases of caries experience, and extractions due to dental caries, in children in each year group (five-year-olds or children and young people aged 0 to 19 years for extractions) of the study population[14] that could be prevented by exposure to drinking water fluoridated at a concentration of at least 0.7mg/L compared to populations exposed to low fluoride concentrations (ie of less than 0.2mg/l). 0.7mg/L is a level at which international evidence suggests we would expect an impact on caries of public health significance. Fluoride concentration category was re-coded into a binary <0.2mg/l and ≥0.7mg/l and modelled against proportion of children with caries experience, and extractions due to dental caries, to derive risk ratios respectively. For the prevalence outcome, risk ratios were determined using a Binomial regression with a log link instead of the logit link used in the main analysis, with the former an acceptable applied method to derive risk ratios while the latter is preferred for modelling proportion data. Stratum specific ratios were reported when interaction by deprivation was present.

The following formula was used to calculate the preventive fraction: 1-RR (lower CI = 1-RR upper CI; upper CI = 1-RR lower CI). Where RR is the risk ratio of the outcome for the exposed (fluoride ≥0.7mg/l) compared to the unexposed group (fluoride of <0.2mg/l), and CI is the confidence interval around this risk ratio.

[14] For the survey data this will only be directly applicable to the children surveyed, and generalisability will depend on the survey sample characteristics being similar to the England average

Post hoc analyses

Prevalence of dental caries experienceand incidence of dental extraction admissions related to dental caries

In order to investigate the association between fluoride exposure and prevalence of dental caries experience at higher concentrations than 0.7mg/l, we split the highest exposure category into 2 categories, leaving 6 in total as follows: <0.1mg/l, 0.1-<0.2mg/l, 0.2-<0.4mg/l, 0.4-<0.7mg/l, 0.7-<0.9mg/l, ≥0.9mg/l. This allowed an assessment of the continuation of trend and/or any potential threshold effect.

Hip fracture admission incidence

In order to investigate the association between fluoride exposure and hip fracture admission incidence at higher concentrations than 0.7mg/l, we split the highest exposure category into 2 categories, leaving 6 in total as follows: <0.1mg/l, 0.1-<0.2mg/l, 0.2-<0.4mg/l, 0.4-<0.7mg/l, 0.7-<0.9mg/l, ≥0.9mg/l.

As a further test of trend that would be less susceptible to weighting by unevenly spaced fluoride concentration categories, we calculated the arithmetic mean fluoride concentration within each fluoride concentration category. All observations in each category were then allocated this concentration, which was then taken as a linear term in the fully adjusted model.

Down's syndrome missing data analysis

Maternal age data were missing for 6% of Down's syndrome count data. We therefore performed a *post hoc* sensitivity analysis whose results would be unaffected by the missing age data. Maternal-age specific live birth risks for Down's syndrome were taken from Morris et al. [65], based on registry data where maternal age was imputed for the 2.6% of pregnancies with this missing[54]; for each local authority the total number of births for each single year of maternal age was multiplied by the risk of having a Down's syndrome birth to estimate the expected number of Down's syndrome cases for mothers of that age. The total number of expected Down's syndrome cases for each local authority was calculated by summing the expected numbers at each maternal age. A Poisson model was then fitted with these expected cases as the denominator.

Bladder cancer incidence

In order to investigate the association between fluoride exposure and incidence of bladder cancer at higher concentrations than 0.7mg/l, we split the highest exposure category into 2 categories, leaving 6 in total as follows: <0.1mg/l, 0.1-<0.2mg/l, 0.2-<0.4mg/l, 0.4-<0.7mg/l, 0.7-<0.9mg/l, ≥0.9mg/l.

As a further test of trend that would be less susceptible to weighting by unevenly spaced fluoride concentration categories, we calculated the arithmetic mean fluoride concentration within each fluoride concentration category. All observations in each category were then allocated this concentration, which was then used as a linear term in the fully adjusted model.

Sensitivity analysis of outcomes with potential under-estimation of past fluoride concentration

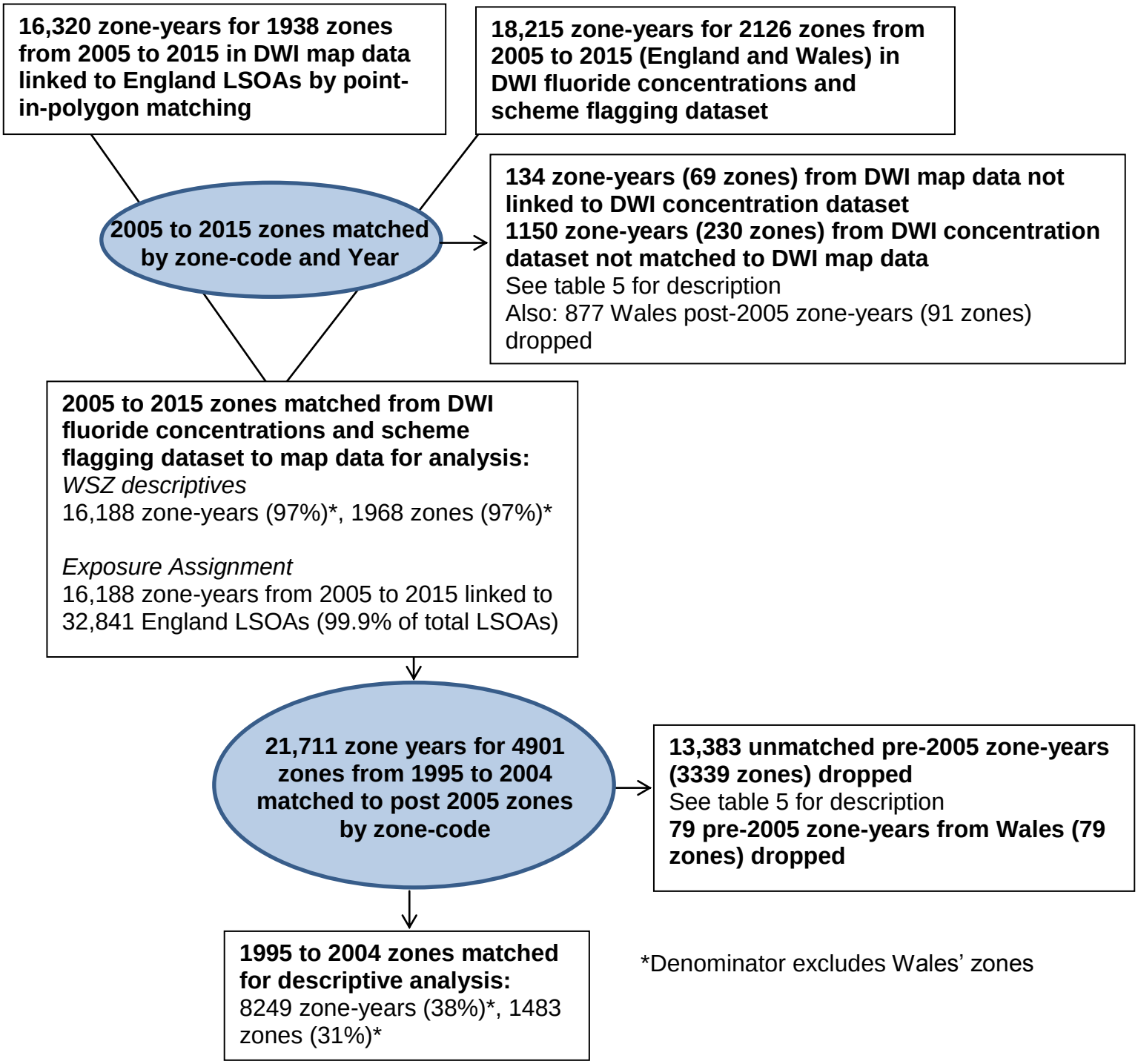
For analyses of outcomes where exposure a long time prior to diagnosis is important, or there is a long ‘lag’ period between exposure to fluoride and outcome (ie hip fracture and cancer outcomes), the exposure marker we used (fluoride exposure during 2005 to 2015), may not have been representative of fluoride exposure in prior decades. Therefore, sensitivity analyses were conducted excluding zones where there was known to be significant operational disruption to a fluoridation scheme during 2005 to 2015, as the typical fluoride exposure in earlier decades would be likely to have been uncertain.

Results

Description of fluoride concentration in water supply zones in England, 1995 to 2015

Selection of water supply zones for descriptive analysis

Figure 1, summarises how water supply zones were selected for analysis.



Description of water supply zones

A total of 134 zone-years[15] from 69 water supply zones were linked to LSOA geography on point-in-polygon analysis, but then did not match zone codes in the main DWI fluoride concentration dataset. No further characteristic information was available for these zones. 33/192 zones flagged as ever fluoridated from 2006-2015 in the DWI dataset had inconsistent flagging. After discussion with the DWI, flagging inconsistencies were resolved for all zones, leaving 170 zones confirmed as ever being fluoridated, of which 7 were noted to have experienced significant disruption to fluoridation operations (see appendix A4 for details of these zones).

A further 1,150 zone-years from 230 zones over 2005 to 2015 were in the DWI fluoride concentration dataset but not matched to zone codes in the WSZ boundary files for point-in-polygon analysis. The characteristics of these zones are shown in Table 5 below, and can be compared to zone-years/zones that were matched between the 2 datasets for the time period, summarised in Table 6. Median fluoride is slightly lower in the un-matched 2005 to 2015 zones, but higher if in the 5.6% in a fluoridation scheme. Fewer annual samples were taken in these unmatched zones; however, the 12 year typical duration of a zone is similar to the matched zones.

On matching zones from post-2005 to their pre-2005 counterparts, 13,833 zone-years (64% of the total 21,632 pre-2005 zone-years) from 3,339 zones were not matched. The characteristics of these zones are shown in Table 5 below, and can be compared to zone-years/zones that were matched between the 2 periods summarised in Table 6, also below. Fluoridation status could not be assigned to zones that were not matched to any zones from 2006 onwards, when fluoride flagging was initiated. Median fluoride was similar, but slightly lower in the un-matched 1995 to 2004 zones (0.1mg/l compared to 0.12mg/l). There was a similar sampling frequency of just a single annual sample in matched and un-matched zones, and the typical zone duration of 8 years was much shorter than matched zones, as expected.

[15] Each water supply zone may contribute varying durations of concentration data, therefore one ‘zone year’ is equivalent to one year of fluoride concentration data for one water supply zone

Table 5. Characteristics of unmatched zone-years from DWI dataset for 2005 to 2015 (n=1150 zone-years for 230 zones), and 1995 to 2004 (n=13,383 zone-years for 3339 zones)

Time period	Fluoridation scheme (%)	Median fluoride (mg/l) (LQ-UQ)	Median fluoride (mg/l) in scheme (LQ-UQ)	Median annual samples (LQ-UQ)	Median years of monitoring data per zone (LQ-UQ)*
95-04	NA**	0.10 (0.08-0.20)	NA**	1 (1-1)	8 (4-9)
05-15	64 (5.6)†	0.10 (0.05-0.23)	0.92 (0.72-0.97)	4 (2-4)	12 (7-12)

**This may be greater than the time period when stratified (eg to 2005 to 2015), as it reflects the total period of existence of a given zone with that unique zone-code and water company code combination; **not possible to assign a fluoridation scheme status; †1138/1150 zone-years assigned a fluoridation status; LQ – Lower Quartile; UQ – Upper Quartile.*

Median fluoride across England of 0.12mg/l, was similar for the 2 time periods. However, median fluoride was slightly higher for fluoridated WSZs in the latter time period (0.84mg/l compared to 0.78mg/l). Most zones matched from the earlier time period contributed data for 20 out of a total 21 year monitoring period, but were only sampled once a year. Most of the zones from the latter time period existed since at least 2004.

Table 6. Characteristics of matched zone-years from DWI dataset for 1995 to 2004 (n=8,249 zone-years for 1483 zones), and 2005 to 2015 (n=16,188 zone-years for 1884 zones).

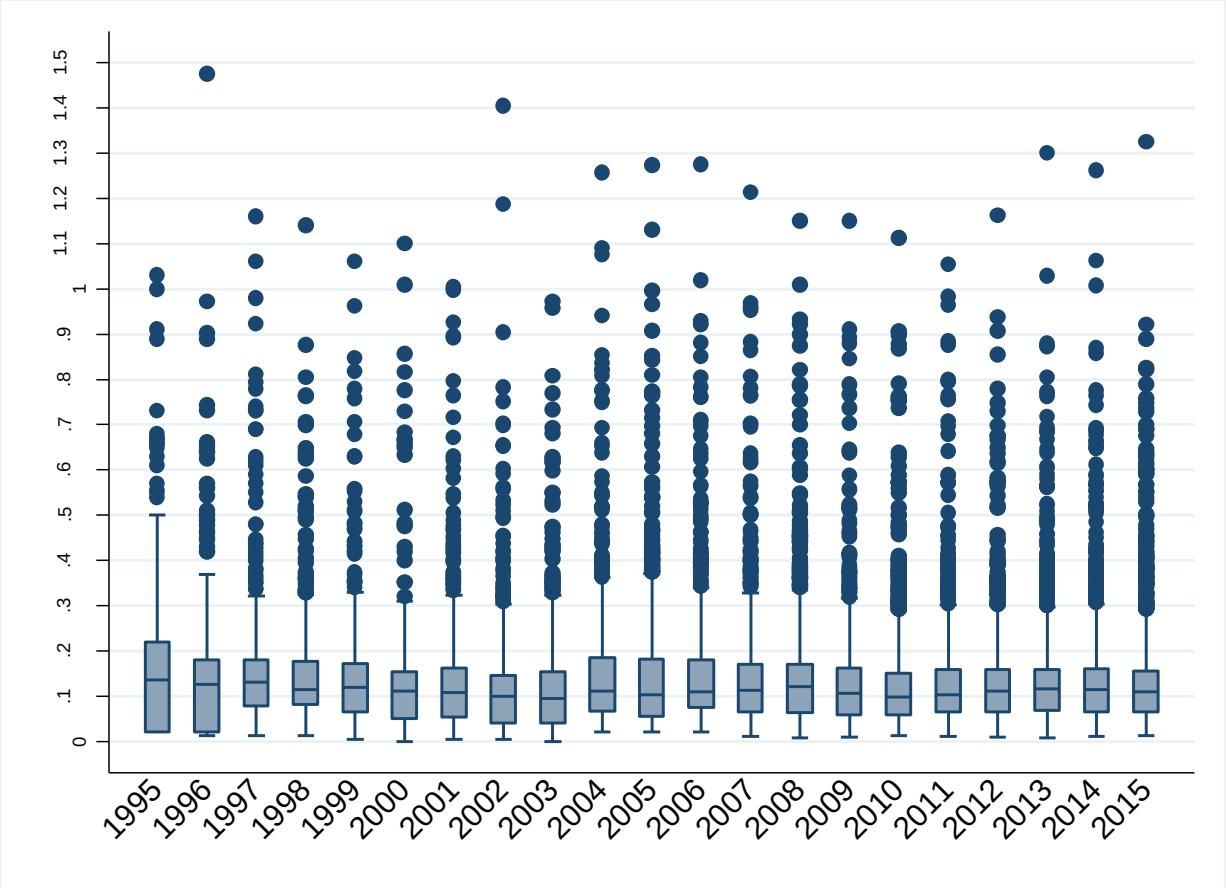
Time period	Fluoridation scheme (%)	Median fluoride (mg/l) (LQ-UQ)	Median fluoride (mg/l) in scheme (LQ-UQ)	Median number of annual samples per zone (LQ-UQ)	Median years of monitoring data per zone (LQ-UQ)*
95-04	491 (6.3)**	0.12 (0.06-0.19)	0.78 (0.57-0.90)	1 (1-6)	20 (17-21)
05-15	1566 (9.7)†	0.12 (0.07-0.21)	0.84 (0.66-0.94)	8 (8-9)	12 (12-20)

**This may be greater than the time period when stratified (eg to 2005 to 2015), as it reflects the total period of existence of a given zone with that unique zone-code and water company code combination; **7791/8249 zone-years assigned a fluoridation status; †16,135/16,188 zone-years assigned a fluoridation status; LQ – Lower Quartile; UQ – Upper Quartile.*

Box plots of annual mean fluoride concentrations from 1995 to 2015 in zones without a fluoridation scheme (see figure below) describes a relatively stable fluoride

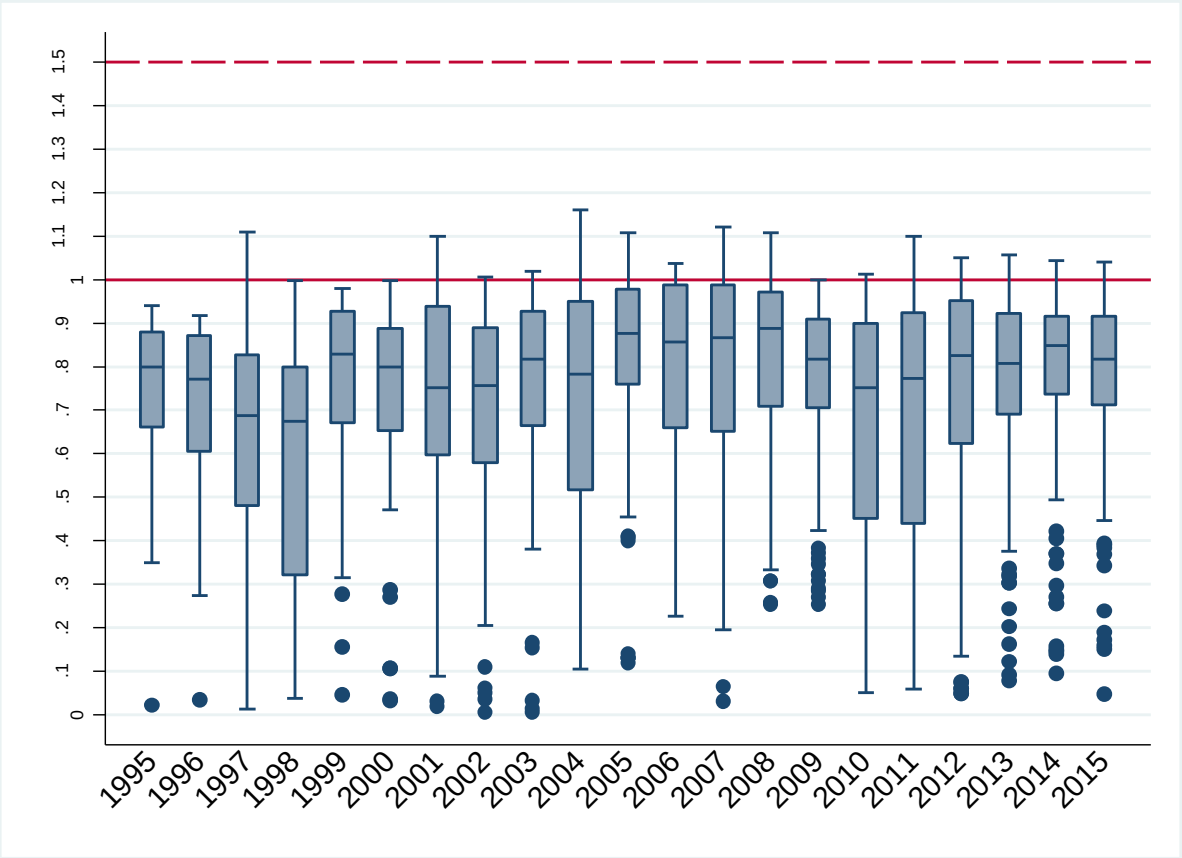
concentration across the monitoring period. Apart from 1995, at least 75% of un-fluoridated zones have fluoride concentrations lower than 0.2mg/l in any year, but there are zones with fluoride concentrations across the range of 0.2mg/l to maximum concentrations of 1.4 to 1.5mg/l. These elevated concentrations likely represent areas with fluoride from geological sources. Fluoride concentrations in areas with a scheme (fig 3) show the median of the annual mean fluoride in these areas can fluctuate from as high as 0.9mg/l to as low as less than 0.7mg/l. 75% of zones were always at concentrations of <1mg/l in each year, and some zones had concentrations of <0.5mg/l (fewer than 25% of zones except for in 1997, 1998, 2010 and 2011), and as low as <0.1mg/l, despite being identified as fluoridated for that year.

Figure 2. Box plot of annual fluoride concentrations in zones without a fluoridation scheme, 1995 to 2015. Boxes represent values from the 25th to 75th quantiles. The solid horizontal line in each box represents the median value. The dots represent 'outlying values'[16]



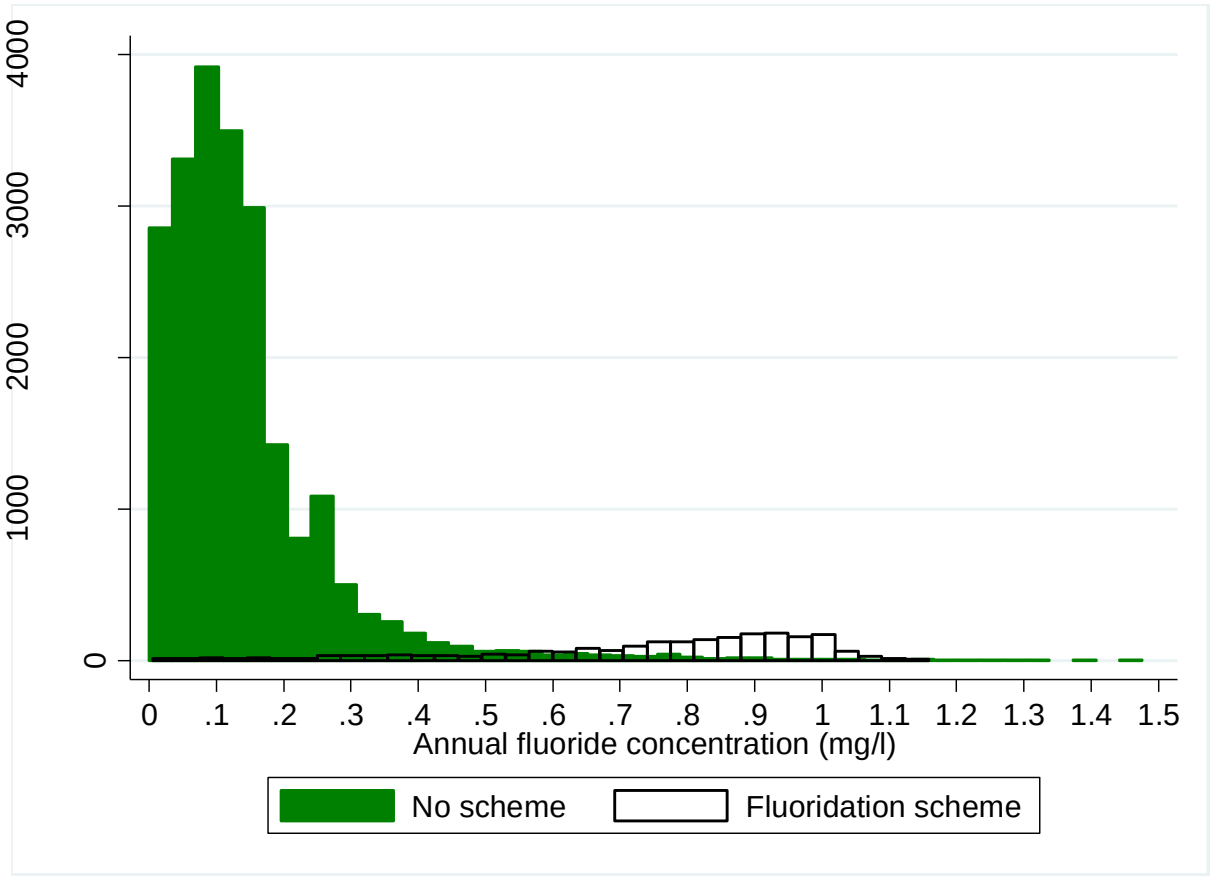
[16] determined by the formula: Q3+1.5*(Q3-Q1) and Q1-1.5*(Q3-Q1), respectively, where Q3 = 75th quantile, and Q1=25th quantile

Figure 3. Box plot of annual fluoride concentrations in zones with a fluoridation scheme, 1995 to 2015. Boxes represent values from the 25th to 75th quantiles. The solid horizontal line in each box represents the median value. The dots represent 'outlying values'[12]. The solid red horizontal line marks the 1mg/l target concentration and the dashed red horizontal line the 1.5mg/l PCV.



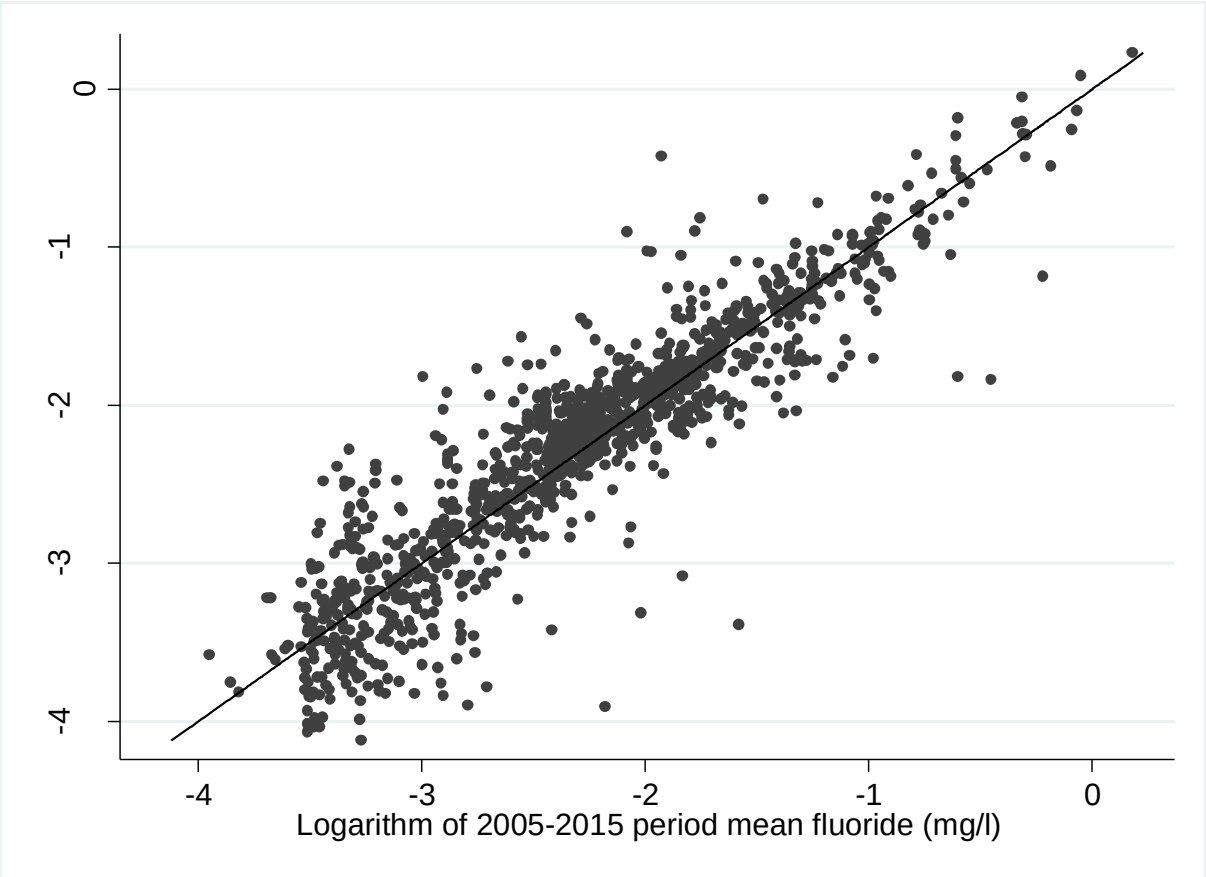
The bimodal distribution of annual fluoride concentrations by presence of a scheme can be appreciated in Figure 4. However, there is overlap in fluoride concentrations in zones with and without a scheme across the range of fluoride concentrations, and the highest concentrations (up to 1.48mg/l) are noted in zones without a scheme ie where fluoride is present from geological sources.

Figure 4. Histogram of annual fluoride concentrations, stratified by presence of fluoridation scheme, England 1995 to 2015



Comparing aggregated period mean fluoride concentrations (see Figure 5 and Figure 6, and Table 7), there was a strong correlation (Spearman Rank coefficient =0.93) between period mean fluoride concentrations for the 2 time periods in un-fluoridated zones. Summary period fluoride statistics were very similar across the time periods.

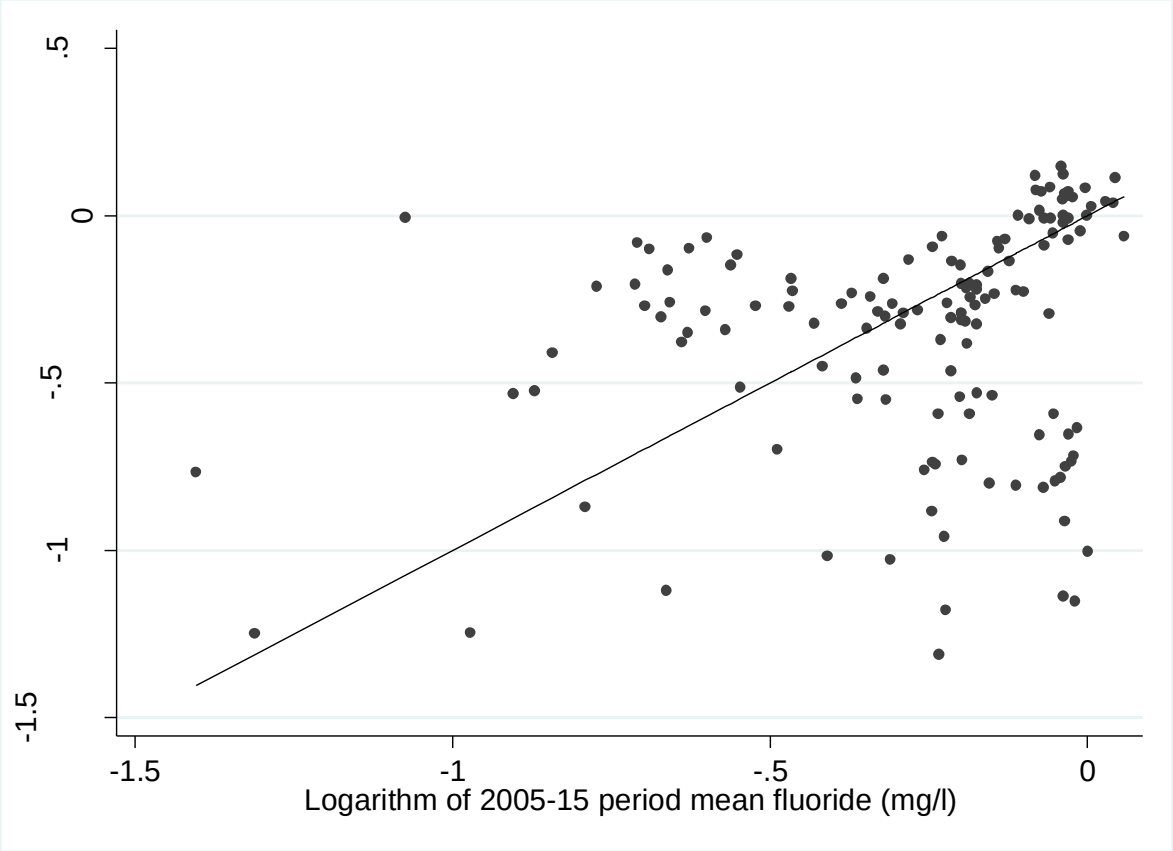
Figure 5. Scatter plot of un-fluoridated* water supply zones comparing 1995 to 2004 and 2005 to 2015 period mean fluoride (mg/l), natural log scale with y=x reference line, England 1995 to 2015†



**Bedford Rural, Bedford Urban South, Bedford Urban Central, Ennerdale North, Ennerdale South, Crummock, Crummock South zones excluded from analysis due to identified partial/total non-operation of fluoridation schemes in 2005 to 2015 period; †For 1424/1477 (1995 to 2004) and 1825/1878 (2005 to 2015) unique zones with fluoridation data.*

The correlation of aggregated period mean fluoride concentrations for fluoridated zones, excluding those where inconsistent fluoridation scheme operation was known, was weak (Spearman Rank coefficient=0.31). The latter period fluoride was slightly higher (mean 0.78mg/l in 2005 to 2015 compared to 0.74mg/l in 1995 to 2004, median 0.84mg/l compared to 0.78mg/l) with a smaller standard deviation (0.16mg/l in 2005 to 2015 compared to 0.22mg/l) and narrower interquartile range (0.23mg/l in 2005 to 2015 compared to 0.33mg/l).

Figure 6. Scatter plot of fluoridated* water supply zones comparing 1995 to 2004 and 2005 to 2015 period mean fluoride (mg/l), natural log scale with y=x reference line, England 1995 to 2015†



**Bedford Rural, Bedford Urban South, Bedford Urban Central, Ennerdale North, Ennerdale South, Crummock, Crummock South zones excluded from analysis due to partial/total non-operation of fluoridation scheme; †For 1424/1477 (1995 to 2004) and 1825/1878 (2005 to 2015) unique zones with fluoridation data.*

Table 7. Water supply zone mean and median period fluoride concentration (mg/l) for 1995 to 2004 and 2005 to 2015, and Spearman rank coefficient, stratified by fluoridation scheme status*, England 1995 to 2015.

Fluoridation Scheme†	Time period	Zones	Mean period fluoride mg/l (SD)	Median period fluoride mg/l (LQ-UQ)	Spearman rank coefficient
Yes	1995-2004	141	0.74 (0.22)	0.78 (0.59-0.92)	-
	2005-2015	161	0.78 (0.16)	0.84 (0.72-0.95)	0.31
No	1995-2004	1283	0.11 (0.12)	0.11 (0.06-0.17)	-
	2005-2015	1664	0.11 (0.12)	0.11 (0.07-0.17)	0.93

**Bedford Rural, Bedford Urban South, Bedford Urban Central, Ennerdale North, Ennerdale South, Crummock, Crummock South zones excluded from analysis due to partial/total non-operation of fluoridation scheme; †For 1424/1477 (1995 to 2004) and 1825/1878 (2005 to 2015) unique zones with fluoridation data; LQ – Lower Quartile; UQ – Upper Quartile.*

Population exposure to fluoridation schemes and fluoride in public water supplies for small and administrative areas

The size of populations assumed exposed to different fluoride concentration categories, and to fluoridation schemes, by statistical/administrative geography in England for the 2005 to 2015 period are summarised below (see Table 8, and Figure 7 and Figure 8). Fluoride concentrations were not available for the Isles of Scilly, and none were recorded during 2005 to 2015 for 2 further LSOAs (both in Richmondshire). The particular fluoride concentration, and percentage of areas fluoridated, varies by the different areal units due to aggregation. Most of the population (70% or more) live in areas where the fluoride concentration in public water supplies is <0.2mg/l, and 9 to 10% where it is greater than 0.7mg/l.

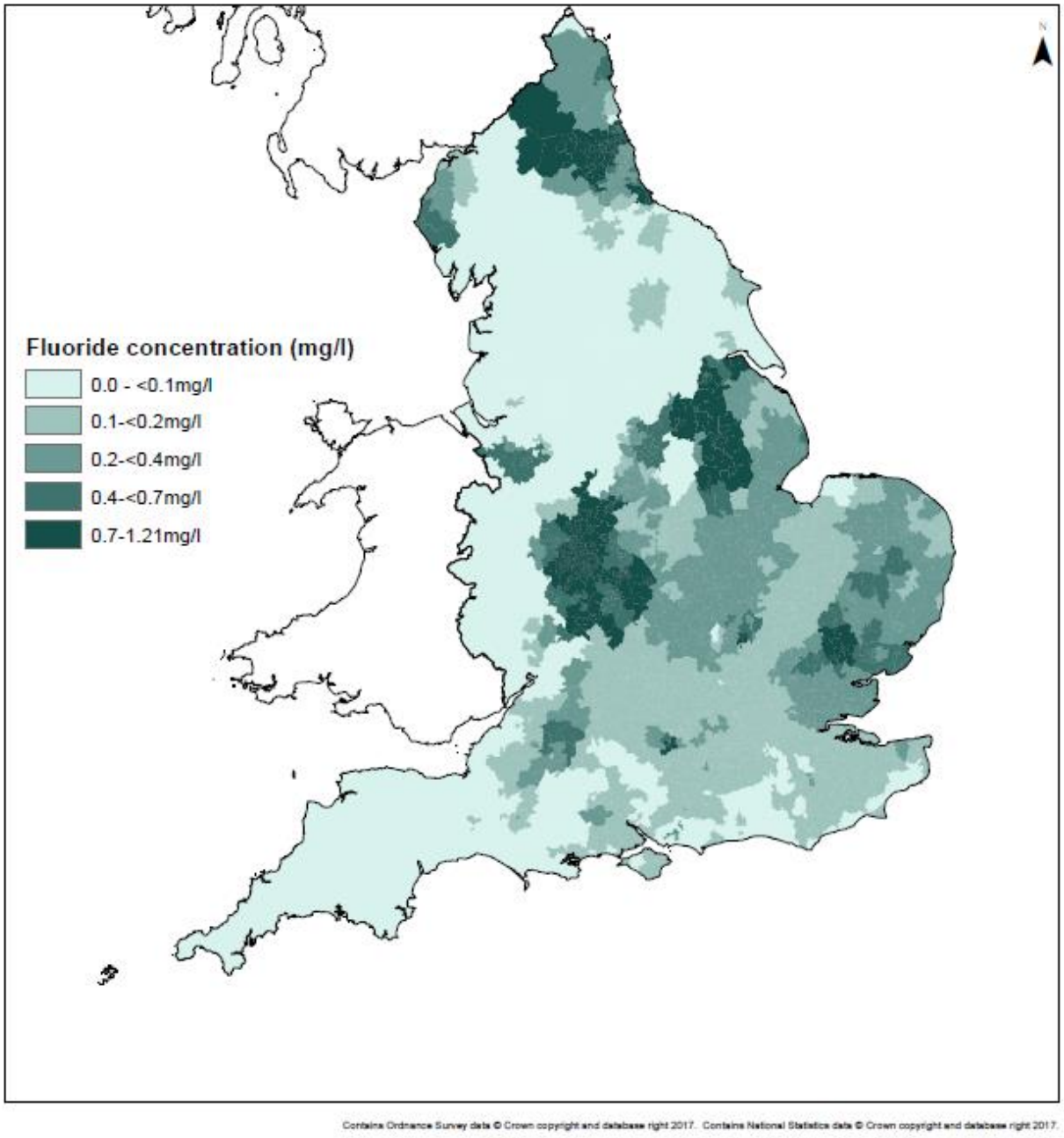
Table 8. Number of areas, and average mid-year resident population, by period mean fluoride concentration and fluoridation scheme status†, England 2005 to 2015.

Area unit (2011 boundaries)	Fluoride concentration (mg/l) category	Number of areas (%)	Population‡ in millions (%)*	Number of areas (%): fluoride scheme†	Population‡ in millions (%)*: fluoride scheme†
LSOA	<0.1	12,588 (38)	19.9 (38)	0 (0)	0 (0)
	0.1-<0.2	11,110 (34)	18.1 (34)	4 (0)	0 (0)
	0.2-<0.4	4,580 (14)	7.3 (14)	82 (2)	0.1 (2)
	0.4-<0.7	1,302 (4)	2.0 (4)	854 (21)	1.3 (20)
	≥0.7	3,261 (10)	5.3 (10)	3,065 (77)	4.9 (77)
	No data	4 (0)	0.0 (0)	0 (0)	0 (0)
	TOTAL	32,844 (100)	52.7 (100)	4,005 (100)	6.4 (100)
MSOA¥	<0.1	2,571 (38)	19.6 (37)	0 (0)	0 (0)
	0.1-<0.2	2,317 (34)	18.3 (35)	0 (0)	0 (0)
	0.2-<0.4	957 (14)	7.5 (14)	20 (2)	0.2 (3)
	0.4-<0.7	280 (4)	2.2 (4)	185 (22)	1.4 (22)
	≥0.7	665 (10)	5.2 (10)	625 (75)	4.9 (77)
	No data	1 (0)	0.0 (0)	0 (0)	0 (0)
	TOTAL	6,791 (100)	52.7 (100)	833 (100)	6.4 (100)
LTLA¥	<0.1	107 (33)	18.4 (35)	0 (0)	0 (0)
	0.1-<0.2	115 (35)	18.3 (35)	0 (0)	0 (0)
	0.2-<0.4	62 (19)	8.5 (16)	2 (6)	0.2 (3)
	0.4-<0.7	19 (6)	2.9 (6)	11 (32)	1.3 (22)
	≥0.7	22 (7)	4.5 (9)	21 (62)	4.4 (75)
	No data	1 (0)	0 (0)	0 (0)	0 (0)
	TOTAL	326 (100)	52.7 (100)	34 (100)	5.9 (100)

*LSOA- Lower layer Super Output Area, MSOA – Middle Layer Super Output Area, LTLA – Lower Tier Local Authority; ‡Average mid-year population for 2005-2015; *May not sum exactly due to rounding; †LSOAs are coded as being supplied by a fluoridation scheme if they have been assigned to a*

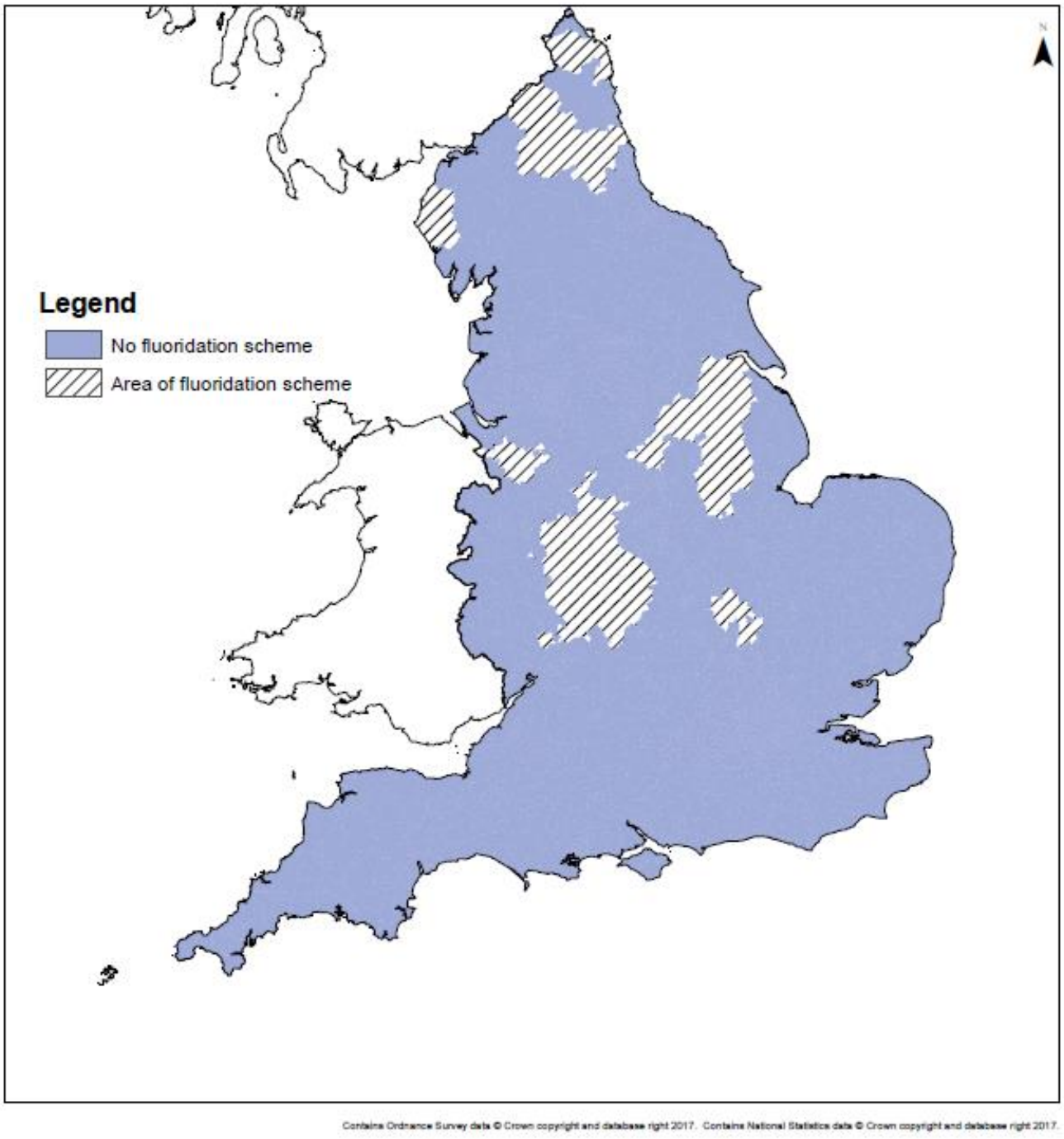
fluoridated water supply zone during 2005 to 2015, using data supplied by the Drinking Water Inspectorate. MSOAs and LTLAs are defined as fluoridated if at least 50% of their constituent LSOAs were coded as fluoridated;[¥] MSOA- and LTLA-level mean *fluoride concentration calculated by taking population weighted mean fluoride concentration of constituent LSOAs, using 2005 to 2015 period population.*

Figure 7. Mean fluoride concentration* (mg/l), England[†] 2005 to 2015. Mapped at Middle Layer Super Output Area level, using 2011 boundaries



**Population weighted by taking population weighted mean fluoride concentration of constituent LSOAs, using 2005 to 2015 period population; [†]Fluoride monitoring data for Scotland and Wales were not within the remit of our report and are therefore not presented*

Figure 8. Areas with fluoridation scheme operating at any time during 2005-2015, England[†]. Mapped at Middle Layer Super Output Area level, using 2011 boundaries



[†]*Fluoridation flagging data for Scotland and Wales were not within the remit of our report and are therefore not presented*

Dental indicators

Prevalence and severity of dental caries in five-year-olds 2014/15

Dental survey data were collected for 111,500 five-year-olds (16.5% of the five-year-old 2014 mid-year population), of which 111,455 (99.96%) were allocated a public water supply fluoride exposure status for 2009 to 2015. Distribution of surveyed five-year-olds by fluoride exposure indicator, area level deprivation score, and estimated percentage of white ethnicity was broadly similar to the national average for five-year-olds (see Table 9).

Table 9. Characteristics of national dental public health survey of five-year-old children 2014 to 2015 and estimated population of five-year-olds in England using mid-year 2014 population estimates

Characteristic	Fluoride concentration (mg/l)	Surveyed: count (%)	England: count (%)
Fluoride concentration (mg/l)	<0.1	33,584 (30.12)	239,162 (35.49)
	0.1-<0.2	42,462 (38.09)	248,537 (36.88)
	0.2-<0.4	16,897 (15.15)	95,071 (14.11)
	0.4-<0.7	5,419 (4.86)	25,175 (3.74)
	≥0.7	13,093 (11.74)	65,842 (9.77)
	No data†	45 (0.04)	169 (0.04)
	TOTAL	111,500 (100.00)	673,956 (100.00)
Deprivation quintile	1 (least deprived)	19,980 (17.92)	120,475 (17.88)
	2	20,487 (18.37)	118,857 (17.64)
	3	21,117 (18.94)	124,584 (18.49)
	4	23,793 (21.34)	141,153 (20.94)
	5 (most deprived)	26,123 (23.43)	168,887 (25.06)
	TOTAL	111,500 (100.00)	673,956 (100.00)
Estimated count & percentage ethnicity*	White ethnicity	87,859 (78.80)	530,858 (78.77)

**Percentage of 0 to 24 year olds of white ethnicity on census 2011 multiplied by five-year-olds surveyed/five-year-old population; †4 LSOAs where 45 children were sampled did not have a fluoride concentration or fluoridation status allocated*

Prevalence of caries experience ($d_3$mft>0)

Prevalence of caries experience ($d_3$mft>0) fell by almost 6% (for a relative reduction of 21%) with increasing fluoride concentration (see Table 10), with the highest prevalence (26.3%) seen in areas with a fluoride concentration of <0.1mg/l, and the lowest in areas with the highest fluoride concentrations >0.7mg/l (20.7%).

Table 10. Prevalence of caries experience ($d_3$mft>0) in five-year-olds sampled for the National Dental Epidemiology Survey, by mean fluoride concentration (mg/l), England 2014 to 2015

Fluoride concentration (mg/l)	**Sample size**	**Number of cases**	**$d_3$mft>0 *prevalence* (%) (95% CI)**
<0.1	33,584	8,837	26.3 (25.8-26.8)
0.1-<0.2	42,462	10,819	25.5 (25.1-25.9)
0.2-<0.4	16,897	3,675	21.8 (21.2-22.4)
0.4-<0.7	5,419	1,316	24.3 (23.2-25.4)
≥0.7	13,093	2,710	20.7 (20.0-21.4)
ALL	111,455	27,357	24.5 (24.3-24.8)

CI – Confidence interval

The crude[17] odds of caries experience ($d_3$mft>0) decreased with increasing fluoride concentration, and this was evident from low concentrations. For example, there was some evidence of a reduction in odds of a five-year-old having experienced caries at fluoride concentrations of 0.1 to 0.19mg/l, compared to children in areas with fluoride concentrations <0.1mg/l (see Table 11). At the highest concentrations, there was very strong evidence of a reduction in the odds of caries experience ($d_3$mft>0), compared to areas with a fluoride concentration of <0.1mg/l, decreasing by 27% (95%CI 23 to 31% p<0.001).

Table 11. Crude odds of caries experience ($d_3$mft>0) in five-year-olds sampled for the National Dental Epidemiology Survey, by mean fluoride concentration (mg/l), England 2014 to 2015.

Fluoride concentration (mg/l)	**Crude odds ratio (95% CI)**	**p value**
<0.1mg/l	Reference	-
0.1-<0.2mg/l	0.96 (0.92-1.00)	0.03
0.2-<0.4mg/l	0.78 (0.74-0.82)	<0.001
0.4-<0.7mg/l	0.90 (0.83-0.97)	0.007
≥0.7mg/l	0.73 (0.69-0.77)	<0.001

[17] Crude here means unadjusted to take account of differing frequencies of other factors that may explain the difference in caries prevalence by fluoride concentration

Robust standard errors

On adjustment for potential confounding, inclusion of ethnicity in the model significantly improved model fit (p<0.001 indicating an independent association between ethnicity and $d_3$mft). In addition, the nature of the association between fluoride concentration and prevalence of caries experience ($d_3$mft>0) varied by area level deprivation, with increasing fluoride concentration resulting in a larger decrease in odds of $d_3$mft in the most deprived children compared to the least deprived children, ie fluoride exposure has a greater impact on the most deprived five-year-olds (p<0.001 for interaction between fluoride concentration and quintile of deprivation). Therefore, stratum-specific odds ratios of the fluoride caries association are presented (see Table 12).

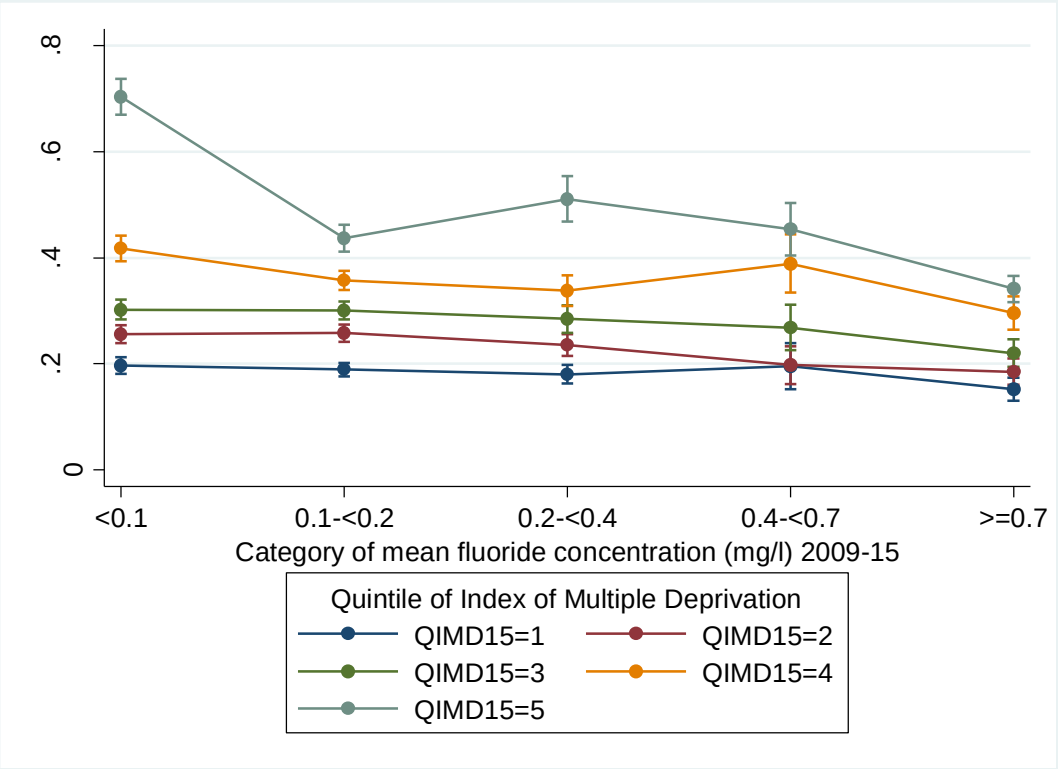
Table 12. Adjusted odds of caries experience ($d_3$mft>0) in five-year-olds sampled for the National Dental Epidemiology Survey, by mean fluoride concentration (mg/l), stratified by quintile of index of multiple deprivation, England 2014 to 2015

Quintile of Index of Multiple Deprivation	Fluoride concentration (mg/l)	Adjusted odds ratio (95% CI)*	p value	Trend test (p value)
1 (least deprived)	<0.1mg/l	Ref	-	0.003
	0.1-<0.2mg/l	0.96 (0.87-1.06)	0.451	
	0.2-<0.4mg/l	0.92 (0.81-1.04)	0.163	
	0.4-<0.7mg/l	0.99 (0.78-1.26)	0.957	
	≥0.7mg/l	0.77 (0.61-0.91)	0.002	
2	<0.1mg/l	Ref	-	<0.001
	0.1-<0.2mg/l	1.01 (0.92-1.10)	0.865	
	0.2-<0.4mg/l	0.92 (0.82-1.03)	0.132	
	0.4-<0.7mg/l	0.77 (0.64-0.94)	0.009	
	≥0.7mg/l	0.72 (0.63-0.84)	<0.001	
3	<0.1mg/l	Ref	-	<0.001
	0.1-<0.2mg/l	0.99 (0.91-1.08)	0.893	
	0.2-<0.4mg/l	0.94 (0.84-1.05)	0.277	
	0.4-<0.7mg/l	0.89 (0.75-1.06)	0.173	
	≥0.7mg/l	0.73 (0.64-0.83)	<0.001	
4	<0.1mg/l	Ref	-	<0.001
	0.1-<0.2mg/l	0.86 (0.79-0.92)	<0.001	
	0.2-<0.4mg/l	0.81 (0.73-0.90)	<0.001	
	0.4-<0.7mg/l	0.93 (0.80-1.09)	0.362	
	≥0.7mg/l	0.71 (0.63-0.80)	<0.001	
5 (most deprived)	<0.1mg/l	Ref	-	<0.001
	0.1-<0.2mg/l	0.62 (0.58-0.67)	<0.001	
	0.2-<0.4mg/l	0.73 (0.66-0.80)	<0.001	
	0.4-<0.7mg/l	0.64 (0.57-0.73)	<0.001	
	≥0.7mg/l	0.48 (0.44-0.53)	<0.001	

**Adjusted for ethnicity. Robust standard errors.*

There was strong statistical evidence that the odds of caries experience ($d_3$mft>0) were lower in children living in areas with the highest compared to the lowest fluoride concentrations at all levels of deprivation. There was also strong statistical evidence for a linear trend at all levels of deprivation (p<0.001 for quintiles 2 to 5, and p=0.003 for quintile 1); alongside almost uniformly decreasing odds ratios this indicated that an increasing exposure to fluoride led to a larger protective effect. The effect of the fluoride deprivation interaction is illustrated in Figure 9. At the highest compared to the lowest fluoride concentration, the odds of caries experience ($d_3$mft>0) were reduced most for five-year-olds living in the most deprived areas (by 52%, 95% CI 47% to 56%), and the least for children in the least deprived areas (23%, 9% to 39%).

Figure 9. Deprivation quintile stratum-specific predicted odds of five-year-old children with caries experience ($d_3$mft>0), by fluoride concentration (n=111,455 children in 24,704 LSOAs), England 2014 to 15.



Adjusted for ethnicity; Robust standard errors; QIMD – Quintile of Index of Multiple Deprivation (1 least deprived, 5 most deprived)

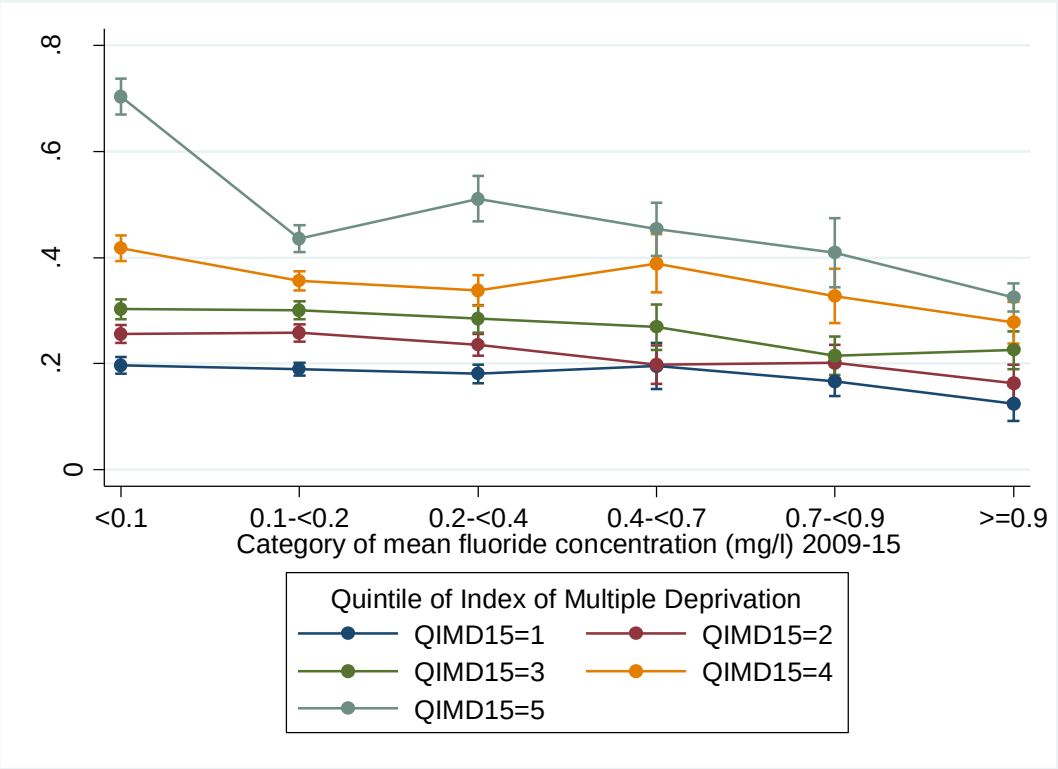
A *post hoc* analysis of splitting the highest fluoride concentration category into 0.7-<0.9mg/l and ≥0.9mg/l revealed a statistically significant interaction between fluoride concentration and deprivation status (p<0.001) as before, and that the odds of caries continued to fall at concentrations up to at least 0.9mg/l (see Table 13, and Figure 10).

Table 13. Adjusted odds of caries experience ($d_3$mft>0) in five-year-olds sampled for the National Dental Epidemiology Survey, by mean fluoride concentration (mg/l) extended to 6 categories, stratified by quintile of index of multiple deprivation, England 2014 to 2015.

Quintile of Index of Multiple Deprivation	Fluoride concentration (mg/l)	Adjusted odds ratio (95% CI)*	p value	Trend test (p value)
1 (least deprived)	<0.1mg/l	Ref	-	0.001
	0.1-<0.2mg/l	0.96 (0.87-1.06)	0.451	
	0.2-<0.4mg/l	0.92 (0.81-1.04)	0.163	
	0.4-<0.7mg/l	0.99 (0.78-1.26)	0.957	
	0.7-<0.9mg/l	0.85 (0.70-1.02)	0.082	
	≥0.9mg/l	0.63 (0.48-0.84)	0.001	
2	<0.1mg/l	Ref	-	<0.001
	0.1-<0.2mg/l	1.01 (0.92-1.10)	0.865	
	0.2-<0.4mg/l	0.92 (0.82-1.03)	0.132	
	0.4-<0.7mg/l	0.77 (0.64-0.94)	0.009	
	0.7-<0.9mg/l	0.79 (0.66-0.94)	0.009	
	≥0.9mg/l	0.64 (0.51-0.80)	<0.001	
3	<0.1mg/l	Ref	-	<0.001
	0.1-<0.2mg/l	0.99 (0.91-1.08)	0.893	
	0.2-<0.4mg/l	0.94 (0.84-1.05)	0.277	
	0.4-<0.7mg/l	0.89 (0.75-1.06)	0.173	
	0.7-<0.9mg/l	0.71 (0.59-0.85)	<0.001	
	≥0.9mg/l	0.75 (0.63-0.88)	0.001	
4	<0.1mg/l	Ref	-	<0.001
	0.1-<0.2mg/l	0.86 (0.79-0.92)	<0.001	
	0.2-<0.4mg/l	0.81 (0.73-0.90)	<0.001	
	0.4-<0.7mg/l	0.93 (0.80-1.08)	0.362	
	0.7-<0.9mg/l	0.78 (0.66-0.93)	0.004	
	≥0.9mg/l	0.66 (0.57-0.77)	<0.001	
5 (most deprived)	<0.1mg/l	Ref	-	<0.001
	0.1-<0.2mg/l	0.62 (0.58-0.67)	<0.001	
	0.2-<0.4mg/l	0.73 (0.66-0.80)	<0.001	
	0.4-<0.7mg/l	0.64 (0.57-0.73)	<0.001	
	0.7-<0.9mg/l	0.58 (0.49-0.69)	<0.001	
	≥0.9mg/l	0.46 (0.42-0.51)	<0.001	

**Adjusted for ethnicity. Robust standard errors.*

Figure 10. Deprivation quintile stratum-specific predicted odds of five-year-old children with caries experience ($d_3$mft>0), by mean fluoride concentration, extended to 6 categories, (n=111,455 children in 24,704 LSOAs), England 2014 to 2015.



Adjusted for ethnicity; Robust standard errors; QIMD – Quintile of Index of Multiple Deprivation (1 least deprived, 5 most deprived)

Prevalence of caries experience ($d_3$mft>0) – monitoring health effects of water supplies within a fluoridation scheme

Considering public water supplies with a concentration of fluoride of at least 0.7mg/l, where fluoride was adjusted as part of a fluoridation scheme, the crude odds of a five-year-old having caries experience ($d_3$mft>0) was 24% lower (OR 0.76, 95% CI 20-28%) than in areas where the fluoride concentration was <0.2mg/l (from any source, though only 5 LSOAs in this low concentration group received fluoridated supplies). When adjusting for deprivation status and ethnicity, the relationship between fluoride source and caries prevalence varied depending on deprivation level, ie there was a statistically significant interaction between fluoride source and deprivation status (p=0.006). Ethnicity, modelled as a categorical variable, significantly improved model fit (p<0.001) and was retained for the final analysis. As an interaction was confirmed, stratum-specific odds ratios are presented in Table 14.

Table 14. Adjusted odds ratios of caries experience ($d_3$mft>0) in five-year-olds sampled for the National Dental Epidemiology Survey 2014 to 2015, by fluoridation status and stratified by index of multiple deprivation, England.

Quintile of Index of Multiple Deprivation	Fluoridation status*	Adjusted OR of children with caries (95% CI)†	p value
1 (least deprived)	No	Ref	
	Yes	0.81 (0.70-0.94)	0.007
2	No	Ref	
	Yes	0.73 (0.63-0.84)	<0.001
3	No	Ref	
	Yes	0.73 (0.64-0.83)	<0.001
4	No	Ref	
	Yes	0.76 (0.68-0.85)	<0.001
5 (most deprived)	No	Ref	
	Yes	0.61 (0.56-0.66)	<0.001

**Yes=fluoride concentration≥0.7mg/l AND in water supply zone with fluoridation scheme during 2009 to 2015, n=12,467 sampled five-year-olds in 2,091 LSOAs. No= fluoride concentration <0.2mg/l, fluoride from any source, n=76,046 five-year-olds in 17,709 LSOAs*

†adjusted for ethnicity. Robust standard errors.

Public health impact measures

The preventive fraction of dental caries ie the percentage of prevalent caries cases in five-year-olds that could be prevented if all five-year-olds with drinking water with <0.2mg/l fluoride instead received at least 0.7mg/l from a fluoridation scheme, ranged from 17%-28%, see Table 15 below. It was lowest in the least deprived quintile (17%, 95% CI 5%-27%), and greatest in the most deprived quintile (28%, 95% CI 24%-32%).

Table 15. Preventive fraction of caries experience ($d_3$mft>0) in five-year-olds in fluoridated areas*, stratified by index of multiple deprivation, England 2014 to 2015.

Quintile of Index of Multiple Deprivation	Preventive fraction %†	Lower – Upper CI
1 (least deprived)	17%	5%-27%
2	23%	13%-32%
3	22%	14%-30%
4	19%	11%-25%
5 (most deprived)	28%	24%-32%

**Yes=fluoride concentration≥0.7mg/l AND in water supply zone with fluoridation scheme during 2009 to 2015, n=12,467 sampled five-year-olds in 2,091 LSOAs. No= fluoride concentration <0.2mg/l, fluoride from any source, n=76,046 five-year-olds in 17,709 LSOAs*

†adjusted for ethnicity. Robust standard errors.

Caries severity (mean $d_3$mft)

The mean severity was 0.92 $d_3$mft (95% CI 0.90, 0.93) in areas with a fluoride concentration of <0.1mg/l and decreased by 36% to 0.59 $d_3$mft (95% CI 0.57, 0.60) in areas with the highest fluoride concentrations ≥0.7mg/l. A general trend of decreasing severity with increasing fluoride concentration can be observed, and this was evident from low concentrations.

Table 16. Mean number of $d_3$mft in five-year-olds sampled for the National Dental Epidemiology Survey, by 2009 to 2015 period mean fluoride concentration (mg/l), England (n=111,455 five-year-olds in 24,704 LSOAs).

Fluoride concentration (mg/l)	Sample size	Mean $d_3$mft (95% CI)*
<0.1	33,584	0.92 (0.90-0.93)
0.1-<0.2	42,462	0.89 (0.88-0.90)
0.2-<0.4	16,897	0.71 (0.69-0.72)
0.4-<0.7	5,419	0.81 (0.79-0.84)
≥0.7	13,093	0.59 (0.57-0.60)
ALL	111,455	0.83 (0.82-0.84)

**Weighted by sample size; CI – Confidence interval*

As detailed in the methods section, in order to allow fitting of a regression model to adjust for the effects of ethnicity and deprivation status, surveyed LSOAs were categorised by the mean number of $d_3$mft per child, as follows:

Table 17. Median number of teeth with caries experience, and range, in five-year-olds sampled for the National Dental Epidemiology Survey, England (n=111,455 five-year-olds in 24,704 LSOAs.

Category of $d_3$mft	Median (LQ-UQ) number of teeth with caries experience ($d_3$mft)	Range
None	0	0
Low	0.33 (0.25-0.50)	0.05-0.63
Medium	1.00 (0.80-1.17)	0.63-1.5
High	2.40 (2.00-3.50)	1.5-16

LQ – Lower Quartile; UQ – Upper Quartile

The crude odds of five-year-olds being in the 'low', 'medium', or 'high' caries severity categories compared to 'none' was significantly higher at 0.1-<0.2mg/l, and 0.4-<0.7mg/l than the reference fluoride concentration (0.1mg/l), with no evidence of a difference at the other fluoride concentrations (see Table 18). When interpreting this table, the odds ratio denotes the relative odds at each fluoride concentration, compared to the reference fluoride concentration (<0.1mg/l), of five-year-olds being in a higher severity $d_3$mft category (or of being in the highest compared to all other categories for the analysis results in the bottom panel of the table below). The crude odds of five-year-olds being in the 'medium' or 'high' categories compared to the 2 lowest categories was lower at 0.2-<0.4mg/l and ≥0.7mg/l compared to the reference fluoride concentration (<0.1mg/l), but with no evidence of a difference at the other concentrations. However, the odds of five-year-olds being in the 'high' caries severity category compared to all lower categories decreased at all fluoride concentrations above the reference (<0.1mg/l), with the largest decrease at the highest fluoride concentration.

Table 18. Crude odds ratios of higher severity $d_3$mft category in five-year-olds sampled for the National Dental Epidemiology Survey, by 2009 to 2015 period mean fluoride concentration (mg/l), England.

D_3mft severity category	**Fluoride concentration (mg/l)**	**Crude OR (95% CI) of higher $d_3$mft category**	**p value**
None vs. Low or medium or high	<0.1	Ref	-
	0.1-<0.2	1.07 (1.01-1.13)	0.033
	0.2-<0.4	0.95 (0.88-1.03)	0.186
	0.4-<0.7	1.25 (1.09-1.42)	0.001
	≥0.7	0.98 (0.89-1.08)	0.699
None or low vs. medium or high	<0.1	Ref	-
	0.1-<0.2	1.03 (0.97-1.09)	0.411
	0.2-<0.4	0.82 (0.76-0.89)	0.000
	0.4-<0.7	0.96 (0.84-1.10)	0.581
	≥0.7	0.66 (0.60-0.73)	0.000
None or low or medium vs. high	<0.1	Ref	-
	0.1-<0.2	0.92 (0.86-0.99)	0.031
	0.2-<0.4	0.70 (0.63-0.78)	0.000
	0.4-<0.7	0.81 (0.68-0.95)	0.012
	≥0.7	0.45 (0.39-0.52)	0.000

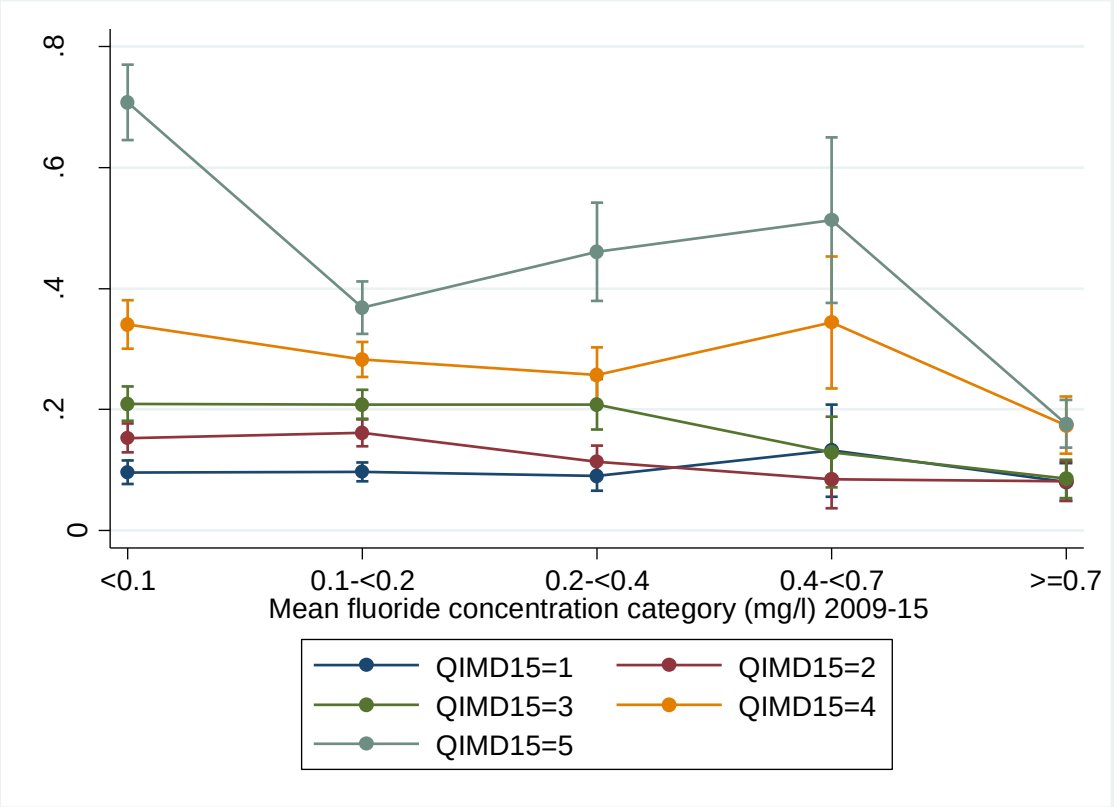
Robust standard errors.

On adjustment for potential confounding, inclusion of ethnicity in the model significantly improved model fit (p<0.001). In addition, the nature of the association between fluoride concentration and caries severity varied by area level deprivation, with increasing fluoride concentration resulting in a larger decrease in odds of being in a higher (more severe) $d_3$mft category in the most deprived children compared to the least deprived children (p<0.001 for interaction between fluoride concentration and quintile of deprivation). Therefore, stratum-specific odds of being in a higher $d_3$mft category with each fluoride concentration, and tests of trend, were calculated and are presented in the appendix (see appendix A5).

The figure below illustrates the association between fluoride concentration and odds of a surveyed five-year-old being in the highest $d_3$mft category (analogous to the bottom panel of Table 18, above), stratified by index of multiple deprivation. There was strong statistical evidence for linear trend within each quintile of deprivation stratum (p<0.001 for quintiles 5-2, and p=0.002 for quintile 1), indicating increased fluoride concentrations were associated with lower odds of being in the 'high' $d_3$mft severity category compared to all other severity categories. However, visualisation of the data in Figure 11, shows there was not a smooth trend, particularly at concentrations of 0.4-<0.7mg/l. Similar falls in odds of being in the 'medium' or 'high' category compared to 'none' or 'low' severity categories (analogous to panel 2 of Table 18 above) were noted,

with strong statistical evidence of trend (p<0.001 for quintiles 5-2, p=0.036 for quintile 1). There was evidence that odds of being in the 'none' compared to all other categories of $d_3$mft did not differ by fluoride concentration (p for trend >0.05 for all quintiles of deprivation).

Figure 11. Deprivation quintile stratum-specific predicted odds* of five-year-old children being in the highest versus any other $d_3$mft category, by fluoride concentration (n=111,455 children in 24,704 LSOAs), England 2014 to 2015.



**Adjusted for ethnicity. Robust standard errors. QIMD15 – Quintile of Index of Multiple Deprivation 2015 (1 is least deprived, 5 most deprived)*

Admission to hospital for extraction of carious teeth in children and young people aged 0 to 19 years

Over 70% of MSOAs lay in WSZs with low (<0.2mg/l) fluoride concentrations, and 10% in WSZs with high (at least 0.7mg/l) fluoride concentrations during the 2007 to 2015 period of interest (see Table 19). The 0 to 19 year old population during 2007 to 2015 (summarised as 'person years') showed a similar distribution.

Table 19. Classification of MSOAs by 2007 to 2015 period fluoride concentration* (mg/l), and person years of observation of 0 to 19 year olds, England.

Fluoride concentration (mg/l)	MSOAs	% of total	person years (millions)†	% of total
<0.1	2,546	37	40.99	36
0.1-<0.2	2,375	35	41.13	36
0.2-<0.4	976	14	16.58	14
0.4-<0.7	277	4	4.24	4
≥0.7	666	10	11.59	10
Missing	1	0.01	0.04	0
Total	6791	100	114.53	100

**Fluoride concentration derived from the mean fluoride concentration from constituent LSOAs, weighted using 0 to 19 year old population; †May not sum exactly due to rounding.*

A total of 832/6790 (12%) of MSOAs with data were served by a fluoridation scheme at any point during the 2007 to 2015 time period.

The crude incidence of cases of children/young people (age 0 to 19) requiring dental extractions in hospital as a result of caries decreased by 267 cases per 100,000 person years at risk (pyar) as fluoride concentration increased from lowest to highest concentration categories. The number of cases decreased from 423 cases per 100,000 pyar (95% CI 420 to 425) in areas with a fluoride concentration of <0.1mg/l to 156 cases per 100,000 pyar (95% CI 154 to 158) in areas with the highest fluoride concentrations, ≥0.7mg/l.

Table 20. Crude incidence of cases of dental extractions due to caries in 0 to 19 year olds in England, by mean fluoride concentration category, England 2007 to 2015.

Fluoride concentration (mg/l)	Cases of extractions due to caries	Person years (millions)	Crude incidence (per 100,000 pyar)	95% CI
<0.1	173,251	40.99	422.7	420.1 – 424.7
0.1-<0.2	123,237	41.13	299.7	298.0 – 301.3
0.2-<0.4	31,215	16.58	188.3	186.2 – 190.3
0.4-<0.7	9,736	4.24	229.6	225.0 – 234.2
≥0.7	18,065	11.59	155.9	153.6 – 158.2
Missing	*	0.04	*	*
Total	355,505	114.53	310.4	309.4 - 311.4

*Pyar – person years at risk; CI – Confidence Interval; *Suppressed count<5 to prevent deductive disclosure*

The crude incidence rate ratio of cases of caries related dental extraction in children and young people aged 0-19 years was 62% lower (95% CI 37% to 77%) in areas with fluoride of ≥0.7mg/l compared to the reference areas (<0.1mg/l).

There was no difference in the strength of association between the mean fluoride concentration and the risk of dental caries related hospital extractions across the different quintiles of deprivation (no interaction present between fluoride concentration and deprivation status (p=0.40)). All covariates significantly improved model fit (p<0.05) and were retained in the final model. The adjusted incidence of admissions for caries-related dental extraction was up to 59% lower (95% CI 33% to 76%) in areas with fluoride of ≥0.7mg/l, compared to the reference areas, and there was strong statistical evidence of a linear trend (p<0.001); alongside generally decreasing risk ratios this provides evidence for decreasing incidence with increasing concentration of fluoride.

Table 21. Crude and adjusted incidence rate ratio of cases of hospital dental extractions due to caries in 0 to 19 year olds, by period mean fluoride concentration (mg/l), England 2007 to 2015.

Fluoride concentration (mg/l)	Crude IRR (95% CI)†	Adjusted IRR* (95% CI) †	p value	P for trend
<0.1mg/l	Reference	Reference	-	<0.001
0.1-<0.2mg/l	0.70 (0.56-0.89)	0.74 (0.62-0.88)	0.001	
0.2-<0.4mg/l	0.46 (0.35-0.61)	0.55 (0.44-0.68)	0.000	
0.4-<0.7mg/l	0.56 (0.39-0.79)	0.61 (0.46-0.80)	0.000	
≥0.7mg/l	0.38 (0.23-0.63)	0.41 (0.24-0.67)	0.000	

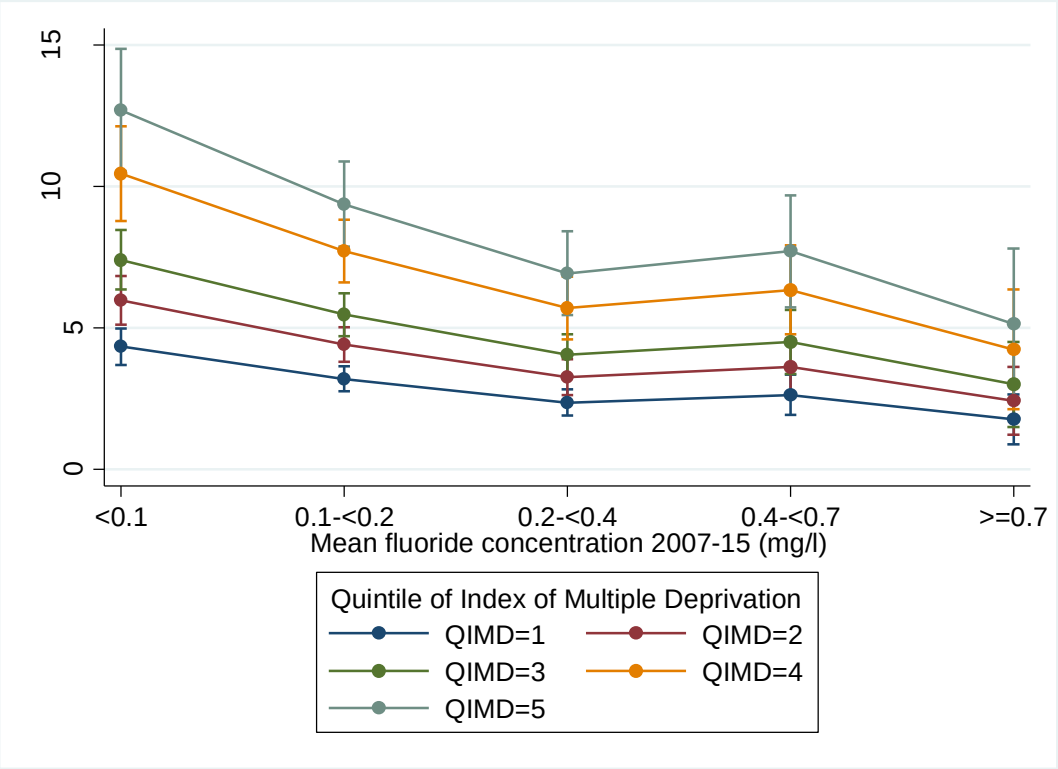
IRR – incidence rate ratio

† Cluster robust standard errors derived by clustering on 325 local authority districts

**Adjusted for age group, gender, ethnicity, index of multiple deprivation*

Even though the relative effect of fluoride does not differ across quintiles of deprivation, the absolute change in number of children with caries does differ because more children and young people aged 0-19 years require caries-related extractions in more deprived areas. Figure 12 illustrates the reduction in mean number of cases of extractions in children and young people aged 0-19 years with dental caries with increasing fluoride concentration per MSOA unit of observation over the 2007 to 2015 time period, after adjustment for age, gender, ethnicity and the size of 0 to 19 year old resident population.

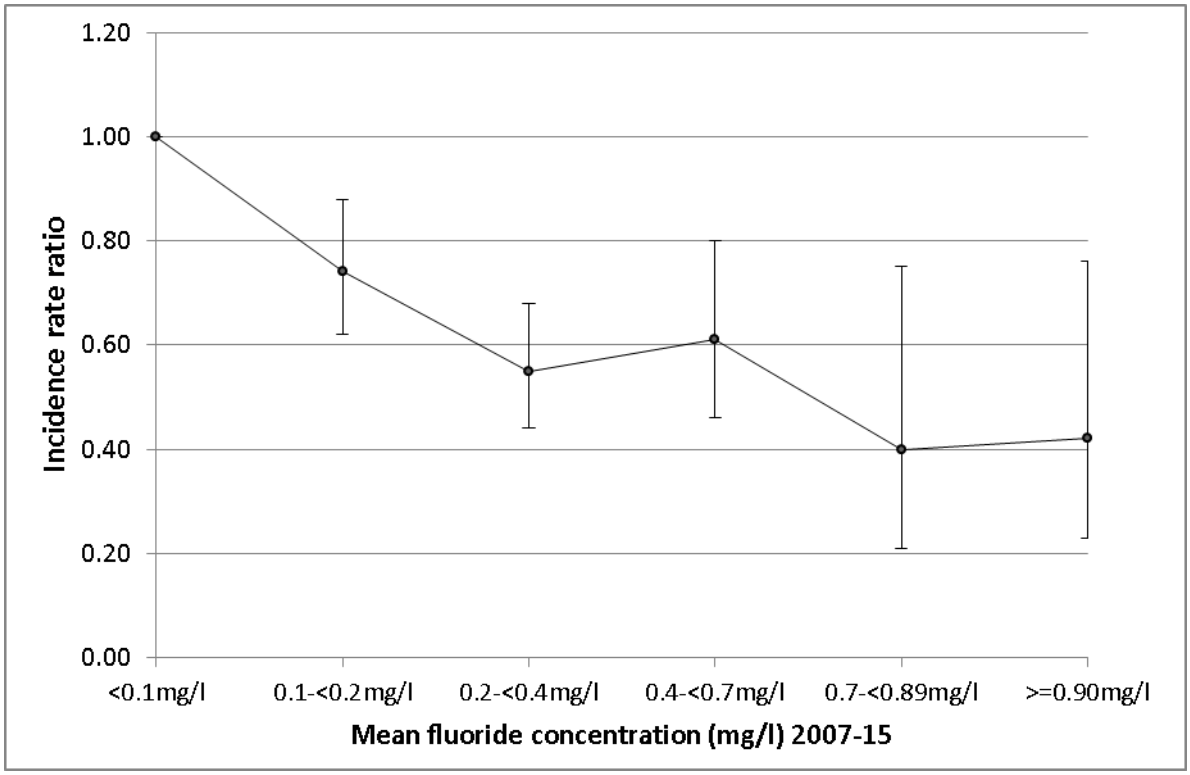
Figure 12. Deprivation quintile stratum-specific predicted mean count of cases of 0 to 19-year-olds requiring caries-related dental extraction per MSOA, by period mean fluoride concentration (mg/l), England 2007 to 2015.



Adjusted for age group, gender, ethnicity, and size of 0-19 year old population; Cluster robust standard errors derived using clustering term on 325 Local Authority Districts; QIMD – Quintile of Index of Multiple Deprivation (1 least deprived, 5 most deprived)

A *post hoc* analysis of splitting the highest fluoride concentration category into 0.7-<0.9mg/l and ≥0.9mg/l revealed that the risk of extractions in hospital due to dental caries did not continue to fall at concentrations up to at least 0.9mg/l (see Figure 13). There was very strong statistical evidence of a linear trend ($p<0.001$).

Figure 13. Incidence rate ratio of cases of 0 to 19 year olds requiring caries-related dental extraction, by period mean fluoride concentration (mg/l), 6 concentration categories, England 2007 to 2015.



Adjusted for ethnicity, age group, gender, index of multiple deprivation. Cluster robust standard errors derived using clustering term on 325 Local Authority Districts

Hospital-based extractions for dental caries: monitoring health effects of water supplies within a fluoridation scheme

Considering public water supplies with a concentration of fluoride of at least 0.7mg/l, where fluoride was adjusted as part of a fluoridation scheme, the crude risk of a 0 to 19-year-old undergoing a dental caries related tooth extraction was 56% lower (IRR 0.44, 95% CI 26% to 74%) than in areas where the fluoride concentration was <0.2mg/l (for this analysis, there were no fluoridated MSOAs with a concentration of <0.2mg/l). When adjusting for deprivation status, gender, age group, and ethnicity, the relationship between fluoride source and caries extractions varied depending on deprivation level, ie there was some evidence of an interaction between fluoride source and deprivation status (p=0.07). Age group and gender significantly improved model fit (p<0.001) and were retained for the final analysis, but ethnicity did not (p=0.29), so was dropped from the model. As an interaction was confirmed, stratum-specific incidence rate ratios are presented in Table 22.

Table 22. Adjusted incidence rate ratios of cases of caries related dental extractions in hospital in 0-19 year olds, by fluoridation status and stratified by index of multiple deprivation, England 2007 to 2015.

Quintile of Index of Multiple Deprivation	Fluoridation status*	Adjusted IRR (95% CI)†	p
1 (least deprived)	No	Ref	
	Yes	0.52 (0.32-0.83)	0.007
2	No	Ref	
	Yes	0.53 (0.35-0.81)	0.003
3	No	Ref	
	Yes	0.55 (0.33-0.90)	0.016
4	No	Ref	
	Yes	0.46 (0.26-0.80)	0.005
5 (most deprived)	No	Ref	
	Yes	0.32 (0.17-0.60)	0.000

**Yes=fluoride concentration≥0.7mg/l AND in water supply zone with fluoridation scheme during 2007 to 2015, in 628 MSOAs with 10.96 million person years of observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 4,893 MSOAs with 82.12 million person years of observation*

†adjusted for age group and gender. Cluster robust standard errors derived using clustering term on 289 local authority districts

Public health impact measures

The preventive fraction of dental caries related admissions for dental extraction ie the percentage of extractions that could be prevented if all children and young people with drinking water with <0.2mg/l fluoride instead received at least 0.7mg/l from a fluoridation scheme, ranged from 45 to 68%, see Table 23. It was similar in the 3 least deprived quintiles (lowest was 45% in quintile 3, 95% CI 10-67%), and greatest in the most deprived quintile (68%, 95% CI 40-83%).

Table 23. Preventive fraction of cases of caries related dental extractions in 0 to 19 year olds in fluoridated areas*, stratified by index of multiple deprivation, England 2007 to 2015.

Quintile of Index of Multiple Deprivation	Preventive fraction %†	Lower – Upper CI
1 (least deprived)	48%	17%-68%
2	47%	19%-65%
3	45%	10%-67%
4	54%	20%-74%
5 (most deprived)	68%	40%-83%

**Yes=fluoride concentration≥0.7mg/l AND in water supply zone with fluoridation scheme during 2007 to 2015, in 628 MSOAs with 10.96 million person years of observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 4,893 MSOAs with 82.12 million person years of observation*

†adjusted for age group and gender. Cluster robust standard errors derived using clustering term on 289 local authority districts

Dental fluorosis

A total of 1904 children, aged 11 to 14 years, resident in the 4 cities studied, participated in the survey. It was possible to score 99.68% (1899) images against the TF index, with 939 images from those resident in non-fluoridated Manchester (466) and Liverpool (473) and 960 images from those resident in fluoridated Newcastle upon Tyne (510) and Birmingham (450). Each of the 4 maxillary incisor teeth received a score using the TF index, the highest score received for 2 or more teeth was recorded.

Table 24. TF scores for subjects by city, for children age 11 to 14 years surveyed in Manchester, Liverpool, Newcastle and Birmingham 2015.

TF Index	Manchester (NF*)		Liverpool (NF)		Newcastle (F**)		Birmingham (F)	
	n	%	n	%	n	%	n	%
TF0	286	61	304	64	195	38	175	39
TF1	154	33	143	30	212	42	176	39
TF2	15	3	16	3	54	11	49	11
TF3	11	2	10	2	43	8	37	8
TF4	0	0	0	0	6	1	9	2
TF5	0	0	0	0	0	0	2	0.4
TF6	0	0	0	0	0	0	1	0.2
TF7	0	0	0	0	0	0	0	0
TF8	0	0	0	0	0	0	1	0.2
Total	466		473		510		450	

*NF, non-fluoridated; **F, fluoridated

The prevalence of any positive score for fluorosis was greater in the fluoridated cities (Newcastle and Birmingham 61%) compared to the non-fluoridated cities (Manchester and Liverpool, 37%). Fluorosis recorded at a level of TF3 (considered to be of mild aesthetic concern) or above, was 10.3% in the 2 fluoridated cities and 2.2% in the non-fluoridated cities. However, there was no difference between the fluoridated and non-fluoridated cities when children and young people themselves reported concerns about the appearance of their teeth which could have resulted from multiple causes (eg fluoride, poor alignment, decay or trauma). Using the Mann-Whitney U tests no statistically significant differences were found in TF between the 2 fluoridated cities ($p=0.351$) or the 2 non-fluoridated cities ($p=0.85$). There was strong statistical evidence of a difference in overall fluorosis prevalence between the fluoridated and the non-fluoridated cities when considering fluorosis to be TF>0 ($p<0.0001$) and for TF>2 ($p<0.0001$).

Non-dental, non-cancer health indicators – hip fracture, kidney stones and Down's syndrome

Hip fracture

MSOA level fluoride concentrations from 2005 to 2015 were used for this analysis. Hip fracture admissions relate to the period 2007 to 2015. Over 70% of MSOAs lay in WSZs with low (<0.2mg/l) fluoride concentrations, and 10% in WSZs with high (at least 0.7mg/l) fluoride concentrations during the 2005 to 2015 exposure period of interest (see Table 25). The population during 2007 to 2015 (summarised as 'person years') showed a similar distribution.

Table 25. Classification of MSOAs by 2005 to 2015 period fluoride concentration* (mg/l), and person years of observation, England.

Fluoride concentration (mg/l)	MSOAs	% of total	person years (millions)†	% of total
<0.1	2,544	38	177.30	37
0.1-<0.2	2,339	34	166.44	35
0.2-<0.4	963	14	67.53	14
0.4-<0.7	278	4	19.58	4
≥0.7	666	10	46.74	10
Missing	1	0.01	0.02	0
Total	6791	100	477.61	100

**Fluoride concentration derived from the mean fluoride concentration from constituent LSOAs, weighted using population; †May not sum exactly due to rounding.*

The crude rate of emergency consultant in-patient episodes with hip fracture between 2007 to 2015 was 118 per 100,000 person-years at risk (pyar) in areas with the highest fluoride concentration, and 121 in areas with the lowest concentration (see Table 26), compared to the overall rate was 112 per 100,000 pyar. Rates were higher in females than males (159 vs 64/100,000 pyar) and in adults aged over 80 (1,580 per 100,000 pyar in adults aged 80+ years vs. 4.5/100,000 pyar in 0 to 49-year-olds).

Table 26. Crude incidence of hip fractures in England, by mean fluoride concentration category, England 2007 to 2015.

Fluoride concentration (mg/l)	Admissions due to hip fracture	Person years (millions)	Crude incidence (per 100,000 pyar)	95% CI
<0.1	214,421	177.30	121.0	120.4 – 121.5
0.1-<0.2	162,428	166.44	97.6	97.1 – 98.1
0.2-<0.4	78,992	67.53	117.0	116.2 – 117.8
0.4-<0.7	24,128	19.58	123.2	121.7 – 124.8
≥0.7	55,171	46.74	118.0	117.1 – 119.0
Missing	20	0.02	97.8	59.7 – 151.1
Total	535,160	477.61	112.1	111.8 – 112.4

Pyar – person years at risk; CI – Confidence Interval

The crude rate of hip fracture episodes was 19% lower (95% CI 13%, 25%; p<0.001) in areas with fluoride concentration 0.1-<0.2mg/l compared to <0.1mg/l (see Table 27). There was no difference in crude rates at other fluoride concentrations, compared to <0.1mg/l.

Table 27. Crude rate ratio of hip fracture admission, by period mean fluoride concentration (mg/l), England 2007 to 2015.

Fluoride concentration (mg/l)	Crude IRR (95% CI)[†]	p value
<0.1mg/l	Reference	
0.1-<0.2mg/l	0.81 (0.75-0.87)	<0.001
0.2-<0.4mg/l	0.97 (0.91-1.03)	0.279
0.4-<0.7mg/l	1.02 (0.93-1.12)	0.699
≥0.7mg/l	0.98 (0.89-1.07)	0.597

IRR – incidence rate ratio

[†] Cluster robust standard errors derived by clustering on 325 local authority districts

When testing for the *a priori* defined potential interaction between age group and fluoride concentration in females, there was strong evidence that the association varied significantly by age (there was a statistically significant interaction between age group and fluoride concentration, p<0.001). As a *post hoc* analysis, the same interaction was tested in males, and was also strongly significant (p<0.001). Adjusted regression analyses are therefore presented stratified by age group and gender (see Table 28). Model fit of the gender-specific models was significantly improved by the addition of ethnicity and deprivation variables (p<0.001 for both variables in both models), and these were retained in the final models.

The association between fluoride concentration and hip-fracture varied by age group. In younger adults aged 0 to 49, fluoride concentrations greater than the minimum exposure category were associated with lower risk of hip fracture admission, with strong statistical evidence of a linear trend (p=0.017 in females and p<0.001 in males). Despite this there was not a smooth change in risk with increasing fluoride concentration, but an immeadiate large reduction in risk (between <0.1mg/l and 0.1-<0.2mg/l) followed by minimal further change as fluoride concentration increased.

There was no clear relationship between fluoride and fracture admission risk in adults 50-64 years of age of either gender. In older adults (65 to 79), fluoride concentrations were associated with increased hip fracture admission risk at concentrations of ≥0.7mg/l, with strong statistical evidence of a linear trend only for females in this age group (p=0.007 for females, p=0.259 for males). In males and females aged at least 80 years, risk of admission was increased at all fluoride concentrations greater than 0.1mg/l. Trend tests again indicated strong statistical evidence for a linear trend (p<0.001 for females and p<0.002 for males). Despite this there was not a smooth change in risk with increasing fluoride concentration, but an immeadiate increase in risk (between <0.1mg/l and 0.1-<0.2mg/l) followed by minimal further change as fluoride concentration increased.

Sensitivity analysis after exclusion of data for MSOAs with significant disruption of fluoridation during 2005 to 2015 revealed no difference of significance in the results (see Table A6 in appendix).

Table 28. Sex-stratified age-specific adjusted rate ratio of hip fracture admission, by period mean fluoride concentration (mg/l), England 2007 to 2015.

Age band (years)	Fluoride concentration (mg/l)	Pyar (millions): female	Admissions: female	Adjusted IRR Females (95% CI)*†	p value	P for trend	Pyar (millions): male	Admissions: male	Adjusted IRR Males (95% CI) *†	P value	P for trend
0-49	<0.1mg/l	55.72	1814	Reference	-	0.017	56.49	3939	Reference	-	<0.001
	0.1-<0.2mg/l	56.45	1388	0.82 (0.76-0.89)	<0.001		57.34	3213	0.86 (0.81-0.92)	<0.001	
	0.2-<0.4mg/l	21.49	591	0.87 (0.79-0.96)	0.004		21.73	1269	0.87 (0.81-0.94)	<0.001	
	0.4-<0.7mg/l	6.03	186	0.95 (0.81-1.12)	0.540		6.10	363	0.87 (0.79-0.96)	0.008	
	≥0.7mg/l	15.23	421	0.87 (0.78-0.98)	0.019		15.43	956	0.89 (0.83-0.95)	0.001	
50-64	<0.1mg/l	16.83	8207	Reference	-	0.808	16.41	5855	Reference	-	0.444
	0.1-<0.2mg/l	14.18	5955	0.92 (0.88-0.97)	0.001		13.76	4417	0.95 (0.85-1.00)	0.064	
	0.2-<0.4mg/l	6.38	2903	0.95 (0.90-1.00)	0.072		6.23	1938	0.89 (0.84-0.96)	0.001	
	0.4-<0.7mg/l	1.92	885	0.95 (0.88-1.03)	0.211		1.89	606	0.91 (0.83-1.01)	0.073	
	≥0.7mg/l	4.17	2079	1.04 (0.96-1.12)	0.360		4.10	1488	1.00 (0.89-1.13)	0.977	
65-79	<0.1mg/l	12.14	38,572	Reference	-	0.007	10.86	17,193	Reference	-	0.259
	0.1-<0.2mg/l	9.41	27,738	0.97 (0.95-1.00)	0.036		8.38	12,866	1.01 (0.97-1.04)	0.778	
	0.2-<0.4mg/l	4.44	14,082	1.01 (0.98-1.04)	0.456		4.09	6062	0.98 (0.94-1.02)	0.264	
	0.4-<0.7mg/l	1.38	4404	1.01 (0.97-1.05)	0.785		1.27	1870	0.93 (0.89-0.98)	0.005	
	≥0.7mg/l	2.99	10,070	1.06 (1.02-1.10)	0.003		2.67	4681	1.08 (1.02-1.14)	0.009	
≥80	<0.1mg/l	5.57	106,446	Reference	-	<0.001	3.25	32,395	Reference	-	0.022
	0.1-<0.2mg/l	4.31	80,835	1.03 (1.00-1.05)	0.006		2.61	26,016	1.04 (1.00-1.07)	0.028	
	0.2-<0.4mg/l	2.03	39,634	1.03 (1.01-1.05)	0.001		1.22	12,513	1.05 (1.02-1.08)	0.002	
	0.4-<0.7mg/l	0.61	11,980	1.03 (1.00-1.06)	0.033		0.37	3834	1.05 (1.01-1.09)	0.008	
	≥0.7mg/l	1.34	26,935	1.05 (1.02-1.09)	0.001		0.79	8541	1.05 (0.99-1.12)	0.078	
Total	-	242.65	385,125	-	-	-	234.94	150,015	-	-	-

*IRR – incidence rate ratio;*Adjusted for deprivation status and ethnicity; † Cluster robust standard errors derived by clustering on 325 local authority districts.*

Results of a *post hoc* analysis of splitting the highest fluoride concentration category into 0.7-<0.9mg/l and ≥0.9mg/l, and taking the fluoride concentration exposure category arithmetic mean fluoride as a linear term to assess further evidence for a potential trend in hip fracture admission risk are presented in Table 29 and Table 30.

In older females (65 to 79), hip fracture admission risk was similar at the 2 highest fluoride concentrations, with wide overlap of confidence intervals. Test of trend on mean fluoride provided strong statistical evidence for a linear trend (p=0.001). In men, the highest fluoride concentration was only very weakly associated with increased fracture admission risk p=0.255), and tests of trend were not supportive of a linear relationship (p=0.107 for trend on mean).

In males and females aged 80+ risk of admission was increased at all fluoride concentrations greater than 0.1mg/l as in the main analysis, except in men at concentrations of 0.7-0.9mg/l where there was no clear association with risk of admission (IRR 1.02, 95% CI 0.94-1.11, p=0.572). Tests of trend on category means were both supportive of a linear relationship. Despite this there was not a smooth change in risk with increasing fluoride concentration, but an immeadiate increase in risk (between <0.1mg/l and 0.1-<0.2mg/l) followed by minimal further change as fluoride concentration increased.

Table 29. Age stratified crude rate ratio of hip fracture admission in females, by period mean fluoride concentration (mg/l) with split highest exposure category, England 2007 to 2015.

Age band (years)	Fluoride concentration (mg/l)	Pyar (millions)	Admissions	Adjusted IRR (95% CI)* †	p value	P trend on category labels	IRR trend on category mean (95% CI) * †	P for trend on category mean
0-49	<0.1mg/l	55.72	1814	Reference	-	0.025	0.90 (0.78-1.04)	0.162
	0.1-<0.2mg/l	56.45	1388	0.82 (0.76-0.89)	<0.001			
	0.2-<0.4mg/l	21.49	591	0.87 (0.79-0.96)	0.004			
	0.4-<0.7mg/l	6.03	186	0.95 (0.81-1.12)	0.540			
	0.7-<0.9mg/l	9.27	257	0.88 (0.78-0.99)	0.034			
	≥0.9mg/l	5.97	164	0.86 (0.71-1.03)	0.103			
50-64	<0.1mg/l	16.83	8207	Reference	-	0.627	1.06 (0.97-1.16)	0.226
	0.1-<0.2mg/l	14.18	5955	0.92 (0.88-0.97)	0.001			
	0.2-<0.4mg/l	6.38	2903	0.95 (0.90-1.00)	0.072			
	0.4-<0.7mg/l	1.92	885	0.95 (0.88-1.03)	0.211			
	0.7-<0.9mg/l	2.48	1199	1.01 (0.93-1.10)	0.815			
	≥0.9mg/l	1.69	880	1.08 (0.97-1.20)	0.187			
65-79	<0.1mg/l	12.14	38,572	Reference	-	0.006	1.08 (1.03-1.13)	0.001
	0.1-<0.2mg/l	9.41	27,738	0.97 (0.95-1.00)	0.036			
	0.2-<0.4mg/l	4.44	14,082	1.01 (0.98-1.04)	0.456			
	0.4-<0.7mg/l	1.38	4404	1.01 (0.97-1.05)	0.786			
	0.7-<0.9mg/l	1.76	5849	1.05 (1.01-1.09)	0.006			
	≥0.9mg/l	1.23	4221	1.07 (1.00-1.14)	0.038			
≥80	<0.1mg/l	5.57	106,446	Reference	-	<0.001	1.06 (1.02-1.10)	0.002
	0.1-<0.2mg/l	4.31	80,835	1.03 (1.00-1.05)	0.006			
	0.2-<0.4mg/l	2.03	39,634	1.03 (1.01-1.05)	0.001			
	0.4-<0.7mg/l	0.61	11,980	1.03 (1.00-1.06)	0.033			
	0.7-<0.9mg/l	0.80	16,024	1.05 (1.01-1.10)	0.024			
	≥0.9mg/l	0.54	10,911	1.05 (1.02-1.09)	0.001			
Total	-	242.65	385,125	-	-	-	-	-

*Pyar – Person years at risk; IRR – incidence rate ratio;*Adjusted for deprivation status and ethnicity; † Cluster robust standard errors derived by clustering on 325 local authority districts.*

Table 30. Age stratified crude rate ratio of hip fracture admission in males, by period mean fluoride concentration (mg/l), England 2007 to 2015.

Age band (years)	Fluoride concentration (mg/l)	Pyar (millions)	Admissions	Adjusted IRR (95% CI)* †	p value	P trend on category labels	IRR trend on category mean (95% CI) * †	P for trend on category mean
0-49	<0.1mg/l	56.49	3939	Reference	-	<0.001	0.89 (0.81-0.97)	0.008
	0.1-<0.2mg/l	57.34	3213	0.86 (0.81-0.92)	<0.001			
	0.2-<0.4mg/l	21.73	1269	0.87 (0.81-0.94)	<0.001			
	0.4-<0.7mg/l	6.10	363	0.87 (0.79-0.96)	0.008			
	0.7-<0.9mg/l	9.37	595	0.91 (0.83-1.00)	0.057			
	≥0.9mg/l	6.06	361	0.86 (0.78-0.94)	0.002			
50-64	<0.1mg/l	16.41	5855	Reference	-	0.471	0.99 (0.85-1.14)	0.854
	0.1-<0.2mg/l	13.76	4417	0.95 (0.85-1.00)	0.064			
	0.2-<0.4mg/l	6.23	1938	0.89 (0.84-0.96)	0.001			
	0.4-<0.7mg/l	1.89	606	0.91 (0.83-1.01)	0.073			
	0.7-<0.9mg/l	2.43	891	1.02 (0.85-1.22)	0.860			
	≥0.9mg/l	1.68	597	0.98 (0.86-1.11)	0.759			
65-79	<0.1mg/l	10.86	17,193	Reference	-	0.232	1.06 (0.99-1.14)	0.107
	0.1-<0.2mg/l	8.38	12,866	1.01 (0.97-1.04)	0.778			
	0.2-<0.4mg/l	4.09	6062	0.98 (0.94-1.02)	0.264			
	0.4-<0.7mg/l	1.27	1870	0.93 (0.89-0.98)	0.005			
	0.7-<0.9mg/l	1.58	2810	1.10 (1.04-1.16)	0.001			
	≥0.9mg/l	1.10	1871	1.05 (0.97-1.14)	0.255			
≥80	<0.1mg/l	3.25	32,395	Reference	-	0.011	1.07 (1.00-1.14)	0.049
	0.1-<0.2mg/l	2.61	26,016	1.03 (1.00-1.07)	0.028			
	0.2-<0.4mg/l	1.22	12,513	1.05 (1.02-1.08)	0.002			
	0.4-<0.7mg/l	0.37	3834	1.05 (1.01-1.09)	0.008			
	0.7-<0.9mg/l	0.48	4996	1.02 (0.94-1.11)	0.572			
	≥0.9mg/l	0.31	3545	1.10 (1.06-1.15)	<0.001			
Total	-	234.94	150,015	-	-	-	-	-

*Pyar – Person years at risk; IRR – incidence rate ratio;*Adjusted for deprivation status and ethnicity; † Cluster robust standard errors derived by clustering on 325 local authority districts.*

Analysis of hip fracture admission risk: monitoring health effects of water supplies within a fluoridation scheme

Considering public water supplies with a concentration of fluoride of at least 0.2mg/l, where fluoride was adjusted as part of a fluoridation scheme, the crude risk of hip fracture admission was 8% higher in males (95% CI 2% to 14%) than in areas where the fluoride concentration was <0.2mg/l (see Table 31). There was no difference in rates for females (p=0.121). Age group, deprivation status, and ethnicity significantly improved model fit (p<0.001) and were retained for the final analyses.

Risk of fracture across the 2 fluoride concentrations did not vary by age group in females (ie there was no interaction between age group and fluoridation status, p=0.58), and this was not tested for in the analysis of males. After adjustment for potential confounders, there was only weak statistical evidence for an association between fluoridation status and hip fracture admission in males (p=0.053), consistent also with no increased risk, but risk was increased by 4% in females (95% CI 1-16%) compared to areas without water fluoridation schemes. Sensitivity analysis after exclusion of data for MSOAs with significant disruption of fluoridation during 2005 to 2015 revealed no difference of significance in the results (see Table A6 in appendix).

Table 31. Crude and adjusted rate ratios of hip fracture admission, by period fluoridation status (mg/l), England 2007 to 2015.

Gender stratification	Fluoridation status*	Crude IRR (95% CI)†	Adjusted IRR (95% CI) †‡	P value
Males	No	Reference	Reference	-
	Yes	1.08 (1.02-1.14)	1.02 (1.00-1.05)	0.053
Females	No	Reference	Reference	-
	Yes	1.07 (0.98-1.16)	1.04 (1.01-1.06)	0.001

*IRR – incidence rate ratio; † Cluster robust standard errors derived by clustering on 293 local authority districts; ‡Adjusted for age, gender, ethnicity, deprivation status; *Yes=fluoride concentration≥0.2mg/l AND in water supply zone with fluoridation scheme during 2005 to 2015, in 833 MSOAs with 58.3 million person years of observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 4889 MSOAs with 343.7 million person years of observation.*

Kidney stones

MSOA level fluoride concentrations from 2005 to 2015 were used for this analysis. Kidney stone admissions relate to the period 2007 to 2015. Over 70% of MSOAs lay in WSZs with low (<0.2mg/l) fluoride concentrations, and 10% in WSZs with high (at least 0.7mg/l) fluoride concentrations during the 2005 to 2015 exposure period of interest (see Table 32). The population during 2007 to 2015 (summarised as ‘person years’) showed a similar distribution.

Table 32. Classification of MSOAs by 2005 to 2015 period fluoride concentration* (mg/l), and person years of observation, England.

Fluoride concentration (mg/l)	MSOAs	% of total	person years (millions)†	% of total
<0.1	2,571	38	177.30	37
0.1-<0.2	2,318	34	166.44	35
0.2-<0.4	956	14	67.53	14
0.4-<0.7	280	4	19.58	4
≥0.7	665	10	46.74	10
Missing	1	0.01	0.02	0
Total	6791	100	477.61	100

**Fluoride concentration derived from the mean fluoride concentration from constituent LSOAs, weighted using population; †May not sum exactly due to rounding.*

The crude rate of emergency consultant in-patient episodes with kidney stones between 2007 to 2015 was 36 per 100,000 person-years at risk (pyar) in areas with the highest fluoride concentration, and 35 in areas with the lowest concentration (see Table 33). The overall rate was 39 per 100,000 pyar.

Table 33. Crude incidence of emergency kidney stone admissions in England, by mean fluoride concentration category, England 2007 to 2015.

Fluoride concentration (mg/l)	Admissions due to kidney stone	Person years (millions)	Crude incidence (per 100,000 pyar)	95% CI
<0.1	62,230	177.30	35.1	34.8-35.4
0.1-<0.2	71,636	166.44	43.0	42.7-43.3
0.2-<0.4	27,149	67.53	40.2	39.7-40.7
0.4-<0.7	7,283	19.58	37.2	36.3-38.1
≥0.7	16,932	46.74	36.2	35.7-36.8
Missing	*	0.02	*	*
Total	185,231	477.61	38.8	38.6-39.0

*Pyar – person years at risk; CI – Confidence Interval; *Suppressed count<5 to prevent deductive disclosure.*

The crude rate of kidney stone episodes was 23% higher (95% CI 15% to 30%) in areas with fluoride concentration 0.1-<0.2mg/l compared to <0.1mg/l (see Table 34). Fluoride concentrations of 0.2-<0.4mg/l were also associated with an increased risk of admission, compared to the reference category (95% CI 7% to 23%). However, there was overlap in the confidence intervals in crude rates at other higher fluoride concentrations compared to <0.1mg/l, indicating no difference.

Model fit of the adjusted models was significantly improved by the addition of ethnicity, age, gender and deprivation variables (p<0.001 for all), and these were retained in the final model. The association between fluoride and kidney stone admission at 0.1-<0.2mg/l, and 0.2-<0.4mg/l persisted after adjustment (p<0.001 for both). There was no association at higher concentrations, and test of trend indicated a linear trend was not present (p=0.533).

Table 34. Crude and adjusted rate ratios of kidney stone admission, by period mean fluoride concentration (mg/l), England 2007 to 2015.

Fluoride concentration (mg/l)	Crude IRR (95% CI)[†]	Adjusted IRR (95% CI) [†*]	P value	P trend
<0.1mg/l	Reference	Reference	-	0.533
0.1-<0.2mg/l	1.23 (1.15-1.30)	1.22 (1.14-1.30)	<0.001	
0.2-<0.4mg/l	1.15 (1.07-1.23)	1.17 (1.10-1.26)	<0.001	
0.4-<0.7mg/l	1.06 (0.96-1.17)	1.07 (0.96-1.18)	0.214	
≥0.7mg/l	1.03 (0.93-1.14)	1.01 (0.86-1.13)	0.857	

IRR – incidence rate ratio; [†] Cluster robust standard errors derived by clustering on 325 local authority districts; Adjusted for age, gender, ethnicity, deprivation status.

Analysis of kidney stone admission risk: monitoring health effects of water supplies within a fluoridation scheme

Considering public water supplies with a concentration of fluoride of at least 0.2mg/l, where fluoride was adjusted as part of a fluoridation scheme, the crude risk of admission for kidney stone was 9% lower (95% CI 1%-17%) than in areas where the fluoride concentration was <0.2mg/l (see Table 35). Age group, deprivation status, ethnicity, and gender significantly improved model fit (p<0.001) and were retained for the final analysis. After adjustment for these factors, the association remained, and risk of admission was 10% lower (95% CI 2%-18%) in areas with water fluoridation schemes.

Table 35. Crude and adjusted rate ratios of kidney stone admission, by period fluoridation status, England 2007 to 2015.

Fluoridation status*	Crude IRR (95% CI)[†]	Adjusted IRR (95% CI) [†‡]	P value
No	Reference	Reference	-
Yes	0.91 (0.83-0.91)	0.90 (0.82-0.98)	0.020

*IRR – incidence rate ratio; [†] Cluster robust standard errors derived by clustering on 293 local authority districts; [‡]Adjusted for age, gender, ethnicity, deprivation status; *Yes=fluoride concentration≥0.2mg/l AND in water supply zone with fluoridation scheme during 2005 to 2015, in 833 MSOAs with 58.3 million person years of observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 4889 MSOAs with 343.7 million person years of observation.*

Down's syndrome

Over 70% of LTLAs lay in WSZs with low (<0.2mg/l) fluoride concentrations, and 6% in WSZs with high (at least 0.7mg/l) fluoride concentrations during the 2011 to 2014 period of interest (see Table 36). The distribution of live births by fluoride concentration during 2012-2014 differed to the distribution of LTLAs, as a higher percentage of births (9% rather than 6%) were in the highest fluoride concentration areas, and fewer (16% rather than 20%) in the 0.2-<0.4mg/l fluoride concentration areas.

Table 36. Classification of LTLAs by 2011 to 2014 period fluoride concentration* (mg/l), and number of live births 2012 to 2014, England.

Fluoride concentration (mg/l)	LTLAs	% of total	Live births	% of total
<0.1	101	31	634,133	31
0.1-<0.2	123	38	806,509	40
0.2-<0.4	64	20	316,579	16
0.4-<0.7	17	5	90,530	4
≥0.7	20	6	172,440	9
Missing	1	0	68	0
Total	326	100	2,020,259	100

**Fluoride concentration derived from the mean fluoride concentration from constituent LSOAs, weighted using number of birth.;*

A total of 33/325 (10%) of LTLAs with data were served by a fluoridation scheme at any point during the 2011 to 2014 time period. Bedford Borough was not considered to have a fluoridation scheme during this period due to disruption to fluoride plant operation since 2009.

The crude incidence of all Down's syndrome, including live births; stillbirths (24+ weeks' gestation); late miscarriages (20 to 23 weeks' gestation) and terminations of pregnancy with fetal anomaly was greater than average in LTLAs with mean fluoride of 0.1-0.2mg/l (see Table 37). Some 7% of cases were not linked to a geography, and therefore could not be assigned a LTLA of residence, and 13% of cases were missing either maternal age or LTLA residence data. Considering only live births, 68 births were missing LTLA residence data, and none were missing maternal age data.

Table 37. Crude incidence of Down's syndrome, by mean fluoride concentration category, England 2012 to 2014.

Fluoride concentration (mg/l)	Cases	Live births	Crude incidence (per 100,000 live births)	95% CI
<0.1	1349	634,133	212.73	201.53-224.39
0.1-<0.2	2390	806,509	296.34	284.58-308.46
0.2-<0.4	707	316,579	223.32	207.16-240.41
0.4-<0.7	238	90,530	262.90	230.55-298.50
≥0.7	368	172,440	213.41	192.16-236.36
Missing Fl data*	400	68	NA	NA
*Missing age or Fl***	*696*	*68*	*NA*	*NA*
Total	5452	2,020,259	269.87	262.76-277.13

*CI – Confidence Interval; Fl – Fluoride concentration; *400/5452 (7%) could not be assigned a fluoride concentration; **696/5452 (13%) cases missing maternal age or fluoride concentration data: 431 cases missing maternal age data, 135 cases missing both maternal age and fluoride concentration data*

Of the cases with LTLA residence data, the proportion missing maternal age data statistically significantly varied by fluoride concentration (p=0.012, see Table 38), cases in the <0.1 and 0.1-<0.2mg/l concentration categories missing the least data.

Table 38. Count and percentage of Down's syndrome cases with missing maternal age data, by fluoride concentration, England 2012 to 2014.

Fluoride concentration	Count of cases (any maternal age)*	Count of cases with age missing*	Percentage of cases with age missing*	p for X^2
<0.1	1349	67	5.0%	0.012
0.1-<0.2	2390	126	5.3%	
0.2-<0.4	707	51	7.2%	
0.4-<0.7	238	20	8.4%	
≥0.7	368	32	8.7%	
Total	5,052	296	5.9%	

**Cases with fluoride concentration data*

On Poisson regression (complete case analysis of cases with both maternal age and fluoride exposure data), the crude incidence rate of Down's syndrome was elevated at fluoride concentrations of 0.1-<0.2mg/l (RR1.39, 95% CI 1.30-1.49), and at 0.4-<0.7mg/l (RR 1.19, 95%CI 1.03-1.38) compared to the lowest fluoride concentration, but there was no effect at other concentrations, including the highest concentration of ≥0.7mg/l (RR 0.96, 95% CI 0.85-1.09) (see Table 39). These associations were incompletely attenuated (0.1-<0.2mg/l) or unchanged (0.4-<0.7mg/l) after adjustment for maternal age, with an 11% increased incidence at 0.1-<0.2mg/l (RR 1.11, 95% CI 1.03-1.19), and a 21% increased incidence at concentrations 0.4-<0.7mg/l (RR 1.21,

95% CI 1.05-1.40), compared to the lowest fluoride concentration. Test of trend revealed no evidence for a linear trend (p=0.941) between higher fluoride concentration and Down's syndrome incidence.

Table 39. Crude and adjusted incidence rate ratio of Down's syndrome (complete case analysis), by period mean fluoride concentration (mg/l), England 2012 to 2014.

Fluoride concentration (mg/l)	Crude IRR (95% CI)†	Adjusted IRR*† (95% CI)	p value	p for trend
<0.1mg/l	Reference	Reference	-	0.941
0.1-<0.2mg/l	1.39 (1.30-1.49)	1.11 (1.03-1.19)	0.003	
0.2-<0.4mg/l	1.02 (0.93-1.13)	0.96 (0.88-1.06)	0.446	
0.4-<0.7mg/l	1.19 (1.03-1.38)	1.21 (1.05-1.40)	0.009	
≥0.7mg/l	0.96 (0.85-1.09)	0.99 (0.88-1.12)	0.912	

*IRR – incidence rate ratio; *Adjusted for maternal age; † Cases with both fluoride and maternal age data only (n=4756).*

Sensitivity analysis to calculate expected age-specific case counts, by applying historic age-specific live birth risks to all births, revealed a higher observed than expected case count at all fluoride concentrations, but most notably at 0.1-<0.2mg/l, and 0.4-<0.7mg/l.

Table 40. Observed number of cases of Down's syndrome by fluoride concentration, England 2012 to 2014, and expected number using historic live birth risk published in 2002.

Fluoride concentration (mg/l)	Observed cases	Expected cases
<0.1mg/l	1,349	1,330
0.1-<0.2mg/l	2,390	2,131
0.2-<0.4mg/l	707	706
0.4-<0.7mg/l	238	186
≥0.7mg/l	368	351
TOTAL	5,052	4,704

On sensitivity analysis using the observed LTLA-level case counts aggregated only by fluoride concentration, and adjusting for maternal age by taking the expected count per LTLA as the offset, thereby comparing the ratio of observed to expected cases, there remained an excess incidence of 11% at 0.1-<0.2mg/l (RR 1.11, 95% CI 1.03-1.18) and 26% at 0.4-0.7mg/l (RR 1.26 95% CI 1.10-1.45). There was no evidence of a trend relationship between fluoride concentration and Down's syndrome incidence (p=0.325).

Table 41. Sensitivity analysis. Crude and adjusted incidence rate ratio of Down's syndrome, by period mean fluoride concentration (mg/l), England 2012 to 2014, using expected incidence calculated using historic live birth risk published in 2002.

Fluoride concentration (mg/l)	Crude IRR (95% CI)†	Adjusted IRR*† (95% CI)	p value	P for trend
<0.1mg/l	Reference	Reference	-	0.325
0.1-<0.2mg/l	1.39 (1.30-1.49)	1.11 (1.03-1.18)	0.003	
0.2-<0.4mg/l	1.05 (0.96-1.15)	0.99 (0.90-1.08)	0.796	
0.4-<0.7mg/l	1.24 (1.08-1.42)	1.26 (1.10-1.45)	0.001	
≥0.7mg/l	1.00 (0.89-1.13)	1.03 (0.92-1.16)	0.565	

*IRR – incidence rate ratio; *Adjusted for maternal age by taking expected count as exposure; † Cases with fluoride data only (n=5052).*

Analysis of Down's syndrome incidence: monitoring health effects of water supplies within a fluoridation scheme

Considering public water supplies with a concentration of fluoride of at least 0.2mg/l where this was only from water fluoridation schemes, the complete case analysis crude risk of Down's syndrome was 22% lower (95% CI 13%-29%) than in areas where the fluoride concentration was <0.2mg/l (see Table 42). After adjustment for maternal age, the association was attenuated, and risk of Down's syndrome was 8% lower, but the 95% confidence interval overlapped one (95% CI 0.84-1.02) in areas with water fluoridation schemes. To attempt to account for missing maternal age data, regression using the observed LTLA-level case counts aggregated only by fluoridation status, and adjusting for maternal age by taking the expected count per LTLA as the offset, thereby comparing the ratio of observed to expected cases also indicated there was no association between incidence of Down's syndrome and a fluoridated water supply (RR 0.97, 95% CI 0.89-1.07, p=0.596).

Table 42. Crude and adjusted rate ratios of Down's syndrome, complete case analysis and using expected incidence calculated using historic live birth risk published in 2002, by period fluoridation status (mg/l), England 2011 to 2014.

Complete case analysis	Fluoridation status*	Crude IRR (95% CI)	Adjusted IRR (95% CI)	P value
Yes	No	Reference	Reference	-
	Yes	†0.78 (0.71-0.87)	†**0.92 (0.84-1.02)	0.125
No	No	Reference	Reference	-
	Yes	¥0.82 (0.75-0.91)	‡0.97 (0.89-1.07)	0.596

*IRR – incidence rate ratio; *Yes=fluoride concentration≥0.2mg/l AND in water supply zone with fluoridation scheme during 2011 to 2014, in 33 LTLAs with 0.22million births. No= fluoride concentration <0.2mg/l, fluoride from any source, in 224 LTLAs with 1.44million births; † regression including only cases with both maternal age and fluoridation status data (n=3977); **Adjusted for maternal age; ‡Adjusted for maternal age by taking the expected number of cases as the exposure; ¥regression including cases with fluoridation status data (n=4217).*

Cancer outcomes

Bladder cancer

MSOA level fluoride concentrations from 2005 to 2015 were used for this analysis. Bladder cancer diagnoses relate to the period 2000 to 2015. Over 70% of MSOAs lay in WSZs with low (<0.2mg/l) fluoride concentrations, and 10% in WSZs with high (at least 0.7mg/l) fluoride concentrations during the 2005 to 2015 exposure period of interest (see Table 43). The population during 2000 to 2015 (summarised as 'person years') showed a similar distribution.

Table 43. Classification of MSOAs by 2005 to 2015 period fluoride concentration* (mg/l), and person years of observation, England.

Fluoride concentration (mg/l)	MSOAs	% of total	person years (millions)†	% of total
<0.1	2,572	38	309.33	37
0.1-<0.2	2,315	34	286.58	35
0.2-<0.4	958	14	117.26	14
0.4-<0.7	280	4	34.11	4
≥0.7	665	10	81.17	10
Missing	1	0.01	0.04	0
Total	6791	100	827.66	100

**Fluoride concentration derived from the mean fluoride concentration from constituent LSOAs, weighted using population; †May not sum exactly due to rounding.*

The crude rate of bladder cancer diagnosis during 2000 to 2015 was 16 per 100,000 person-years at risk (pyar) in areas with the highest fluoride concentration, and 19 in areas with the lowest concentration (see Table 44). The overall rate was 17 per 100,000 pyar.

Table 44. Crude incidence of bladder cancer diagnosis in England, by mean fluoride concentration category, England 2000 to 2015.

Fluoride concentration (mg/l)	Bladder cancer diagnoses	Person years (millions)	Crude incidence (per 100,000 pyar)	95% CI
<0.1	57,834	309.33	18.7	18.5-18.9
0.1-<0.2	43,361	286.58	15.2	15.0-15.3
0.2-<0.4	21,011	117.26	17.9	17.7-18.2
0.4-<0.7	6,468	34.11	19.0	18.5-19.4
≥0.7	13,157	81.17	16.2	15.9-16.5
Missing	7	0.04	19.6	7.9-40.4
Total	141,838	827.66	17.1	17.1-17.2

Pyar – person years at risk; CI – Confidence Interval

On Poisson regression analysis, the crude rate of bladder cancer diagnosis was 19% lower (95% CI 15% to 30%) in areas with fluoride concentration 0.1-<0.2mg/l compared to <0.1mg/l (see Table 45). Bladder cancer incidence was also inversely associated with fluoride concentrations of at least 0.7mg/l (13% lower, 95% CI 3%-22%) compared to the reference category (95% CI 7% to 23%). However, there was no statistical evidence of a difference in crude rates at other fluoride concentrations, compared to <0.1mg/l.

Model fit of the adjusted model was significantly improved by the addition of ethnicity, age, gender and deprivation variables (p<0.001 for all), and these were retained in the final model. The association between fluoride and bladder cancer incidence at 0.1-<0.2mg/l was lost after adjustment (p=0.434). The association at concentrations ≥0.7mg/l was weakened, but remained after adjustment (RR 0.93, 95% CI 0.88-0.98). There was statistical evidence of a trend, but examination of this result alongside the adjusted risk ratios suggested a potential threshold effect above 0.7mg/l, rather than a linear relationship. Sensitivity analysis after exclusion of data for MSOAs with significant disruption of fluoridation during 2005 to 2015 revealed no difference of significance in the results (see Table A6 in appendix).

Table 45. Crude and adjusted rate ratios of bladder cancer, by period mean fluoride concentration (mg/l), England 2007 to 2015.

Fluoride concentration (mg/l)	Crude IRR (95% CI)[†]	Adjusted IRR (95% CI) [†*]	P value	P trend
<0.1mg/l	Reference	Reference	-	0.027
0.1-<0.2mg/l	0.81 (0.76-0.86)	0.99 (0.96-1.02)	0.434	
0.2-<0.4mg/l	0.96 (0.91-1.01)	1.00 (0.97-1.03)	0.897	
0.4-<0.7mg/l	1.01 (0.91-1.13)	1.00 (0.95-1.05)	0.902	
≥0.7mg/l	0.87 (0.78-0.97)	0.93 (0.88-0.98)	0.004	

IRR – incidence rate ratio; [†] Cluster robust standard errors derived by clustering on 325 local authority districts; Adjusted for age, gender, ethnicity, deprivation status.

Results of a *post hoc* analysis of splitting the highest fluoride concentration category into 0.7-<0.9mg/l and ≥0.9mg/l, and taking the fluoride concentration exposure category arithmetic mean fluoride as a linear term to assess further evidence for a potential trend in bladder cancer risk are presented in Table 46. The risk of bladder cancer was similar at both the highest fluoride concentration categories (RR 0.92, 95% CI 0.86-0.98 for 0.7-<0.9mg/l, and 0.94, 95% CI 0.89-0.99 for ≥0.9mg/l). Both trend tests provided statistical evidence for a linear relationship (p=0.012 for trend on category mean fluoride concentration), but examination of this result alongside the adjusted risk ratios still suggested a potential threshold effect above 0.7mg/l.

Table 46. Adjusted rate ratios of bladder cancer, by period mean fluoride concentration (mg/l), England 2007 to 2015.

Fluoride concentration (mg/l)	Adjusted IRR (95% CI) †*	P value	P trend on category label	IRR trend (95% CI)	P for trend on category mean
<0.1mg/l	Reference	-	0.021	0.93	0.012
0.1-<0.2mg/l	0.99 (0.96-1.02)	0.434		(0.87-	
0.2-<0.4mg/l	1.00 (0.97-1.03)	0.897		0.98)	
0.4-<0.7mg/l	1.00 (0.95-1.05)	0.902			
0.7-<0.9mg/l	0.92 (0.86-0.98)	0.015			
≥0.9mg/l	0.94 (0.89-0.99)	0.017			

IRR – incidence rate ratio; † Cluster robust standard errors derived by clustering on 325 local authority districts; Adjusted for age, gender, ethnicity, deprivation status.

Analysis for bladder cancer incidence: monitoring health effects of water supplies within a fluoridation scheme

Considering public water supplies with a concentration of fluoride of at least 0.2mg/l, where this was only from water fluoridation schemes, the crude risk of bladder cancer was not different than in areas where the fluoride concentration was <0.2mg/l (p=0.522, and see Table 47). Deprivation status and ethnicity significantly improved model fit (p<0.001), and were retained in the model with gender and age group for the final analysis. After adjustment for these factors, there was a statistically significant association, and bladder cancer incidence was 6% lower (95% CI 2%-10%) in areas with a fluoridation scheme. Sensitivity analysis after exclusion of data for MSOAs with significant disruption of fluoridation during 2005 to 2015 revealed no difference of significance in the results (see Table A6 in appendix).

Table 47. Crude and adjusted rate ratios of bladder cancer diagnosis, by period fluoridation status, England 2000 to 2015.

Fluoridation status*	Crude IRR (95% CI)†	Adjusted IRR (95% CI) †‡	P value
No	Reference	Reference	-
Yes	0.97 (0.88-1.07)	0.94 (0.90-0.98)	0.002

*IRR – incidence rate ratio; † Cluster robust standard errors derived by clustering on 293 local authority districts; ‡Adjusted for age, gender, ethnicity, deprivation status; *Yes=fluoride concentration≥0.2mg/l AND in water supply zone with fluoridation scheme during 2005 to 2015, in 833 MSOAs with 101.3 million person years of observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 4889 MSOAs with 595.1million person years of observation.*

Osteosarcoma in 0 to 49-year-olds

LTLA level fluoride concentrations from 2005 to 2015 were used for this analysis. Osteosarcoma diagnoses relate to 0 to 49 year-olds for the period 1995 to 2015. 68% of LTLAs lay in WSZs with low (<0.2mg/l) fluoride concentrations, and 7% in WSZs with high (at least 0.7mg/l) fluoride concentrations during the 2005 to 2015 period (see Table 48). The distribution of population by fluoride concentration was similar.

Table 48. Classification of LTLAs by 2005 to 2015 period fluoride concentration* (mg/l), and person years at risk in 0 to 49-year-olds, 1995 to 2015, England.

Fluoride concentration (mg/l)	LTLAs	% of total	Person years (millions)	% of total
<0.1	107	33	244.18	34
0.1-<0.2	115	35	252.74	36
0.2-<0.4	62	19	114.02	16
0.4-<0.7	19	6	38.01	5
≥0.7	22	7	61.28	9
Missing	1	0	0.03	0
Total	326	100	710.26	100

**Fluoride concentration derived from the mean fluoride concentration from constituent LSOAs, weighted using number of births*

A total of 34/325 (10%) of LTLAs with data were served by a fluoridation scheme at any point during the 2005 to 2015 time period.

The crude rate of osteosarcoma diagnosis during 1995 to 2015 was 0.25 per 100,000 person-years at risk (pyar) in areas with the highest fluoride concentration, and 0.27 per 100,000pyar in areas with the lowest concentration (see Table 49). The overall rate was 0.27 per 100,000 pyar.

Table 49. Crude incidence of osteosarcoma in 0-49 year-olds, by mean fluoride concentration category, England 1995 to 2015.

Fluoride concentration (mg/l)	Osteosarcoma diagnoses	Person years (millions)	Crude incidence (per 100,000 pyar)	95% CI
<0.1	659	244.18	0.27	0.25-0.29
0.1-<0.2	690	252.74	0.27	0.25-0.39
0.2-<0.4	300	114.02	0.26	0.23-0.30
0.4-<0.7	116	38.01	0.31	0.25-0.37
≥0.7	150	61.28	0.25	0.21-0.29
Missing	*	0.03	*	*
Total	1,916	710.26	0.27	0.26-0.28

*Pyar – person years at risk; CI – Confidence Interval; *Suppressed count<5 to prevent deductive disclosure*

On Poisson regression analysis, the crude rate of osteosarcoma diagnosis did not differ by fluoride concentration (p>0.05 for all).

Model fit of the adjusted model was not significantly improved by the addition of ethnicity and deprivation variables (p>0.10 for both), therefore only age and gender were retained in the final model. The absence of association between fluoride concentration and osteosarcoma incidence remained after adjustment (p values were all well above 0.05 for all categories of fluoride), and the test of trend also did not provide evidence for a linear trend (p=0.569). Sensitivity analysis after exclusion of data for LTLAs with disruption to fluoridation schemes revealed no difference of significance in the results (see Table A6 in appendix).

Table 50. Crude and adjusted rate ratios of osteosarcoma in 0 to 49 year olds, by period mean fluoride concentration (mg/l), England 1995 to 2015.

Fluoride concentration (mg/l)	Crude IRR (95% CI)	Adjusted IRR (95% CI) *	p value	p for trend
<0.1mg/l	Reference	Reference	-	0.569
0.1-<0.2mg/l	1.01 (0.91-1.13)	1.04 (0.93-1.15)	0.511	
0.2-<0.4mg/l	0.97 (0.85-1.12)	0.99 (0.86-1.13)	0.852	
0.4-<0.7mg/l	1.13 (0.93-1.38)	1.14 (0.94-1.39)	0.191	
≥0.7mg/l	0.91 (0.76-1.08)	0.90 (0.75-1.07)	0.228	

IRR – incidence rate ratio; Adjusted for age and gender

Analysis of osteosarcoma incidence: monitoring health effects of water supplies within a fluoridation scheme

Considering public water supplies with a concentration of fluoride of at least 0.2mg/l, where this was only from water fluoridation schemes, the crude risk of osteosarcoma was not different than in areas where the fluoride concentration was <0.2mg/l (p=0.727, and see Table 51). Deprivation status and ethnicity did not significantly improve model fit (p>0.10), and therefore only age and gender were retained in the model for the final analysis. Adjustment for these factors led to little change in the risk ratio, and osteosarcoma incidence was no different (p=0.550) in areas with water fluoridation schemes. Sensitivity analysis after exclusion of data for Allerdale, Bedfordshire and Copeland revealed no difference of significance in the results (see Table A6 in appendix).

Table 51. Crude and adjusted rate ratios of osteosarcoma in 0 to 49 year olds, by period fluoridation status (mg/l), England 1995 to 2015.

Fluoridation status*	Crude IRR (95% CI)	Adjusted IRR (95% CI)‡	P value
No	Reference	Reference	-
Yes	0.97 (0.84-1.13)	0.96 (0.83-1.11)	0.550

*IRR – incidence rate ratio; ‡Adjusted for age and gender; *Yes=fluoride concentration≥0.2mg/l AND in water supply zone with fluoridation scheme during 2005 to 2015, in 34 LTLAs with 80.1 million person years of observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 222 LTLAs with 496.9million person years of observation.*

Discussion

Value of this report

In 2014, the last health monitoring report on Fluoridation for England concluded that: "This monitoring report provides evidence of lower dental caries rates in children living in fluoridated compared to non-fluoridated areas. There was no evidence of higher rates of the non-dental health indicators studied in fluoridated areas compared to non-fluoridated areas. Although the lower rates of kidney stones and bladder cancer found in fluoridated areas are of interest, the population-based, observational design of this report does not allow conclusions to be drawn regarding any causative or protective role of fluoride; similarly, the absence of any associations does not provide definitive evidence for a lack of a relationship." This report updates that assessment and provides more detail in several respects:

- the population exposure to fluoridation is presented in more detail, and accounts for changes in water supply zone geography over time, decreasing misclassification of exposure
- in addition to comparing rates of health outcomes in fluoridated areas with non-fluoridated areas as before, we have compared rates of health outcomes across the full spectrum of fluoride concentrations from very low to medium to higher fluoride levels (whether the latter are adjusted by a fluoridation scheme or present due to geology). By doing this, we could also consider if there was a linear trend
- the association between fluoride and hip fracture was suspected to vary by age and gender, hence we incorporated this into the design and analysis of this report
- the estimates of association are more precise as most are based on significantly larger numbers from more years of data

Exposure description

Our analysis of routine fluoride monitoring data detailed how the population of England receives public water supplies with a range of fluoride concentrations, even in areas without fluoridation schemes. Average 2005 to 2015 fluoride concentrations reached up to 1.21mg/l, with the highest concentrations in Hartlepool, an area without a fluoridation scheme where fluoride instead comes from geological sources. However, the large majority (92%) of the 10% of the population that received water with a fluoride concentration of at least 0.7mg/l lived in an area supplied by a fluoridation scheme. Most people (72%) lived in areas with relatively low average fluoride concentration (<0.2mg/l), and relatively fewer (18%) in areas between 0.2mg/l to less than 0.7mg/l. Where fluoridation schemes were present, the median fluoride concentration was 0.84mg/l in 2005 to 2015, much higher than in non-fluoridated WSZs (0.11mg/l).

Annually, the fluoride concentration in WSZs with schemes were typically 0.7mg/l-0.9mg/l, below the target concentration of 1mg/l. We observed a relatively wide interquartile range of around 0.2mg/l – 0.3mg/l indicating variation in achieved fluoride concentrations, re-emphasising the need to use achieved fluoride concentrations when considering use of fluoride as an exposure in health outcomes analyses.

On comparison of mean period fluoride concentrations between 1995 to 2004 and 2005 to 2015 in fluoridated WSZs and non-fluoridated WSZs, only non-fluoridated areas exhibited a very strong correlation (Spearman rank 0.93), with a weak correlation (0.31) in fluoridated WSZs. Limitations in ability to match a large proportion of WSZs across the 2 time periods mean these results should be treated cautiously (see limitations section below). The difference between period median fluoride in the 2 periods for fluoridated zones was not large (0.06mg/l), implying fluoride concentrations were not likely, on average, to be greatly different between the 2 periods. However, this poor correlation means there is greater uncertainty in being able to confidently assign a long-term exposure within a narrow concentration range. This would be of most relevance for health outcomes with a likely long lag period from exposure to initiation of pathology, such as cancer and possibly bone fractures, in populations living in areas supplied by fluoridation schemes.

Dental outcomes

The main finding of this report is of strong statistical evidence for a highly clinically significant reduction in dental caries, including hospital admission for extraction, with increasing levels of fluoride in water supplies.

Dental caries

Dental caries is an extremely common oral disease affecting children and young people in England, and although children's oral health has improved, 25% of five-year-olds in England have dental caries(1). This average figure masks an uneven distribution. When examined at the upper tier local authority level, prevalence estimates range from 56% in Blackburn with Darwen to 14% in South Gloucestershire. Children living in deprived communities have also been shown to consistently have poorer oral health than children living in more affluent communities(1). Our analysis showed that prevalence of caries experience ($d_3$mft>0) fell by nearly 6% (unadjusted estimate[18]), a relative reduction of 21%, and the mean $d_3$mft reduced by 36% (unadjusted estimate[18]), as fluoride concentration increased from <0.1mg/l to at least 0.7mg/l. At all levels of

[18] Unadjusted estimates, rather than deprivation stratum specific adjusted estimates, are given here to easily convey a single summary measure of effectiveness to compare with the wider evidence base. Adjusted estimates, given the change observed from between crude and adjusted odds ratios, would likely be similar or of greater magnitude.

deprivation the odds of having experience of caries were significantly lower in five-year-old children living in areas with the highest compared to the lowest fluoride concentrations, and an incremental increase in exposure to fluoride led to a larger protective effect. Beneficial effects were seen even at concentrations as low as 0.1-0.2mg/l for five-year-olds living in relatively more deprived areas, though increased risk of exposure misclassification at these lower fluoride concentrations means this must be interpreted cautiously (see the limitation section below for a fuller discussion). The odds, adjusted for ethnicity, of having caries experience were reduced by 23% (9%-39%) for five-year-olds living in the least deprived areas and 52% (95% CI 47%-56%) for five-year-olds living in the most deprived areas at concentrations of ≥0.7mg/l, compared to the lowest fluoride concentration (<0.1mg/l). Such large reductions in relative odds of caries experience, in the context of high absolute risk of caries, are extremely significant from a public health perspective. It also appears, when examining concentration of fluoride in the water supply above the level of 0.7mg/l the odds of having experience of caries continued to fall up to at least 0.9mg/l. The odds of experiencing more severe caries also decreased as fluoride concentration increased.

While the overall trend was for reduction in caries prevalence and severity among five-year-old children with increasing fluoride levels in drinking water, there was not a smooth linear relationship, with a flattening of the downward slope at concentrations between 0.2mg/l and 0.7mg/l. This may reflect the true caries-fluoride relationship, instability of associations due to the relatively small population receiving water with these concentrations, limitations in the data (eg resulting from differential misclassification of exposure category at these concentrations), or residual/un-measured confounding obscuring the true association. In particular, we were unable to directly adjust for cariogenic dietary factors and oral hygiene behaviours, or area level factors such as differing provision of primary care dentistry. Further studies will be needed to confirm the true nature of the relationship.

The preventive fraction of dental caries estimates the percentage decrease in the number of cases of caries if all five-year-olds with drinking water with <0.2mg/l fluoride instead received at least 0.7mg/l from a fluoridation scheme[19]. We estimated the fall would be 17% in the least deprived areas, rising to 28% in the most deprived areas. Given that 70% of the population of five-year-olds received water supplies where fluoride concentrations were less than 0.2mg/l, potentially many children could benefit from fluoridation. In addition to lowering caries prevalence in five-year-olds at all levels of deprivation, the impact would be greatest in children in the most deprived areas, also narrowing dental health inequalities.

[19] For example a preventive fraction of 20% would result in an absolute decrease of caries prevalence from 25% to 20%

Published reviews of the research evidence demonstrate that water fluoridation is associated with reduced levels of dental caries in populations served by this public health measure. Following evaluation of the evidence, a Cochrane Database Systematic Review found water fluoridation resulted in children having 35% fewer decayed, missing and filled deciduous teeth, in keeping with our findings, and there was an absolute reduction in the prevalence of children with caries experience of 15% (95% CI 11%-19%)[19]. This reduction in prevalence is larger than our findings but drew on analysis of studies largely undertaken before 1975. A possible explanation for this difference is that, in contrast to studies from earlier decades, there have been secular changes in diet and an increased use of fluoride containing dental products. This is likely to have contributed to the large reduction in the prevalence of caries over this period, and therefore decreased the absolute benefit of water fluoridation, though the relative effectiveness may still be similar[16]. In support of this, other more contemporary studies[18, 66] have found absolute reductions in caries prevalence of between 3%-11%in five-year-olds, closer to the findings of this monitoring report. In any case, as discussed above, the reductions we have observed offer significant public health benefits. The results of this monitoring, within the confines of the data used, are therefore in keeping with the other evidence.

The nature of water fluoridation is such that the whole population receiving the water supply is able to benefit without the need for individuals to change their behaviour or comply with advice of healthcare professionals, thereby also contributing to the narrowing of dental health inequalities. This is in keeping with our findings of a more rapid decline in prevalence of dental caries experience, and severity, with increasing fluoride concentration for the most deprived compared to the least deprived five-year-olds. These findings add further weight to the conclusions of the York report[29], and Australian NHMRC report[20], that there is evidence that fluoridation narrows oral health inequalities in children.

Dental admissions

Hospital admissions for caries-related dental extractions were common, averaging approximately 40,000 per year. The incidence of admission was 59% lower (95% CI 33% to 76%) in areas where the concentration of fluoride was ≥0.7mg/l, compared to the reference areas (<0.1mg/l). It also appears the trend between decreasing incidence of dental extraction and increasing concentration of fluoride is significant, though the shape of the relationship between fluoride concentration and incidence of dental extraction was not a smooth line. The potential reasons for this, and the implications, are the same as those noted above for dental caries experience. The preventive fraction of extractions in hospital secondary to dental caries, ie the percentage of extractions prevented, were all children currently exposed to <0.2mg/l fluoride instead exposed to at least 0.7mg/l from a fluoridation scheme, ranged from 45-68% depending on their level of deprivation, and was greatest in the most deprived quintile (68%, 95%

CI 40-83%). Dental treatment under general anaesthesia (GA), presents a small but real risk of life-threatening complications for children so a reduction in the number of dental procedures carried out under GA of this magnitude offers significant benefits. This reduction is also likely to have noticeable effects on the relative costs of dental service provision due to the high costs associated with hospital admission.

The evidence regarding the effects of fluoridation on caries related hospital admissions is more sparse; consequently a greater degree of caution should be used when interpreting our findings. However, the existing evidence appears to be consistent in both direction and strength of association, and is strongly supported by the comprehensive evidence base linking reduction in caries and caries severity with water fluoridation. Five studies included in the Australian NHMRC review found a reduction in the rate of hospitalisation in areas with fluoridated water supplies[18, 20, 67-70]. In 2 of these studies where effect estimates were reported by the NHMRC, admission rates were 43 to 55% lower, in agreement with the findings of this report[18, 20, 69].

The direction and trend in association between fluoride concentration/fluoridation and caries prevalence, severity, and dental extractions were similar, and this consistency strengthens confidence in our findings. There were, however, some differences between findings for dental caries prevalence/severity, and hospital dental extractions. The benefits of concentrations greater than 0.7mg/l seen for caries prevalence were not evident for dental extractions. Additionally, like caries prevalence there was a difference in effect of fluoridation by deprivation status on hospital admissions for extractions when considering the binary analysis (ie by fluoridation scheme). However, there was no statistical evidence of a difference in the relative effect of fluoride by deprivation status when considering the multi-categoric analysis. As such, the evidence from our report is less clear as to whether hospital admissions for extractions are impacted more by fluoridation schemes in more deprived rather than less deprived populations. Even though the relative effect of fluoride may not differ across quintiles of deprivation, the absolute change in number of children with caries did differ, because more children and young people aged 0 to 19 years required caries related extractions in more deprived areas. Thus, fluoridation schemes are still likely to narrow dental health inequality in terms of hospital admission for dental extractions. It is uncertain whether these differences between the dental extractions and caries prevalence findings reflect differences in the outcome (admissions for extraction reflecting the more severe end of the caries spectrum of disease), populations studied, or data sources.

There are known considerations affecting data quality; an evaluation of dental general anaesthetics in Yorkshire and the Humber found that not all units carrying out dental extractions for children under a general anaesthetic were using the HES coding system[71]; this is also likely to be the case in other parts of the country, thus the HES figures may not be fully comparable between areas. However, there is no reason to suppose that services in fluoridated areas are, in general, likely to record this activity

differently to services in non-fluoridated areas. The rate of HES extractions performed is only one measure of secondary healthcare need, and may under-estimate population caries burden, for example if there are constraints in service delivery such as operating theatre availability limiting the number of extractions undertaken.

Fluorosis

In the study by Pretty et al. (2016) the prevalence of any positive score for fluorosis was greater in the fluoridated cities (Newcastle and Birmingham 61%) compared to the non-fluoridated cities (Manchester and Liverpool, 37%)[7]. Fluorosis considered to be of at least mild aesthetic concern was seen in 10.3% of surveyed children in the fluoridated cities and 2.2% in the non-fluoridated cities. It should be noted that fluorosis will reflect fluoride consumption from any source, not of water fluoridation per se. Other sources of fluoride include toothpaste, foodstuffs and fluoride supplements and it has not been possible, in this study, to examine all the potential sources of exposure to fluoride. As the authors of the study stated, there may also have been mis-reporting of past residence. The 2015 survey results suggested a possible increase in levels of very mild fluorosis (TF1) in both non-fluoridated Manchester and fluoridated Newcastle compared with a 2012 survey undertaken in those cities[72] but this may be due to methodological changes. Further monitoring appears justified.

In addition to looking at the prevalence and severity of fluorosis, this paper also measured differences in children's satisfaction with the appearance of their teeth. From the 1888 responses (99% response rate for both groups) there was no significant difference in the mean aesthetic score between respondents from fluoridated and non-fluoridated cities (p=0.572). The results from this survey suggest that, in the age group considered, the presence of fluorosis does not appear to cause aesthetic concern or, where it does cause concern there is an equal level of dissatisfaction due to other factors eg trauma, orthodontic malalignment or caries. There is nothing to suggest the levels of malalignment of teeth or trauma would differ between fluoridated and non-fluoridated areas yet it would be anticipated that the levels of caries are lower in fluoridated regions.

Non-dental health indicators

Hip fracture

In the 2014 report the crude incidence rates were about 7% higher in fluoridated compared to non-fluoridated areas, with the difference being 0.7%, ie only slightly higher after adjusting for sex, age, deprivation and ethnicity; confidence intervals overlapped one, indicating this was a non-significant difference. This report demonstrated some statistically significant findings in relation to fluoridation and hip fractures, but these require cautious interpretation. The difference in crude incidence

rates was virtually identical to the 2014 report, being 7% and 8% for females and males respectively. In areas with a fluoridation scheme the adjusted rate of hip fractures was 4% (95% CI 1 to 6%) higher in females. A complex relationship between fluoride exposure and hip fracture was noted on multi-categorical analysis. This relationship depended on age, without a gender-specific effect. No clear pattern of association was observed for the 50 to 64 or 65 to 79 age groups. In people aged 0-49, fluoride concentrations greater than the minimum exposure category were associated with lower risk of hip fracture admission (typically 13 to 14%) whereas in older adults (80+), fluoride concentrations of at least 0.1mg/l were generally associated with a slightly increased hip fracture admission risk (typically 3 to 5%). This effect size is small, and therefore less likely to be due to a causal relationship. Nonetheless, there was a highly significant test for linear trend across the 5 categories of exposure in older females and to some extent older males.

Despite this strong statistical evidence of a trend, inspection of the multi-categorical analysis results did not reveal a smooth concentration-dependent increase in hip fracture risk with increasing fluoride concentration, providing a less compelling case for a true linear relationship. Splitting the highest fluoride concentration category did not provide additional evidence for a linear trend. Residual or unmeasured confounding could account for the association seen: hip fracture risk is a function of bone mineral density, age, prior fragility fracture, parental history of hip fracture, smoking, systemic corticosteroid use, excess alcohol intake and rheumatoid arthritis [(73)].

Adjustment of our crude estimates for age, ethnicity, and deprivation, and gender stratification, at area-level, is unlikely to have adequately taken all these other factors into account. Exposure misclassification (see the limitations section below for a full discussion) may also play a role, given the change in risk was fairly uniform between the lowest fluoride concentration (at greatest risk of exposure misclassification) and all higher concentrations. The inconsistencies in hip fracture admission risk by age, often small effect sizes, lack of trend by fluoride concentration, probable residual and unmeasured confounding, and potential for exposure misclassification do not provide convincing evidence of a causal association, either protective or adverse.

These results simply raise the possibility that there is an association, the direction of which changes across the life course, between fluoridation and hip fractures. Previous studies have suggested some evidence for a biphasic effect of fluoride ingestion, with an increase in bone strength following moderately high intakes and reduced bone strength and increased fracture risk following higher long-term intakes. The precise dose-response relationship is unclear[(31, 74)]. Fluoride in bone is expected to increase in concentration over time with many years of exposure, although it is also released from the bone during bone re-modelling[(32)]. It is plausible that following excessive intakes of fluoride over many years that older people may become more at risk of bone fracture. The US NRC 2006 review noted animal evidence suggesting that bone weakened as

bone-fluoride densities increased above a threshold, and broader scientific evidence, including epidemiological studies in humans, show that under certain conditions fluoride can weaken bone and increase the risk of fractures[27]. However, the US NRC scientific committee concluded that this risk was only likely following lifetime exposure to fluoride at drinking-water concentrations of 4 mg/L or higher, compared with exposure to 1 mg/l, ie at much higher concentrations than to which the England population is exposed[27]. Similarly, the European Food Safety Authority (EFSA) has advised that a fluoride intake below an upper intake limit of 0.12 mg/kg bw/day, (0.12mg/kg bw/day would be consistent with a very high intake unlikely to occur at drinking water fluoride concentrations observed in England) is unlikely to increase the risk of bone fracture[31].

A 2015 meta-analysis of 14 observational studies concluded that chronic fluoride exposure from drinking water does not significantly increase or decrease the risk of hip fracture (RR = 1.05; 95% CIs = 0.96 to 1.15), but heterogeneity was significant ($P < 0.001$, $I2 = 82.8\%$), and that further high quality studies addressing potential confounding factors and exposure misclassification were needed[75]. Sources of heterogeneity were unclear even after meta-regression for country, gender, study quality, adjustment for covariates and sample size. A sub-group meta-analysis only of female participants over 65 also found evidence of no association between exposure to fluoride in drinking water and hip fracture (RR = 1.04, 95% CIs = 0.97 to 1.12) again with substantial evidence of heterogeneity ($P < 0.001$, $I2 = 86.3\%$), meaning an age-specific effect within this age/gender group is unlikely but there is inconsistency between studies[75]. The meta-analysis authors also described the risk/odds ratios of hip fracture by fluoride concentration categories for individual studies, which demonstrated no dose-response relationship with hip fracture. Despite the statistical evidence for an association between exposure to fluoride and increase in hip fracture in the elderly in this report, considered in the wider epidemiological and toxicological context, there is consensus that the overall available weight of evidence does not indicate an increased risk of hip fracture from long-term (many years) fluoride intakes arising from fluoridated drinking water at the concentrations observed in England ie around 1.0 mg/L[20, 22, 24, 27, 32, 74, 76].

Kidney stones

This monitoring report, in accordance with the findings of the 2014 monitoring report found strong statistical evidence of a negative association between fluoridation and emergency admissions due to kidney stones. The adjusted incidence rate was 10% lower in both reports (95% CI 2% -18% for the 2018 report) in areas with a fluoridation scheme. However, the picture is more complex when the association between admissions and fluoride concentration categories are examined: an increase in fluoride concentration from <0.1mg/l to 0.1-<0.2mg/l saw an increase in risk of 22 % (95% CI 14%-30%), and 17% (95% CI 10-26%) for those exposed to 0.2-<0.4mg/l, but no

increased risk from concentrations above 0.4mg, implying any excess risk of kidney stones on exposure to low fluoride concentrations is confined to concentrations of 0.1-<0.4mg/l. There was no linear trend between fluoride concentration and incidence. The inconsistent relationship between fluoride and risk of admission, absence of linear trend, and neutral associations at higher fluoride concentrations make a causal association improbable. Exposure misclassification is also more likely to have occurred at lower fluoride concentrations (see the limitations section for a fuller discussion), making the interpretation of different admission rates between the lowest fluoride concentrations more uncertain.

Previous ecological level research has provided inconsistent evidence of an association between fluoride and kidney stone risk, but this may have occurred as a result of confounding – both residual and from variables not included in the analyses – and bias. Juuti & Heinonen (1980) investigated the incidence of kidney stones in Finnish hospital districts with different levels of fluoride in drinking water[77]. The study found that at fluoride concentrations of 1.5 mg/L or greater, the standardised hospital admission rates for urolithiasis (kidney stones) were increased by about one-sixth. No differences were found between areas with fluoride concentrations of ≤ 0.49 mg/L and 0.50 – 1.49 mg/L; a separate comparison of a fluoridated city [1 mg/L] and a referent city [< 0.49 mg/L fluoride] found a 25% lower rate of urolithiasis in the fluoridated city. Singh et al. (2001) carried out an extensive examination of more than 18,700 people living in India where fluoride concentrations in the drinking water ranged from 3.5 to 4.9mg/L. Patients were interviewed for a history of urolithiasis and examined for symptoms of skeletal fluorosis, and various urine and blood tests were conducted. The patients with clear signs and symptoms of skeletal fluorosis were 4.6 times more likely to develop kidney stones[78]. Malnutrition among the study population probably increased the risk of kidney stones formation.

Risk factors for kidney stones include age, male gender, genetic susceptibility, dehydration, and dietary factors[60, 79]; rate differences seen in this report between areas may have occurred because of variations in the prevalence of these risk factors, which in turn could be associated with ecological level fluoridation status. Dietary differences could potentially reflect urban versus rural lifestyles. Attempts were made to control for age, gender, deprivation and ethnicity differences between MSOAs in this report, but the ecological level analysis and use of broad categories increases the likelihood that residual confounding may be responsible for some, or all, of the difference seen.

This report was reliant on admission with, and subsequent correct coding of, kidney stones. If there were systematic differences in admission and coding practices between fluoridated and non-fluoridated areas, this could lead to a spurious association. Additionally, kidney stones are associated with co-morbidity and medication use; the

presence of chronic illness may lead to migration to, or less emigration from, urban areas, so potentially increasing the association with fluoridation status.

Down's syndrome

Complete case analysis demonstrated an 11% increased incidence at 0.1-<0.2mg/l (95% CI 3-19%), and a 21% increased incidence at concentrations 0.4-<0.7mg/l (95% CI 5-40%). Importantly, there was evidence of no increased incidence at the highest fluoride concentrations (p=0.912), and no linear trend (p=0.941). In areas with a fluoridation scheme receiving a fluoride concentration of ≥0.2mg/l there was no strong statistical evidence for an association between fluoridation and Down's incidence, consistent with the above findings. In the absence of increasing risk with the highest fluoride concentration, and no linear relationship, a causal relationship between exposure to fluoride and Down's syndrome is very improbable.

Maternal age and uptake of antenatal screening are the key determinants of the number of pregnancies where Down's syndrome occurs and is detected (as many affected pregnancies may spontaneously miscarry, leading to under-ascertainment in the absence of screening)[53]. Missing data on maternal age means these results may be at least partly explained by selection bias (ie of cases only with maternal age data). We performed a sensitivity analysis using a method that would not be reliant on case maternal age data, which calculated estimates of the expected number of cases given the population size and age structure, and historic Down's syndrome live birth risk estimates. After accounting for missing age data in this way, excess risks of Down's syndrome were still observed at 0.1-<0.2mg/l and at 0.4-0.7mg/l. Live-birth Down's syndrome risks were estimated using a method that assumes a certain proportion of cases detected at termination of pregnancy would survive to term, after accounting for fetal losses from miscarriages[65].

A limitation of our approach was that we did not account for this reduction in the observed cases ascertained following termination of pregnancy due to likely fetal losses by miscarriage. This is likely to have contributed to the higher observed than expected case numbers in all fluoride exposure concentration categories. However, it is unlikely the proportion of observed cases ascertained following termination would vary significantly by fluoride concentration, resulting in a global rather than differential over-estimate of observed cases by fluoride concentration. This is in keeping with the very similar results observed between the sensitivity analysis and main analysis.

This similarity in findings, after accounting for missing maternal age data, indicates variation in case ascertainment due to geographical/population differences in screening offer and uptake, variation in case reporting to the registry, and registry data limitations are more likely explanations for the excess risk observed at 0.1-<0.2mg/l and at 0.4-0.7mg/l. Some 7% of Down's syndrome cases are not reported to the register[53]. There

are important regional differences in screening for Down's syndrome in England[80], a factor not accounted for in our analysis and driven by health service factors[81], ethnic background and potentially other social factors[82]. We also could not perform further analyses to account for missing case address data, which occurred in 7% of cases and may vary by fluoride concentration. Other limitations entailed by our use of an ecological study design also apply to this Down's syndrome analysis, and are discussed further in the limitations section below.

A systematic review by Whiting et al (2001) identified 6 ecological studies investigating any association between drinking water fluoride levels and Down's syndrome[83]; all were considered to be of low validity. Two of the 6 studies, both by the same author, demonstrated a positive association between fluoride levels in drinking water and Down's syndrome but did not adjust for any confounding variables, most notably maternal age; the conclusion of the systematic review was that the evidence for any association was inconclusive.

Bladder cancer

In the 2014 report a significantly lower rate of bladder cancer was noted, being 8% lower in fluoridated areas, based on analyses on cancer registrations 2000 to 2010 adjusting for sex, age and deprivation. In the current report results are similar with a significantly lower incidence of 6% (2% to 10%) in areas with ≥0.2mg/l fluoride. A similar reduction in incidence of 7% (2% to 12%) was observed at the highest compared to lowest fluoride concentration in the multi-categorical analysis. No association was demonstrated at concentrations lower than 0.7mg/l, and there was unconvincing evidence of a linear trend, making a causal association less likely. There may be a threshold effect above 0.7mg/l, however, the risk of bladder cancer was similar at both the highest fluoride concentration categories when these were further subdivided. This is less supportive of a true threshold association above 0.7mg/l, as higher concentrations do not further decrease risk.

As previously described for kidney stones and hip fracture, possible explanations include confounding, and bias. The risk of bladder cancer is higher in males, and increases dramatically with age [84, 85]; adjusting for these variables at an ecological level may have resulted in residual confounding in the relationship between fluoridation and bladder cancer. Smoking is a powerful independent risk factor for bladder cancer[85], and was only indirectly adjusted for in this report, using deprivation status as a proxy.

In previous ecological level research Yang et al (2000) reported an increased relative risk for bladder cancers in females of 2.79 [95% CI 1.41 – 5.55] in areas of higher compared to lower fluoride concentrations[86]. The relative risk for bladder cancers in males was non-significant [RR 1.29, 95% CI 0.75 – 2.15]. It was considered improbable

for a bladder cancer effect to be gender specific and the authors attributed this to a chance finding as a result of the multiple comparisons carried out in the study analysis. Overall, the study concluded that the suggestion that the fluoride level of water supplies is associated with an increase in cancer mortality in Taiwan was not supported[86]. A cohort study of cryolite mill workers with occupational exposure to fluoride dust found an elevated risk of bladder cancer, though the workers' exposure was much greater than population exposure through drinking water supplies, limiting applicability of this evidence[87]. Available data are too limited, therefore, to provide a plausible explanation of a protective effect for fluoride.

Osteosarcoma – in 0 to 49-year-olds

This monitoring report demonstrated no evidence of an association between fluoridation and osteosarcoma in 0 to 49-year-olds on both binary and multi-categoric analysis, consistent with the majority of research to date.

A positive association between fluoride ingestion and osteosarcoma has been suggested, but remains an area of controversy as available evidence is limited in extent and validity[29]. Fluoride is taken up preferentially in bones, leading to the suggestion that effects on this tissue, including carcinogenesis, are biologically plausible.

A single animal study demonstrated some evidence of a dose-response association between fluoride ingestion and osteosarcoma in male rats at drinking water doses of 100mg/l and higher[88], whereas individual human case-control studies have produced conflicting results. In an exploratory analysis looking at age-specific rates Bassin et al (2006) demonstrated an association between fluoride ingestion and osteosarcoma in males only[35]. In their study the strongest association was at ages 6 to 8 years, the authors suggesting biological plausibility related to timing of a growth spurt. This study has however received criticism because of 'multiple limitations' in design, analysis and presentation of findings[27, 89], and a further study using biological samples from the same cases and controls did not show any association between biological measurements of bone fluoride and osteosarcoma[90]. In contrast Gelberg et al (1995) demonstrated no increased risk of osteosarcoma related to fluoride exposure, and demonstrated a negative association in males[91]. Further case-control studies have demonstrated no association between fluoridation and osteosarcoma [92-94].

The majority of previous ecological level research has not demonstrated any association between fluoridation and osteosarcoma incidence in: Ireland[95]; The US[96-98]; and international studies using multiple cancer registries[99]. One small study involving a total of 20 cases demonstrated an increased risk of osteosarcoma among males under 20 years of age in fluoridated versus non-fluoridated municipalities in New Jersey, but did not take into account potential confounding variables[100].

A recent ward-level ecological study using data from Great Britain population-based cancer registries (1980 to 2005) found no association between measured fluoride levels in drinking water (2004 to 2006) and osteosarcoma. The methodology in the study by Blakey et al (2014) was similar to that used in this monitoring report, using routine health statistics for indicators and confounding variables, and geographic information systems to match small areas to water supply zones[101].

The ecological nature of our report means the absence of an association does not provide definitive evidence for a lack of a relationship. However, this monitoring report is consistent with the majority of previous ecological level studies and the York report which concluded there was no clear association between fluoridation and osteosarcoma[30].

Limitations

Exposure description

Selection bias

As we have only been able to compare WSZs with stable identifiers over time, we are in effect selecting a sample of WSZs with durable identifiers across the time periods, which may have resulted in differential selection of zones with more/less stable fluoride concentrations. This would only impact on our results if WSZs with stable fluoride concentrations were differentially likely to change ownership (resulting in change in their unique identifier), which would seem unlikely. This is of most concern for unmatched WSZs from 1995 to 2004 zones, as 62% were not matched to 2005 to 2015 zones for comparison (whereas only 3% of 2005 to 2015 WSZs with data could not be used in this analysis as they could not be linked to map data). However, the median fluoride concentrations and fluoride sampling frequency were similar for both matched and un-matched 1995 to 2004 WSZs, giving more confidence in our findings.

Information bias

We analysed routine fluoride concentration monitoring data collated for water quality verification; the sampling method was not designed for the purposes of health monitoring, which brings limitations. Though sample points were randomly chosen or selected so as to be representative of the wider WSZ, precision (due to sampling frequency) and accuracy (due to the location of sampling and/or measurement methods used) are likely to have been less optimal than could be achieved from a survey designed specifically for research purposes. However, the long time periods of data collection and relatively uniform sampling procedures used will have negated

some of these concerns. Studies to validate the routine monitoring data could be considered.

The number of annual monitoring samples increased in 2005 to 2015 compared to 1995 to 2004 (to a median of 8 from a median of 1), indicating a change in the frequency of fluoride concentration monitoring. This or other changes which we have not measured may have introduced misclassification if this resulted in a change in precision of WSZ fluoride concentration estimation across the 2 time periods. When comparing fluoride concentrations in WSZs with and without a scheme between 1995 to 2004 and 2005 to 2015, we only excluded WSZs where disruption to fluoridation was detected by inconsistent flagging of fluoridated WSZs reported to DWI by water companies. This is likely to not take into account shorter term disruption, potentially weakening correlations across the time periods for fluoridated WSZs if disruption varied by time period.

Fluoride and health outcomes analysis

Biases resulting from exposure misclassification, and aggregation

There are recognised limitations of the ecological design used for this report. The estimates derived from our models may not reflect the risk at an individual level (the 'ecological fallacy'), but rather reflect the average risk of the population living in an area fluoridated to that degree. For example, the lower rate of bladder cancer in fluoridated areas cannot be taken, without further corroborating evidence from other study designs/methods, to mean a lower individual risk of bladder cancer with increased personal fluoride consumption.

Use of an ecological level, indirect estimate of exposure to fluoride and fluoridation of water supplies may result in misclassification of exposure. Our exposure assessment did not take into account individual consumption of fluoride from all sources. In addition to that measured in this report, personal intake of fluoride depends on levels of tap water consumption, dietary factors such as tea and soft drink consumption, and use of dentifrices (eg, toothpaste, mouthwash), and if these are not accounted for then exposure misclassification can result. As fluoride in water is only the dominant source at relatively high fluoride concentrations (>0.7mg/l), this misclassification is likely more important in the lower fluoride concentration ranges. Consequently, interpretation of differences in relative risk/odds between populations exposed to differing fluoride concentrations in the lower ranges (eg <0.2mg/l compared to <0.4mg/l) is more uncertain, particularly in the absence of a clear trend. There are other potential causes of exposure misclassification: although clear geographical demarcation of water quality zones is available, some residents of a non-fluoridated LSOA travel to work or attend school in a neighbouring fluoridated area and vice versa. Additionally, the exposure model used does not take into account duration of exposure to fluoride/fluoridation over

the life course (or effects of migration to and from fluoridated areas), or frequency of exposure.

The method used to allocate a fluoride concentration exposure to geographic units of analysis relied on determination of location of LSOAs within WSZs, using the population weighted centroid of the LSOA. This means that, for LSOAs on the edges of WSZs and that therefore are not wholly located within a single WSZ, some of the LSOA population will have their fluoride exposure misclassified. This is unlikely to introduce a large bias, as for many of these areas this would be the minority of the population, and neighbouring WSZs would likely have a similar fluoride concentration in any case. However, in LSOAs with dispersed populations, and where neighbouring WSZs have more strongly contrasting fluoride concentrations, more significant misclassification will result. Using even smaller areas (eg 'output areas') to allocate concentrations may have minimised this error, but would have been very time-consuming to perform for each year of exposure data available, an approach required to minimise another risk of misclassification from changing WSZ geographies over time. As such, the method used provided a reasonable balance of granularity of exposure for the resources available, but formal quantification of the resulting misclassification would be useful future research.

Our use of routine fluoride/fluoridation monitoring data to allocate exposure in this monitoring study may have resulted in bias. This is also discussed under the exposure description information bias section, above. Sub-optimal precision and accuracy of measurement of exposure to fluoride/fluoridation schemes may have resulted in misclassification. Additionally, there will be further misclassification of exposure where aggregation to larger geographic units of analysis was required to achieve better model fit. For health outcomes where a 'lag' period in exposure was likely we conducted sensitivity analyses to attempt to account for potential misclassification of exposure to fluoride in water supplies pre-2005 due to disruption of fluoridation schemes post-2005, which would have potentially resulted in uncertain earlier fluoride exposure. There was no change of significance to our results. However, the weak correlation between fluoride concentrations pre- and post-2005 in fluoridated areas, despite excluding WSZs with disrupted fluoridation, indicates we are likely to have misclassified exposure in other WSZs. This is only of significance for health outcomes with a 'lag' between exposure and outcome, ie osteosarcoma, bladder cancer and potentially also hip fracture. For these reasons, and those noted in the paragraphs above, a degree of exposure misclassification is inevitable, which may weaken or strengthen an apparent association in an ecological analysis[102].

Findings should not be extrapolated to ineligible populations (those receiving private water supplies).

Sampling error, non-sampling error, and selection bias

As we are using dental caries survey data, not data on the whole population, a difference between the sample estimate and true (unknown) population value is possible (due to chance when children are sampled), and is termed the 'sampling error'[(103)]. This is quantified by the standard error of the mean and cannot be corrected for. Deviation of the estimate from the true population value may also be due to systematic error, or 'non-sampling' error. This can be thought of as due to the survey methods and execution, and can include selection bias. An important selection bias from the sampling method could stem from only sampling mainstream schools, and the requirement for positive consent[20] – children attending private schools, who are home-schooled, or whose parents did not consent, will have been excluded. If caries prevalence and severity varies between the sampled and non-sampled this could introduce bias. However, this is less likely to be differential by fluoride concentration. Sampling and non-sampling error may affect the external validity (generalisability) of our findings. We cannot change the sample taken, but we examined the generalisability of our findings by tabulating the distribution of characteristics (eg proportion within IMD quintile, white ethnic group, fluoride concentration categories) of sampled children[21], and five-year-olds from all LSOAs, so as to compare the sample to the England average. This description showed the sampled group to be broadly representative of the five-year-old population of England.

For other outcomes, our study design does not utilise a sample, instead analysing outcome frequency in the whole of the eligible population, ruling out sampling error. Selection bias may still occur, however, if fluoride concentration data or covariate or outcome data availability is limited to certain populations/geographies/periods within the study population, though wide coverage of fluoride concentration data and covariate data were achieved. Outcome data is expected to be highly complete for data sources generated from disease registries or compulsory reporting systems (cancer and Down's syndrome outcome), and for payment based systems (HES for secondary care) where the outcome is reliably diagnosed and treated in that setting, resulting in a payment claim (hip fracture in secondary care). For kidney stones, which may not result in admission from accident and emergency/primary care, and for caries extraction, which may be performed in primary care, selection bias was possible. This was, however, less likely to occur dependent on fluoride concentration. Another possible selection bias could have resulted from differential access to healthcare services and opportunity for diagnosis ('diagnostic access bias')[(104)]. However, because the NHS offers a universal and comprehensive healthcare system to the whole population, a

[20] Written parental consent was required for children to be examined in the survey
[21] See table 9

significant impact was less likely, though variations in access and/or uptake for Down's syndrome screening may have affected our results.

Information bias

Routine data used for several outcomes in this study, particularly HES data, can be of poor completeness, accuracy and timeliness. However, there is little reason to suspect these factors would differ by fluoridation exposure, therefore the most likely outcome would be non-differential error obscuring the exposure outcome relationship.

Residual and unmeasured confounding

Associations between environmental exposures and non-communicable disease outcomes are typically of low strength and easily obscured by confounding factors. Despite attempting to control for these factors, these will be measured at the ecological level and several important factors will not be measured at all (eg high sugar intake, access to primary dental care for dental caries). This means we may not have adequately controlled for all important confounders, resulting in residual or unadjusted confounding. This may result in either under- or over-estimation of any exposure outcome associations. We used the index of multiple deprivation 2015 to adjust for differences in socioeconomic status, because, as detailed in the methods section, socioeconomic status has been demonstrated to correlate well with potential confounders for which we did not have data available for use in our models. However, as an area-level composite indicator, this may not always accurately reflect individual-level socioeconomic status, nor all the facets of socioeconomic status that are most important for our health outcomes. Data used to construct IMD 2015 scores were collected in 2012 to 2013. There may be a concern that data gathered in 2012 to 2013 was not representative of the various exposure periods of interest used in this report, but temporal comparisons have shown area-based deprivation is relatively consistent between versions of the IMD[105, 106].

Conclusion and recommendations for future monitoring and research

Conclusion

The findings of this 2018 monitoring report are consistent with the view that water fluoridation is an effective and safe public health measure to reduce the prevalence and severity of dental caries, and reduce dental health inequalities.

The methods described in this report have provided a more detailed description of population exposure to fluoride in public water supplies than in the 2014 report, and consequently a more in-depth examination of the association between fluoridation and health outcomes.

The more comprehensive analyses used in this report allow us to demonstrate the benefits of fluoridation in more detail: the reduction in caries prevalence and severity is significant and most clearly so in more deprived areas, contributing to a reduction in dental health inequalities. The effect of fluoridation on admission for dental extraction was substantial and there was some evidence of a difference by deprivation status. The absolute number of admissions in children and young people aged 0 to 19 years were most reduced in the most deprived areas, due to their greater baseline risk. The nature of water fluoridation is such that the whole population receiving the water supply is able to benefit without the need for individuals to change their behaviour or comply with advice of healthcare professionals, thereby contributing to the narrowing of dental health inequalities.

We have also been able to explore associations with potential adverse health effects in more detail: despite statistical evidence of associations between exposure to fluoridation and certain health effects in this report, the overall analysis and weight of evidence means causal associations are unlikely.

The ecological design of this report has some limitations. We can estimate the potential exposure to fluoride in water using the concentration as a proxy, but we do not know how much people drink or whether they have other sources of fluoride. Additionally, the adjustment for factors other than fluoride/fluoridation that may influence the health outcomes studied can only be done on the basis of area averages, which may incompletely adjust for these factors. Therefore, this report alone does not allow conclusions to be drawn regarding any causative or protective role of fluoride; similarly, the absence of any associations does not provide definitive evidence for a lack of a relationship. This is particularly the case for non-dental health outcomes, where the weight of wider epidemiological evidence for a causal relationship at drinking water

fluoride concentrations typical of those in England, and toxicological evidence for a biological mechanism of action, is generally much more limited. It may be beneficial to further evaluate outcomes in other populations, with contrasting fluoride levels, and alternative study designs, to assess if these findings can be replicated.

Recommendations for future monitoring and research

PHE continues to keep the evidence base under review and we will consult with local authorities prior to publication of a further report within the next 4 years.

Future monitoring reports may consider a more in-depth survey of drinking water fluoride concentrations to validate the routine fluoride concentration monitoring data. Use of alternative methods to allocate fluoride concentration exposures to geographic units of analysis (eg using an even smaller area approach than LSOAs) could also be compared to quantify possible misclassification, and to select optimal methods, given the resources available. More sophisticated statistical modelling techniques should also be considered, such as statistical models to perform analyses at smaller geographies, improving exposure classification, and more sophisticated dose-response modelling, taking fluoride concentration as a continuous variable. Alternative study designs and data sources may allow studies using individual level data with better adjustment for potential confounding variables. Lack of quality routine datasets on some health outcomes has limited the choice of outcomes to monitor. The working group may consider using the fluoride exposure dataset in conjunction with research databases with data on participants in England, eg from primary care or the UK Biobank, or in collaboration with cohort studies with participants in England to address these outcomes. PHE, with direction from the working group, is exploring whether primary care datasets can be used to investigate a potential relationship between fluoride concentration and hypothyroidism.

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Appendix

A1. Characteristics of the different geographic units of analysis used in this report

Table A1. Characteristics of geographic units of analysis[107]

Unit of analysis	Acronym	Number in England	Average population 2011
Lower layer Super Output Area 2011	LSOA	32,844	1614
Middle layer Super Output Area 2011	MSOA	6791	7806
Lower Tier Local Authority*	LTLA	326	162,615

*Also known as local authority district

A2. Confounder data details and sources

Table A2. Confounders for potential inclusion in multivariable models, geographic level of availability, and data source.

Outcome	Confounders for potential inclusion	Age bands (years) for adjustment	Geographic level	Source
Dental Caries prevalence	<u>For all dental outcomes:</u> Deprivation†, ethnicity	NA all same age	LSOA	Ethnicity: Census 2011, Deprivation: IMD2015
Dental caries extractions	Age†, gender, ethnicity, deprivation†	0-4, 5-9, 10-14, 15-19	MSOA	Age and gender: ONS Mid-year person estimate (MYPE)

Non-dental, non-cancer Down's syndrome	Maternal age†	<25, 25-29, 30-31, 32-33, 34-35, 36-37, 38-39, 40-41, 42years+	LTLA	ONS live births
Kidney stone	Age†, gender†, deprivation, ethnicity	0-24, 25-49, 50+	MSOA	<u>For both kidney stone and hip fracture</u> Age & Sex: ONS MYPE, Ethnicity: Census 2011, Deprivation: IMD 2015
Hip fracture	Gender† will be stratified, so adjust for age† and deprivation, ethnicity	0-49, 50-64, 65-79, 80years +	MSOA	
Cancer outcomes Bladder carcinoma	<u>For all cancer outcomes:</u> Age†, gender†, deprivation, ethnicity	0-64, 65-79, 80+	MSOA	As above
Primary osteosarcoma (<50years)		0-24, 25-49	LTLA	

†Variables to be kept in multivariable regardless of Wald testing for improved model fit

A3. Fluoridation status of local authorities

Local authorities where some of the population receive a water supply with adjusted fluoride levels.

Upper-tier local authorities include unitary authority councils, county councils, metropolitan borough councils, London borough councils, City of London and Isles of Scilly.

Lower-tier local authorities include non-metropolitan district councils, unitary authority councils, metropolitan borough councils, London borough councils, City of London and Isles of Scilly.

County and unitary "ever Fluoridated" during 2005-2015 for report purposes
Bedford Borough Council See notes
Birmingham City Council Yes
Cambridgeshire County Council No
Central Bedfordshire Council No
Cheshire East Council No
Cheshire West and Chester Council No
County Durham Council No
Coventry City Council Yes
Cumbria County Council No
Derbyshire County Council No
Dudley Metropolitan Borough Council Yes
Gateshead Council Yes
Leicestershire County Council No
Lincolnshire County Council Yes
Newcastle-upon-Tyne City Council Yes
North East Lincolnshire Council No
North Lincolnshire Council Yes
North Tyneside Council Yes
Northumberland County Council No
Nottinghamshire County Council No
Sandwell Metropolitan Borough Council Yes
Shropshire Council No
Solihull Metropolitan Borough Council Yes
Staffordshire County Council Yes
Walsall Metropolitan Borough Council Yes
Warwickshire County Council Yes
Wolverhampton City Council Yes
Worcestershire County Council No

District and borough	
Allerdale Borough Council	Yes
Ashfield District Council	Yes
Bassetlaw District Council	Yes
Bolsover District Council	Yes
Bromsgrove District Council	Yes
Cannock Chase District Council	Yes
Copeland Borough Council	Yes
Derbyshire Dales District Council	No
East Staffordshire Borough Council	Yes
Huntingdonshire District Council	No
Lichfield Borough Council	Yes
Lincoln City Council	Yes
Mansfield District Council	Yes
North Kesteven District Council	Yes
North Warwickshire Borough Council	Yes
North West Leicestershire District Council	No
Nuneaton and Bedworth Borough Council	Yes
Redditch District Council	Yes
Rugby Borough Council	Yes
South Derbyshire District Council	No
South Kesteven District Council	Yes
South Staffordshire Council	Yes
Stratford on Avon District Council	Yes
Tamworth Borough Council	Yes
Warwick District Council	Yes
West Lindsey District Council	Yes
Wychavon District Council	Yes
Wyre Forest District Council	No

Notes: Fluoridation status by local authority was only relevant for a limited number of indicators where data were not analysed at LSOA or MSOA level. Due to prolonged fluoride plant non-operation in certain water supply zones, meaning very limited/no fluoridation took place during the exposure period, Bedford Borough was regarded as un-fluoridated for the 2011-2014 Down's syndrome outcome analysis, but was considered fluoridated for the osteosarcoma outcome analysis.

A4. Water supply zones with significant disruption to operations

Table A4. Water supply zones with significant disruption to operations, England 2006 to 2015.

Zone code	Region	Years affected
ANGZMW23	Bedford Rural	2009-2015
ANGZMW25	Bedford Urban South	2009-2015
ANGZMW26	Bedford Urban Central	2009-2015
UUTZ031	Ennerdale North	2012-13
UUTZ032	Ennerdale South	2012-13
UUTZ028	Crummock	2007-13
UUTZ029	Crummock South	2007-9

Please see 'exposure indicator descriptive analysis', and 'data management' in methods section, for more information page for the reason why these data were collated

A5. Dental caries survey generalised ordinal logistic regression multivariable analysis results, stratified by quintile of index of multiple deprivation

Group 1 – Adjusted odds of being in average number of teeth with $d_3$mft group 'low', 'medium' or 'high' vs 'none'

Deprivation Quintile	Fluoride concentration	Odds*	95% CI	p for trend
1 (least deprived)	<0.1mg/l	0.76	0.67-0.84	0.155
	0.1-<0.2mg/l	0.77	0.70-0.84	
	0.2-<0.4mg/l	0.89	0.77-1.01	
	0.4-<0.7mg/l	1.07	0.70-1.43	
	≥0.7mg/l	0.76	0.61-0.91	
2	<0.1mg/l	1.03	0.93-1.14	0.337
	0.1-<0.2mg/l	1.01	0.91-1.10	
	0.2-<0.4mg/l	1.10	0.95-1.25	
	0.4-<0.7mg/l	1.11	0.80-1.42	
	≥0.7mg/l	0.82	0.66-0.98	
3	<0.1mg/l	1.21	1.09-1.33	0.311
	0.1-<0.2mg/l	1.21	1.10-1.32	
	0.2-<0.4mg/l	1.25	1.07-1.44	
	0.4-<0.7mg/l	1.28	0.93-1.63	
	≥0.7mg/l	1.07	0.87-1.28	
4	<0.1mg/l	1.56	1.40-1.72	0.626
	0.1-<0.2mg/l	1.69	1.53-1.85	
	0.2-<0.4mg/l	1.37	1.17-1.57	
	0.4-<0.7mg/l	1.80	1.31-2.29	
	≥0.7mg/l	1.54	1.25-1.84	
5 (most deprived)	<0.1mg/l	2.51	2.27-2.74	0.340
	0.1-<0.2mg/l	2.28	2.01-2.56	
	0.2-<0.4mg/l	2.25	1.85-2.64	
	0.4-<0.7mg/l	4.01	2.78-5.24	
	≥0.7mg/l	2.51	2.05-2.97	

*Adjusted for ethnicity

Group 2 – Adjusted odds of being in average number of teeth with $d_3$mft group 'medium' or 'high' versus 'low' or 'none'

Deprivation Quintile	Fluoride concentration	Odds*	95% CI	p for trend
1 (least deprived)	<0.1mg/l	0.30	0.26-0.34	0.036
	0.1-<0.2mg/l	0.31	0.27-0.34	
	0.2-<0.4mg/l	0.32	0.27-0.37	
	0.4-<0.7mg/l	0.32	0.19-0.45	
	≥0.7mg/l	0.20	0.15-0.26	
2	<0.1mg/l	0.43	0.38-0.48	<0.001
	0.1-<0.2mg/l	0.44	0.39-0.49	
	0.2-<0.4mg/l	0.42	0.35-0.48	
	0.4-<0.7mg/l	0.34	0.23-0.46	
	≥0.7mg/l	0.28	0.21-0.35	
3	<0.1mg/l	0.60	0.54-0.66	<0.001
	0.1-<0.2mg/l	0.56	0.51-0.61	
	0.2-<0.4mg/l	0.57	0.48-0.65	
	0.4-<0.7mg/l	0.49	0.35-0.64	
	≥0.7mg/l	0.30	0.23-0.38	
4	<0.1mg/l	0.85	0.77-0.94	<0.001
	0.1-<0.2mg/l	0.81	0.74-0.88	
	0.2-<0.4mg/l	0.69	0.59-0.79	
	0.4-<0.7mg/l	0.90	0.66-1.14	
	≥0.7mg/l	0.55	0.44-0.66	
5 (most deprived)	<0.1mg/l	1.64	1.49-1.78	<0.001
	0.1-<0.2mg/l	1.14	1.01-1.27	
	0.2-<0.4mg/l	1.26	1.06-1.47	
	0.4-<0.7mg/l	1.49	1.12-1.86	
	≥0.7mg/l	0.84	0.70-0.98	

*Adjusted for ethnicity

Group 3 – Adjusted odds of being in average number of teeth with $d_3$mft group 'high' versus 'none', 'low' or 'medium'

Deprivation Quintile	Fluoride concentration	Odds*	95% CI	p for trend
1 (least deprived)	<0.1mg/l	0.10	0.08-0.12	0.003
	0.1-<0.2mg/l	0.10	0.08-0.11	
	0.2-<0.4mg/l	0.09	0.07-0.11	
	0.4-<0.7mg/l	0.13	0.06-0.21	
	≥0.7mg/l	0.08	0.05-0.11	
2	<0.1mg/l	0.15	0.13-0.18	<0.001
	0.1-<0.2mg/l	0.16	0.14-0.18	
	0.2-<0.4mg/l	0.11	0.09-0.14	
	0.4-<0.7mg/l	0.08	0.04-0.13	
	≥0.7mg/l	0.08	0.05-0.11	
3	<0.1mg/l	0.21	0.18-0.24	<0.001
	0.1-<0.2mg/l	0.21	0.18-0.24	
	0.2-<0.4mg/l	0.21	0.17-0.25	
	0.4-<0.7mg/l	0.13	0.07-0.19	
	≥0.7mg/l	0.09	0.05-0.12	
4	<0.1mg/l	0.34	0.30-0.38	<0.001
	0.1-<0.2mg/l	0.28	0.25-0.31	
	0.2-<0.4mg/l	0.26	0.21-0.30	
	0.4-<0.7mg/l	0.34	0.24-0.45	
	≥0.7mg/l	0.17	0.13-0.22	
5 (most deprived)	<0.1mg/l	0.71	0.65-0.77	<0.001
	0.1-<0.2mg/l	0.37	0.32-0.41	
	0.2-<0.4mg/l	0.46	0.38-0.54	
	0.4-<0.7mg/l	0.51	0.38-0.65	
	≥0.7mg/l	0.18	0.14-0.22	

*Adjusted for ethnicity

A6. Sensitivity analyses for analyses of hip fracture, bladder cancer, and osteosarcoma

Hip fracture

Table A6i. Crude rate ratio of hip fracture admission, by period mean fluoride concentration (mg/l), England* 2007 to 2015

Fluoride concentration (mg/l)	Crude IRR (95% CI)†	p value
<0.1mg/l	Reference	
0.1-<0.2mg/l	0.81 (0.75-0.87)	<0.001
0.2-<0.4mg/l	0.97 (0.91-1.03)	0.287
0.4-<0.7mg/l	1.02 (0.93-1.13)	0.629
≥0.7mg/l	0.98 (0.89-1.07)	0.597

**Excluding MSOAs with significant disruption to fluoridation during 2005 to 2015; IRR – incidence rate ratio; † Cluster robust standard errors derived by clustering on 325 local authority districts.*

Table A6ii. Sex-stratified age-specific adjusted rate ratio of hip fracture admission, by period mean fluoride concentration (mg/l), England* 2007 to 2015.

Age band (years)	Fluoride concentration (mg/l)	Adjusted IRR Females (95% CI) ǂ†	p value	P for trend	Adjusted IRR Males (95% CI) ǂ†	P value	P for trend
0-49	<0.1mg/l	Reference	-	0.017	Reference	-	<0.001
	0.1-<0.2mg/l	0.82 (0.76-0.89)	<0.001		0.86 (0.81-0.92)	<0.001	
	0.2-<0.4mg/l	0.87 (0.79-0.96)	0.004		0.87 (0.81-0.94)	<0.001	
	0.4-<0.7mg/l	0.96 (0.81-1.14)	0.645		0.89 (0.81-0.99)	0.035	
	≥0.7mg/l	0.87 (0.78-0.98)	0.019		0.89 (0.83-0.95)	0.001	
50-64	<0.1mg/l	Reference	-	0.785	Reference	-	0.449
	0.1-<0.2mg/l	0.92 (0.88-0.97)	0.001		0.95 (0.89-1.00)	0.063	
	0.2-<0.4mg/l	0.95 (0.90-1.00)	0.072		0.89 (0.84-0.96)	0.001	
	0.4-<0.7mg/l	0.96 (0.88-1.04)	0.274		0.91 (0.82-1.01)	0.075	
	≥0.7mg/l	1.04 (0.96-1.12)	0.360		1.00 (0.89-1.13)	0.979	
65-79	<0.1mg/l	Reference	-	0.010	Reference	-	0.241
	0.1-<0.2mg/l	0.97 (0.95-1.00)	0.035		1.01 (0.97-1.04)	0.789	
	0.2-<0.4mg/l	1.01 (0.98-1.04)	0.464		0.98 (0.94-1.02)	0.295	
	0.4-<0.7mg/l	1.00 (0.96-1.04)	0.890		0.93 (0.89-0.98)	0.005	
	≥0.7mg/l	1.06 (1.03-1.10)	0.002		1.08 (1.02-1.14)	0.009	
≥80	<0.1mg/l	Reference	-	<0.001	Reference	-	0.021
	0.1-<0.2mg/l	1.03 (1.01-1.05)	0.006		1.03 (1.00-1.07)	0.029	
	0.2-<0.4mg/l	1.03 (1.01-1.06)	0.001		1.05 (1.02-1.08)	0.001	
	0.4-<0.7mg/l	1.04 (1.01-1.07)	0.019		1.06 (1.02-1.10)	0.005	
	≥0.7mg/l	1.05 (1.02-1.09)	0.001		1.05 (0.99-1.12)	0.079	

**Excluding MSOAs with significant disruption to fluoridation during 2005 to 2015; IRR – incidence rate ratio; ǂAdjusted for deprivation status and ethnicity; † Cluster robust standard errors derived by clustering on 325 local authority districts.*

Table A6iii. Crude and adjusted rate ratios of hip fracture admission, by period fluoridation status (mg/l), England* 2007 to 2015.

Gender stratification	Fluoridation status**	Crude IRR (95% CI)†	Adjusted IRR (95% CI) †‡	P value
Males	No	Reference	Reference	-
	Yes	1.08 (1.02-1.15)	1.03 (1.00-1.05)	0.024
Females	No	Reference	Reference	-
	Yes	1.07 (0.98-1.17)	1.04 (1.01-1.06)	0.001

**Excluding MSOAs with significant disruption to fluoridation during 2005 to 2015; IRR – incidence rate ratio; † Cluster robust standard errors derived by clustering on 292 local authority districts; ‡Adjusted for age, gender, ethnicity, deprivation status; **Yes=fluoride concentration≥0.2mg/l AND in water supply zone with fluoridation scheme during 2005 to 2015, in 799 MSOAs with 55.8 million person years of observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 4889 MSOAs with 343.7 million person years of observation.*

Bladder cancer

Table A6iv. Crude and adjusted rate ratios of bladder cancer, by period mean fluoride concentration (mg/l), England* 2007 to 2015.

Fluoride concentration (mg/l)	Crude IRR (95% CI)†	Adjusted IRR (95% CI) †‡	P value	P trend
<0.1mg/l	Reference	Reference	-	0.026
0.1-<0.2mg/l	0.81 (0.76-0.86)	0.99 (0.96-1.02)	0.440	
0.2-<0.4mg/l	0.96 (0.90-1.01)	1.00 (0.97-1.03)	0.870	
0.4-<0.7mg/l	1.02 (0.91-1.15)	1.00 (0.95-1.05)	0.903	
≥0.7mg/l	0.87 (0.78-0.97)	0.93 (0.88-0.98)	0.004	

**Excluding MSOAs with significant disruption to fluoridation during 2005 to 2015; IRR – incidence rate ratio; † Cluster robust standard errors derived by clustering on 325 local authority districts; ‡Adjusted for age, gender, ethnicity, deprivation status.*

Table A6v. Crude and adjusted rate ratios of bladder cancer diagnosis, by period fluoridation status (mg/l), England* 2000 to 2015.

Fluoridation status**	Crude IRR (95% CI)†	Adjusted IRR (95% CI) †‡	P value
No	Reference	Reference	-
Yes	0.96 (0.87-1.06)	0.93 (0.89-0.97)	0.002

**Excluding MSOAs with significant disruption to fluoridation during 2005 to 2015; IRR – incidence rate ratio; † Cluster robust standard errors derived by clustering on 292 local authority districts; ‡Adjusted for age, gender, ethnicity, deprivation status; **Yes=fluoride concentration≥0.2mg/l AND in water supply zone with fluoridation scheme during 2005 to 2015, in 799 MSOAs with 97 million person years of*

observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 4887 MSOAs with 595 million person years of observation.

Osteosarcoma

Table A6vi. Crude and adjusted rate ratios of osteosarcoma in 0-49 year olds, by period mean fluoride concentration (mg/l), England* 1995 to 2015.

Fluoride concentration (mg/l)	Crude IRR (95% CI)	Adjusted IRR (95% CI) ‡	P value	P trend
<0.1mg/l	Reference	Reference	-	0.623
0.1-<0.2mg/l	1.01 (0.91-1.13)	1.04 (0.93-1.15)	0.511	
0.2-<0.4mg/l	0.98 (0.85-1.12)	0.99 (0.86-1.13)	0.857	
0.4-<0.7mg/l	1.17 (0.95-1.43)	1.18 (0.96-1.44)	0.115	
≥0.7mg/l	0.91 (0.76-1.08)	0.90 (0.75-1.07)	0.228	

**LTLAs with significant disruption to fluoridation operations excluded; IRR – incidence rate ratio; ‡ Adjusted for age and gender*

Table A6vii. Crude and adjusted rate ratios of osteosarcoma in 0-49 year olds, by period fluoridation status (mg/l), England* 1995 to 2015.

Fluoridation status**	Crude IRR (95% CI)	Adjusted IRR (95% CI) ‡	P value
No	Reference	Reference	-
Yes	0.99 (0.85-1.14)	0.97 (0.83-1.12)	0.652

**Allerdale, Bedfordshire, and Copeland excluded; IRR – incidence rate ratio; ‡Adjusted for age and gender; **Yes=fluoride concentration≥0.2mg/l AND in water supply zone with fluoridation scheme during 2005 to 2015, in 31 LTLAs with 75.9 million person years of observation. No= fluoride concentration <0.2mg/l, fluoride from any source, in 222 LTLAs with 496.9million person years of observation.*