Water fluoridation
Health monitoring report for England 2014
About Public Health England

Public Health England’s mission is to protect and improve the nation’s health and to address inequalities through working with national and local government, the NHS, industry and the voluntary and community sector. PHE is an operationally autonomous executive agency of the Department of Health.

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Executive summary

Background

Dental caries (tooth decay) is a significant public health problem in England. Sizeable inequalities in the incidence of caries exist between affluent and deprived communities, and it is a common cause of hospital admissions in children.

Fluoride is a naturally occurring mineral found in water in varying amounts. It is also present in some food. During the early twentieth century, lower levels of tooth decay were found to be associated with certain fluoride levels in drinking water. This observation led ultimately to water fluoridation schemes, which adjust levels of the mineral in community water supplies in an effort to reduce tooth decay.

In some parts of England the level of fluoride in the public water supply has been adjusted to one mg per litre (one part per million). Currently, around six million people live in areas with fluoridation schemes. Many schemes have been operating for over 40 years.

Public Health England monitoring role

PHE, on behalf of the secretary of state for health, is required by legislation to monitor the effects of water fluoridation schemes on the health of people living in the areas covered, and to produce reports at no greater than four-yearly intervals. This report fulfils this requirement and will be used as part of an ongoing dialogue with local authorities prior to publication of a further report within the next four years. This executive summary refers to areas with adjusted fluoride levels as ‘fluoridated’.

The report looks at indicators of health in people in fluoridated and non-fluoridated areas. Key findings are:

Dental health indicators

Dental health of five-year olds

On average, five-year olds in fluoridated areas are 15% less likely to have had tooth decay than those in non-fluoridated areas.

When deprivation and ethnicity (important factors for dental health) are taken into account, five-year olds in fluoridated areas are 28% less likely to have had tooth decay than those in non-fluoridated areas.

[Note: The above calculations are odds ratios. The chances of a child not having had tooth decay are calculated for fluoridated areas, and then for non-fluoridated areas. A comparison of their respective odds is then made. Statistically, this way of describing the relationship between the two sets of children is clearer and more accurate than the form of words originally used in this executive summary]
Dental health of 12-year olds
On average, 12-year olds in fluoridated areas are 11% less likely to have had tooth decay than those in non-fluoridated areas.

When deprivation and ethnicity are into account, 12-year olds in fluoridated areas are 21% less likely to have had tooth decay than those in non-fluoridated areas.

Impact of dental health inequalities
The reduction in tooth decay in children of both ages in fluoridated areas appears greatest among those living in the most deprived local authorities.

Hospital admissions of children aged one to four
In fluoridated areas there are 45% fewer hospital admissions of children aged one to four for dental caries (mostly for extraction of decayed teeth under a general anaesthetic) than in non-fluoridated areas.

Dental fluorosis (mottles or flecks on teeth caused by fluoride)
A previous study of fluoridated Newcastle upon Tyne and non-fluoridated Manchester found that the number of 12-year old children with moderate dental fluorosis or more (fluorosis score of TF4 and above) is very low, at around 1% in Newcastle and 0.2% in Manchester.

Children in fluoridated Newcastle upon Tyne are more likely than those in non-fluoridated Manchester to develop fluorosis of any level. However, children in fluoridated Newcastle have less tooth decay than those in non-fluoridated Manchester.

Non dental health indicators
In comparing a range of selected health indicators in fluoridated and non-fluoridated areas, statistical adjustments were made to take account of population differences in age, gender, deprivation and ethnicity.

Hip fractures
There was no evidence of a difference in the rate of hip fractures between fluoridated and non-fluoridated areas.

Kidney stones
There was evidence that the rate of kidney stones was lower in fluoridated areas than non-fluoridated areas.

All-cause mortality
While there was some evidence that the rate of deaths from all recorded causes was lower in fluoridated areas than non-fluoridated areas, the size of the effect was small.
**Down’s syndrome**
There was no evidence of a difference in the rate of Down’s syndrome in fluoridated and non-fluoridated areas.

**Bladder cancer**
There was evidence that the rate of bladder cancer was lower in fluoridated areas than non-fluoridated areas.

**Osteosarcoma (a form of bone cancer) among under 25-year olds**
There was no evidence of a difference in the rate of osteosarcoma between fluoridated and non-fluoridated areas.

**Osteosarcoma (a form of bone cancer) among people aged 50 and over**
There was no evidence of a difference in the rate of osteosarcoma between fluoridated and non-fluoridated areas.

**All cancer**
There was no evidence of a difference in the rate for all types of cancer between fluoridated and non-fluoridated areas.

**Conclusion**
The report provides further reassurance that water fluoridation is a safe and effective public health measure. PHE continues to keep the evidence base under review and will use this report as part of an ongoing dialogue with local authorities before publishing a further report within the next four years.
1 Preface

Public Health England (PHE), on behalf of the secretary of state for health, 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 fulfils this requirement and will be used as part of an ongoing dialogue with local authorities, prior to publication of a further report within the next four years.

2 Background

2.1 Water fluoridation schemes

Tooth decay, also known as dental decay or dental caries, is a disease that affects people at all life stages and affects both primary (baby) and permanent (adult) teeth. Dental caries occurs when oral bacteria produce acids that demineralise the tooth surface, allowing the bacteria to progressively invade the tooth. Eating and drinking sugary food and drink fuels acid formation by oral bacteria.

While symptom-free in the early stages, if unchecked, dental decay can damage the tooth structurally and cause pain and sepsis. Treatment usually involves the restoration (repair) of the affected tooth, but, if decay is extensive, treatment may involve the extraction of the tooth. Restoration typically involves the removal of infected tooth tissue and its replacement with some material, ranging from cements, resins or dental amalgam to crowns. Treated teeth are at increased risk of future failure and re-treatment is commonplace, as is loss of the tooth when it can no longer be restored.

Dental caries is a significant public health problem internationally and, despite reductions in prevalence since the 1970s, remains so in England. Sizeable inequalities still exist between affluent and deprived communities and dental caries is one of the most common causes of hospital admission in children.

Fluoride is a naturally occurring mineral found in water in varying amounts. It is also present in certain foods. In the early 20th century, lower levels of tooth decay were found to be associated with certain fluoride levels in drinking water. This observation ultimately led to the introduction of water fluoridation schemes to adjust fluoride levels in community water supplies, in an effort to reduce levels of decay 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, in many instances, on intervention by dental professionals.

The first water fluoridation scheme was introduced in the USA in 1945, in the city of Grand Rapids, Michigan and there is now extensive coverage of the USA 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 six million people across 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 Humber.

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 water companies are regulated by the Drinking Water Inspectorate and operate according to codes of practice. Water fluoridation schemes aim to achieve a level of one part of fluoride per million parts of water (1ppm or 1mg of fluoride per litre of water). The maximum amount of fluoride permitted in drinking water is 1.5 mg fluoride per litre of water.

Some water supplies in England, serving around a third of a million people, naturally contain levels of fluoride close to those which fluoridation schemes seek to achieve. Water companies publish details of the levels of fluoride in their supplies and this information is normally available on their websites.

2.2 Monitoring the health effects of fluoridation schemes

Section 90A of the Water Industry Act 1991 requires a “relevant authority” which 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 and publish 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 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 which had effect immediately prior to 1 April 2013. In practice, the secretary of state's fluoridation functions are exercised by PHE.

On the basis that all current water fluoridation schemes in England were in operation immediately prior to the "appointed day" for the purposes of the legislation, section 90A requires the publication of the first report on these arrangements by 25 March 2014. Subsequent reports are required at no greater than four-yearly intervals, beginning with the date on which the last report was published, unless the scheme in question is terminated.

This report, produced by PHE, is designed to satisfy these requirements with respect to the current water fluoridation schemes in England.
2.3 Selection of health indicators

There are two evidence-based dental effects of fluoridation: on levels of dental decay and on levels of dental fluorosis. This report therefore considers levels of dental decay and of dental fluorosis in fluoridated and non-fluoridated parts of the population.

The selection of indicators for possible non-dental effects is more complex. People in some parts of England have been exposed for generations to levels of naturally-occurring fluoride which are the same as or close to levels achieved by fluoridation schemes. These schemes in England have been in existence for almost fifty years and now cover some six million people. Over 200 million people in the USA have a fluoridated drinking water supply. However, no adverse health effects have been proven from water fluoridation schemes. The range of health conditions which 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 a particular allegation.

Given those considerations, and the fact that the monitoring programme is not and cannot be a programme of research, PHE has decided that the content of this first report should be proportionate to the theoretical risk of harm to health and should reflect the practicalities of the availability of data of acceptable quality. PHE is committed to keeping the evidence base for fluoridation under review, and will be consulting with local authorities before determining the content of the subsequent health monitoring report due within a further four years.

The possible effects of fluoride in water have been extensively studied and reviewed over the last 50 years. In the UK the most recent review was undertaken by the NHS Centre for Reviews and Dissemination based at the University of York and published in 2000. The Medical Research Council subsequently, in 2002, reported to the Department of Health its advice on future research priorities. The US National Research Council reported in 2006 and the Australian National Health and Medical Research Council reported in 2007.

PHE has drawn on these authoritative sources in selecting a number of indicators of health conditions for inclusion in this first monitoring report. The chosen indicators of various health conditions have been selected based on the evidence base, theoretical plausibility, potential impact on population health, the quality and availability of data, and the validity of the indicator. 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.
### Table 1. Selected indicators for fluoride health effects monitoring programme

<table>
<thead>
<tr>
<th>Condition</th>
<th>Indicator selected following assessment of the evidence base</th>
<th>Rationale for inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental caries</td>
<td>Decayed, missing and filled teeth (d3mft/D3MFT)</td>
<td>Evidence of reduction in dental caries in areas where water fluoride levels are adjusted to 1ppm</td>
</tr>
<tr>
<td>Dental fluorosis</td>
<td>TF score</td>
<td>Evidence for dental fluorosis associated with fluoride intake</td>
</tr>
<tr>
<td>Bone health</td>
<td>Hip fracture</td>
<td>Water fluoridation can increase normal dietary intake of fluoride by some 50% and about half of the fluoride ingested is taken up by bone with possible implications for its mechanical properties. An effect of fluoridation on the risk of fracture, adverse or beneficial is theoretically plausible. Hip fracture is a common and serious condition. The MRC report (2002) 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.</td>
</tr>
<tr>
<td>Renal effects</td>
<td>Incidence of kidney stones</td>
<td>Most ingested fluoride is excreted via the kidney, which is therefore exposed to relatively high fluoride concentrations</td>
</tr>
<tr>
<td>Mortality</td>
<td>All causes</td>
<td>Catch-all measurement</td>
</tr>
<tr>
<td>Birth defects</td>
<td>Incidence of Down’s syndrome</td>
<td>As fluoride can cross the placenta, the possibility of fluoride having a cytogenetic effect on the developing foetus is theoretically plausible. The York Review (2000) and the MRC report (2002) concluded that the evidence for the association between water fluoride level and the incidence of Down’s syndrome was insufficient and inconclusive.</td>
</tr>
<tr>
<td>Cancer</td>
<td>Bladder cancer incidence</td>
<td>Theoretical plausibility arises because fluoride is excreted in the urine and the bladder lining is therefore exposed to relatively high concentrations</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma incidence in those aged &lt;25 years and those aged ≥50 years</td>
<td>Theoretical plausibility arises from deposition of fluoride in bone and a mitogenic effect on osteoblasts</td>
</tr>
<tr>
<td></td>
<td>Overall cancer incidence rate</td>
<td>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.</td>
</tr>
</tbody>
</table>
3 Aims and objectives

3.1 Aims
The overall aim of this report is to monitor the health effects of water fluoridation arrangements through the use of observational data to compare rates of selected indicators in fluoridated versus non-fluoridated areas in England. Areas supplied by water with adjusted fluoride levels are referred to as “fluoridated” and those that are not as “non-fluoridated” for the purposes of this report. “Naturally fluoridated” refers to areas naturally fluoridated to a level close to that hoped to be achieved by fluoridation schemes.

3.2 Specific objectives
To compare the rates of the dental and non-dental health indicators listed in table 2 among residents of fluoridated versus non-fluoridated areas of England.

4 Methods

4.1 Assessment of fluoridation status
Ecological level exposure to fluoridated water was estimated at lower super output area (LSOA), lower tier and upper tier (see appendix) local authority level. The term ecological in this context refers to the assessment of exposure at an area rather than individual level.

4.1.1 LSOA level exposure
The Drinking Water Inspectorate provided the boundaries of all English water quality zones (WQZs) in digital format with a binary variable attached indicating whether they were subject to fluoridation schemes in 2012. Using ESRI ArcGIS geographic information systems (GIS), the population weighted centroid for each 2001 LSOA in England was assigned a fluoridation status – fluoridated yes/no – depending on the WQZ it was located within; LSOAs identified as being located within WQZs naturally fluoridated to a level of 1ppm were given a separate classification.

4.1.2 Local authority level
Lower tier local authorities were considered fluoridated if more than 50% of their component LSOAs were situated within a fluoridated WQZ. Prior knowledge of local authorities included in fluoridation schemes was validated by overlaying local authority boundaries onto WQZs using GIS and inspecting the proportion of their component LSOAs within fluoridated areas. Using data on the proportion of the population covered at lower-tier local authority level, a fluoridation status was assigned at upper-tier local authority level using ONS population estimates. Local authorities where greater than 50% of constituent LSOAs were classified as naturally fluoridated were excluded from
all analyses. While there is no scientific difference between naturally occurring and added fluoride in the water that comes out of consumers’ taps, the monitoring programme was specifically designed to measure the health effects on populations where fluoride level in water has been adjusted (ie, where the naturally occurring fluoride level has been augmented through a fluoridation scheme). Additionally, any further information known, such as fluoridation plant inactivity for an extended period of time, was taken into account in data analysis and this is detailed in subsequent sections where relevant.

4.2 Indicators and confounding variable data

Table 2 presents a list of the indicators used in this report, and for each the source of data, indicator measure, geographical level, time-period studied and a priori confounding variables examined are presented. All indicators were studied by aggregating data for all fluoridated versus all non-fluoridated areas. Levels of indicators are highly dependent on factors that vary between different areas of England, including age- and gender-distribution, deprivation and ethnicity. It is therefore imperative to take into account these factors by using adjusted comparisons when evaluating the effects of fluoridation. Crude rates cannot be used as a measure of the association between fluoridation and indicators.

Table 2. Health indicators studied, data sources, geographical analysis level, time-period and potential confounders.

<table>
<thead>
<tr>
<th>Health Indicator</th>
<th>Source of data</th>
<th>Indicator measure</th>
<th>Geographical level of exposure</th>
<th>Time-period</th>
<th>A priori potential confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental caries</td>
<td>National Dental Epidemiology Programme for England</td>
<td>Presence of caries at five years old and 12 years old as mean d3mft/D3MFT score and prevalence of any d3mft/D3MFT</td>
<td>Lower-tier local authority</td>
<td>2012 (five-year olds) 2009 (12-year olds)</td>
<td>Deprivation, ethnicity</td>
</tr>
<tr>
<td>Admissions with dental caries ages 1-4 years</td>
<td>Annual Report of the Chief Medical Officers 2012</td>
<td>Hospital admission with dental caries</td>
<td>Upper-tier local authority</td>
<td>2009-2012</td>
<td>Deprivation, ethnicity</td>
</tr>
<tr>
<td>Dental fluorosis</td>
<td>Published research data</td>
<td>TF score</td>
<td>City</td>
<td>2008-2009</td>
<td>Deprivation</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>Hospital episode statistics</td>
<td>Emergency admission; 1st or 2nd diagnosis</td>
<td>LSOA</td>
<td>2007-2013</td>
<td>Age, gender, deprivation, ethnicity</td>
</tr>
<tr>
<td>Kidney stones</td>
<td>Hospital episode statistics</td>
<td>Emergency admission; 1st or 2nd diagnosis</td>
<td>LSOA</td>
<td>2007-2013</td>
<td>Age, gender, deprivation, ethnicity</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Office of National Statistics</td>
<td>Death</td>
<td>LSOA</td>
<td>2009-2012</td>
<td>Age, gender, deprivation, ethnicity</td>
</tr>
</tbody>
</table>
4.2.1 Dental indicators

4.2.1.1 Dental caries

Dental caries data was obtained from the most recent surveys of five (2012) and 12-year old children (2009) undertaken for the National Dental Epidemiology Programme for England. These surveys involved visual examination of children’s teeth by trained and calibrated examiners who followed a nationally agreed protocol, providing comparable data which were reported by lower tier local authority.

Mean severity of tooth decay (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 (d3mft/D3MFT). Prevalence is typically reported as the percentage of children with decay experience (ie, with one or more obviously decayed, missing (due to decay) and filled teeth or %d3mft>0/%D3MFT>0). The use of lower and upper case letters denotes primary (lower case) and permanent (upper case) dentitions; primary teeth (d3mft) being reported in five-year-old children and permanent teeth (D3MFT) in 12-year-old children. In these surveys 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, which is widely accepted in the literature, acknowledging that it provides an underestimate of the true prevalence and severity of disease but improves the validity of the results and inter/ intra examiner reproducibility and reliability.

The dental caries indicators obtained from these survey data at local authority level were: mean d3mft (or D3MFT) – the mean number of decayed, missing teeth or filled teeth per child; prevalence of any d3mft (or D3MFT) – the percentage of children...
examined with d3mft>0. Deprivation, as measured by Index of Multiple Deprivation (IMD 2010) score and ethnicity – proportion of total population that is of white ethnicity, from 2011 census estimates – were considered to be a priori confounders.

4.2.1.2 Dental admissions
The data presented in this report on dental general anaesthetics are from the Annual Report of the Chief Medical Officers (CMO) 2012, ‘Our children deserve better: prevention pays’. The data is the underlying data for map 19 Dental health: hospital admission rate for dental caries in children aged 1-4 years, per 100,000 children aged 1-4 years, by local authority, 2009-2012. Data was available at upper tier (including unitary) local authority level.

The data source for the aforementioned CMO report was hospital episode statistics (HES) for children aged 1-4 years admitted with a primary diagnosis code of K02 (dental caries). The data was reported as admission rate for dental caries per 100,000 population aged 1-4 years. Data for the number of 1-4-year-olds in each local authority was obtained from ONS, Mid-2009-2011 population estimates; single year of age and sex for local authorities in England; estimated resident population; based on/revised in the light of the results of the 2011 census. The data was collated by the Child and Maternal Health Intelligence network and were published on 1 August 2013.

4.2.1.3 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.

The most recent reporting of fluorosis prevalence in England was measured using the TF index, in Newcastle upon Tyne (fluoridated) and Greater Manchester (non-fluoridated). To mitigate dental examiner bias and assist differential diagnoses, fluorosis evaluations were undertaken remotely by 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. The results of this study were reported by McGrady et al. (2012).

The methodology used in the study by McGrady et al. (2012) has been developed further (to include advanced fluorescent imaging and simultaneous white light photography) and is currently being deployed across four populations in England to provide additional information on fluorosis prevalence and severity. Pending any further data being available the results presented here are those of McGrady et al. (2012).

4.2.1.4 Statistical analysis
Statistical analysis was performed using Stata (Stata Corp, College Station, TX, USA)

4.2.1.4.1 Mean d3mft
Analysis was carried out at lower-tier local authority level. Mean d3mft was treated as a numerical indicator and summary statistics, initially crudely, then weighted by local authority individual year (five or 12 years old) population size, were calculated.
aggregated by fluoridation status. Weighting was carried out using analytic weights to take account of the use of mean d3mft score from local authority sampling areas with differing numbers of children – larger weighting was given to larger population sizes.

Following assessment of the distribution of the indicator, weighted linear regression was used to test the association between fluoridation status as a binary variable and mean d3mft. Initial univariate analysis was performed, followed by the construction of multivariable model.

As previously described, deprivation and ethnicity were considered to be a priori confounders and tested in models. Both variables were coded into quintiles (indicator variables) and included as ordered or non-ordered categorical variables depending on visual inspection of box-plots and likelihood ratio test between models containing the independent variables in different forms – the null hypothesis being no deviation from an assumption of a linear relationship between the independent and dependent variables.

A reverse step-wise procedure was employed to build the final multivariable model; all a priori confounding variables were initially included, then removed in order of those with the weakest association with the indicator first, and the resultant models were compared by inspection of the exposure-indicator effect size and likelihood ratio test. A variable was kept in the model if exclusion appeared to change the association between exposure and indicator using 10% as a guide, or the p-value for the LR test was less than 0.1.

An a priori interaction between deprivation quintiles and fluoridation status was tested, followed by an exploratory analysis with deprivation coded as binary, most deprived quintile compared to the combined four least deprived quintiles. A formal test for interaction was then carried out using a likelihood ratio test between models with and without inclusion of an interaction term between fluoridation status and the binary deprivation variable – the null hypothesis being no evidence of interaction.

4.2.1.4.2 Prevalence of any d3mft/D3MFT
Analysis was carried out at lower-tier local authority level. Summary statistics for prevalence of any d3mft/D3MFT, initially crudely, then weighted by local authority individual year (five or 12 years old) population size, were calculated by fluoridation status; subsequent univariate and multivariable analysis was performed to test the association between fluoridation status and prevalence of any d3mft/D3MFT. Deprivation, as measured by IMD 2010 score, and ethnicity – proportion of all population white from the 2011 census – were considered as a priori confounders. The association between fluoridation and prevalence of any d3mft/D3MFT was tested using generalised linear models (binomial distribution), weighted using analytical weights as previously described, with robust standard errors. A reverse step-wise procedure was employed to build the final multivariable model. All a priori confounding variables and the indicator were initially included, then removed in order of those with the weakest association with the indicator first, and the resultant models were compared by inspection of the exposure-indicator effect size and likelihood ratio test. A variable was kept in the model if exclusion appeared
to change the association between exposure and indicator using 10% as a guide, or the p-value for the likelihood ratio test was less than 0.1.

An a priori interaction between deprivation quintiles and fluoridation status in their association with prevalence of any d3mft/D3MFT was explored graphically, followed by an exploratory analysis with deprivation coded as binary, most deprived quintile compared to the combined four least deprived quintiles. A formal test for interaction could not be performed in Stata using these models with robust standard errors; if the effect of fluoridation appeared to differ between the most deprived and the combined four least deprived quintiles, stratum-specific estimates were calculated.

4.2.1.4.3 Dental admissions
Dental admission analysis was carried out at upper-tier local authority level. The count of number of admissions and denominator of population (all children aged 1-4 years) were used to calculate a crude rate for aggregated fluoridated and non-fluoridated areas separately.

Negative binomial models were used to model the association between fluoridation status and the count of admissions at upper tier local authority level, using the (natural logarithm of) population (all children aged 1-4 years) as the offset. Potential confounding variables considered a priori were deprivation – as measured by IMD 2010; and ethnicity – proportion of the population white, from 2011 census estimates at upper-tier local authority level.

A reverse step-wise procedure was employed to build the final multivariable model. All a priori confounding variables and the indicator were initially included, then removed in order of those with the weakest association with the indicator first, and the resultant models were compared by inspection of the exposure-indicator effect size and likelihood ratio test. A variable was kept in the model if exclusion appeared to change the association between exposure and indicator using 10% as a guide, or the p-value for the LR test was less than 0.1.

An a priori interaction between deprivation quintiles and fluoridation status in their association with dental admissions was tested, followed by an exploratory analysis with deprivation coded as binary, most deprived compared to the combined four least deprived quintiles. A formal test for interaction was then carried out using a likelihood ratio test between models with and without inclusion of an interaction term between fluoridation status and the deprivation variable – the null hypothesis being no evidence of interaction.

4.2.1.4.4 Dental fluorosis
As described in section 4.2.1.3. this report refers to the results of a recent study by McGrady et al. (2012). PHE has commissioned research that will provide further data from additional populations in England and will be presented in a later report.
4.2.2 Non-dental health indicators

4.2.2.1 Hip fracture
The indicator studied was the number of hip fracture in-patient consultant episodes per LSOA in England recorded in HES according to the following case definition; admission date between April 2007 and March 2013; 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, were removed.

A priori confounding variables examined were age – proportion of population above 65 years old; gender – proportion of the population male, both obtained from 2010 Office of National Statistics (ONS) mid-year estimates at 2001 LSOA level; deprivation – measured by IMD 2010; ethnicity – proportion of the population white, from ONS 2011 census data at 2011 LSOA level. Recent ethnicity estimates were used as significant changes are likely to have occurred between the 2001 and 2011 censuses, although this approach was unable to allocate a variable status to any LSOA that underwent a boundary change between these years.

4.2.2.2 Kidney stones
The indicator studied was the number of kidney stones in-patient consultant episodes per LSOA in England recorded in HES according to the following case definition; admission date between April 2007 and March 2013; 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 were removed.

A priori confounding variables examined were age – proportion of population above 25 years old; gender – proportion of the population male, both obtained from 2010 Office of National Statistics mid-year estimates at 2001 LSOA level; deprivation – measured by IMD 2010; ethnicity – proportion of the population white, from ONS 2011 census data at 2011 LSOA level. Ethnicity from the 2011 census was used for reasons described in the previous section 4.2.2.1.

4.2.2.3 All-cause mortality
The total all-cause mortality, recorded as the count of deaths, was obtained at LSOA level from ONS data for Jan 2009-Jan 2012; these years were used as mortality was relatively stable during this period following reductions over preceding years. A priori confounding variables examined were age – proportion of population above 65 years old; gender – proportion of the population male, both obtained from 2010 ONS mid-year estimates at 2001 LSOA level; deprivation – measured by IMD 2010; ethnicity – proportion of the population white, from ONS 2011 census data at 2011 LSOA level. Ethnicity from the 2011 census was used for reasons described in the previous section 4.2.2.1.

4.2.2.4 Down’s syndrome
Cases of Down’s syndrome, according to lower tier local authority, were obtained from the National Down Syndrome Cytogenetic Register (NDSCR). The case definition included all cases of Down’s syndrome in England, including: live births; stillbirths (24+
weeks’ gestation); late miscarriages (20-23 weeks’ gestation); terminations of pregnancy with foetal anomaly; 2009-2012 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 and Wales submit a completed form for each such diagnosis and its variants to the National Down Syndrome Cytogenetic Register. Since its inception the register has captured data for an estimated 93% of all diagnosed births and pregnancy terminations to residents of England and Wales.

Cases of Down’s syndrome were categorised according to year of outcome for live births, stillbirths (24+ weeks’ gestation) and late miscarriages (20-23 weeks’ gestation) and by expected year of outcome for terminations of pregnancy with foetal anomaly.

The risk of a Down’s syndrome birth is highly associated with maternal age, therefore this variable was considered as an a priori confounder. Counts of live births at lower tier local authority level by individual year of maternal age were supplied on request from ONS. Morris et al. (2002) have published maternal-age specific risks for Down’s syndrome; for each local authority the total number of births for each single year of maternal age is multiplied by the risk of having a Down’s syndrome birth to estimate the expected number of Down’s syndrome births for mothers of that age. The total number of expected Down’s syndrome births for each local authority is calculated by summing the expected numbers at each maternal age. A Poisson model is then fitted with these expected births as a measure of the exposure rather than the total number of births.

4.2.2.5 Cancer
Cancer data was extracted from the National Cancer Registration Service.

4.2.2.5.1 Bladder cancer
The case definition for bladder cancer was; all primary invasive bladder cancer in England recorded in cancer registries with date of diagnosis between 2000 and 2010 inclusive; ICD-10 code C67.

A priori confounding variables examined were age – proportion of the population over 65 years old; gender - proportion of the population male, both obtained from ONS individual mid-year year estimates for 2000-2010; deprivation – as measured by IMD 2010; ethnicity – obtained from 2011 census at 2011 LSOA level.

4.2.2.5.2 Osteosarcoma
Osteosarcoma was considered as an indicator separately for those aged less than 25 years, and those aged above 50 years, to reflect the bimodal distribution of incidence and differences in aetiology between age groups. Additionally, for those less than 25 years old gender-specific analysis was performed in consideration of suggestions made by previous research.
4.2.2.5.2.1 Osteosarcoma under 25 years
The case definition for osteosarcoma was all cases in England recorded in cancer registries with date of diagnosis between 1995 and 2010 aged less than 25 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 Intelligence Network 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 ten years after the introduction of the majority of fluoridation schemes. A priori confounding variables examined were: age – proportion of the population under 25 in each quinary age band; gender – proportion of the population under 25 male, both obtained from individual mid-year ONS estimates from 1995-2010; deprivation – IMD 2010; ethnicity – obtained from 2011 census at 2011 LSOA level.

4.2.2.5.2.2 Osteosarcoma over 50 years
The case definition for osteosarcoma was all cases in England recorded in cancer registries with date of diagnosis between 1995 and 2010 aged 50 years and over at the time of diagnosis; ICD-10 codes 9180 to 9195 suffix 3. A priori confounding variables examined were: proportion of the over 50s population who were over 65 years old; proportion of the over 50s population male, both obtained from individual mid-year ONS estimates from 1995-2010; deprivation – IMD 2010; ethnicity – obtained from 2011 census at 2011 LSOA level.

4.2.2.5.3 All cancer
The case definition for all cancer was all cases of cancer in England excluding non-melanoma skin cancer recorded in cancer registries with date of diagnosis between 2007 and 2010; ICD-10 codes C00 to C97 excluding C44. A priori confounding variables examined were: age – proportion of the population over 65 years old; gender - proportion of the population male – both obtained from ONS individual mid-year estimates for 2010; deprivation – as measured by IMD 2010; ethnicity – obtained from 2011 census at 2011 LSOA level.

4.2.2.6 Statistical methods
In all analyses performed the primary exposure of interest was: resident at time of diagnosis in an area subject to fluoridated water supplies – yes/no.

4.2.2.6.1 Statistical methods – hip fracture, kidney stones, all-cause mortality
An ecological analysis was carried out at LSOA level; for each LSOA a count of indicator was produced by combining individual case data for the entire time period. Initial descriptive data was performed followed by calculation of the crude rate (incidence density) for aggregated indicators in fluoridated and non-fluoridated areas separately, dividing the total count by the relevant population during the time period studied.

Negative binomial models, chosen as there was evidence of over-dispersion in the count data, ie, variance greater than the mean, were then used to model the association between fluoridation status and indicator; counts included were offset against the
(natural logarithm of) relevant population – calculated from 2010 ONS mid-year estimates multiplied by the number of years studied. Following initial univariate analysis, multivariable models were constructed to test the association between fluoridation status and the indicator adjusted for a priori confounding variables.

All confounding variables were divided into quintiles and included as non-ordered categories (indicator variables) – so as not to assume any underlying distribution between these exposures and the indicator. The large number of analysis units (LSOAs) in the analysis made formal likelihood ratio tests of linear versus non-linear inclusion of categorical variables highly powered and so liable to over-interpretation.

A reverse step-wise procedure was employed to build the final multivariable model. All a priori confounding variables and the indicator were initially included, then removed in order of those with the weakest association with the indicator first, and the resultant models at each stage were compared by inspection of the exposure-indicator effect size and likelihood ratio test. A variable was kept in the model if exclusion appeared to change the association between exposure and indicator – using a guide of 10%, or the p-value for the LR test was less than 0.1.

**4.2.2.6.2 Statistical methods – bladder cancer, osteosarcoma under 25 years, osteosarcoma over 50 years, all cancer**

An ecological analysis was carried out at LSOA level; for each LSOA a count of indicator was produced by combining individual case data for the entire time period.

In addition to calculation of crude rates, direct standardisation to the European standard population structure was performed to present comparable rates per 100,000 relevant population, for aggregated fluoridated and aggregated non-fluoridated LSOAs. The association between fluoridation status and indicators was then tested in univariate and multivariable models as outlined in section 4.2.2.6.1. Additionally, for osteosarcoma in those less than 25 years old, all analyses were carried out separately for males and females.

**4.2.2.6.3 Statistical methods – Down’s syndrome**

Following assessment of over-dispersion in the Down’s syndrome count data using a likelihood ratio test in a negative binomial model, Poisson regression was used to test the association between fluoridation and the incidence of Down’s syndrome.

An initial univariate analysis was performed with the total number of live births in each local authority as the exposure in the Poisson model. To adjust for maternal age, a subsequent model was produced with the expected number of Down’s syndrome births as a measure of the exposure rather than the total number of births, using the methodology outlined in section 4.2.2.4.
5. Results

5.1 Fluoridation status

A fluoridation status for 2012 was assigned to all 32,482 LSOAs (2001 boundaries) in England: 28,433 (87.5%) were not fluoridated; 3,991 (12.3%) were fluoridated; 58 (0.2%) were considered naturally fluoridated.

Of the 326 lower-tier local authority areas in England, one was naturally fluoridated, 34 (10.7%) were considered to be fluoridated, of which 25 (8.0% total) received 100% LSOA coverage, and nine (2.8%) more than 50% but less than complete coverage. Of the 291 lower-tier local authorities considered non-fluoridated, 280 (85.9% total) received no fluoridation and 11 (3.4%) received some fluoridation to 50% or less of their LSOAs.

At upper-tier local authority level (n=152) one area was considered naturally fluoridated, and 15 (9.9%) fluoridated, of which 3 (2.0%) received more than 50% but incomplete coverage; and 12 (7.9%) received 100% coverage. Of the 136 (89% total) areas considered to be non-fluoridated; 11 (7.2%) received some coverage to 50% or less constituent LSOAs, the remainder receiving no fluoridation.

Hartlepool, an area naturally fluoridated to a level close to that hoped to be achieved by fluoridation schemes, was excluded from both lower and upper-tier local authority level analyses. Allerdale, in the main supplied by a fluoridation plant that had not been in operation from 2006 to 2013, was treated as non-fluoridated or excluded from lower-tier local authority analyses depending on the indicator studied, as indicated in subsequent sections. Bedford Borough Council was similarly considered depending on the indicator studied, as the fluoridation plant supplying a large part of this area had not been operational since 2009.

5.2 Dental indicators

5.2.1 12-year olds

There were 326 lower-tier local authorities in the dataset: Hartlepool and Allerdale were excluded, leaving 324 areas in the analysis. The number of 12-year olds resident in the 324 lower-tier local authorities was 606,119. The mean proportion of children sampled in each local authority was 18% (s.d. 14%; range 2.4% - 97%).

Of the 324 LAs 33 (10%) were fluoridated, representing a 12-year old population of 70,473 (12%). Mean D3MFT data was missing from 4/33 (12%) of fluoridated and 23/291 (7.9%) non-fluoridated areas (p=0.50 Fisher's exact test). Of the 297 local authorities with indicator data 257 (87%) were entirely non-fluoridated; 11 (3.7%) had some but less than 50% of constituent LSOAs fluoridated; seven (2.4%) had greater than 50% but not universal fluoridation; and 22 (7.4%) were entirely fluoridated.
5.2.1.1 Mean D3MFT

The mean D3MFT was 0.71 (95% CI 0.68, 0.75) in non-fluoridated areas compared to 0.63 (95% CI 0.58, 0.68) in fluoridated areas; weighted for population size of local authorities the mean D3MFT was 0.76 (95% CI 0.72, 0.79) in non-fluoridated areas compared to 0.65 (95% CI 0.61, 0.69) in fluoridated areas. Mean D3MFT, weighted for relevant population size of local authority, was 0.10 lower (95% CI -0.20, -0.01; p=0.03) in fluoridated compared to non-fluoridated areas. In multivariable models adjusted for deprivation and ethnicity there was strong evidence that mean D3MFT was lower in fluoridated compared to non-fluoridated areas (-0.19; 95% CI -0.27, -0.11; p<0.001).

There was no evidence of an interaction between fluoridation status and deprivation across all quintiles (p=0.64 using test for interaction). In an exploratory analysis the reduction in mean D3MFT associated with fluoridation appears to be greater in most deprived compared to the combined four least deprived quintiles (graph 1); there was some statistical evidence (p=0.02 using test for interaction) that the effect of fluoridation differs between the most deprived and the combined four least deprived quintiles. Mean D3MFT was 0.07 lower (95% CI -0.17, 0.04; p=0.21) in fluoridated areas compared to non-fluoridated areas of the combined four least deprived quintiles; whereas this mean score was 0.25 lower (95% CI -0.44, -0.07; p<0.01) in fluoridated areas of the most deprived quintile.

Graph 1. Mean D3MFT score (2009) in non-fluoridated and fluoridated areas subdivided by the combined four least deprived quintiles (lowest four) compared to the most deprived quintile (highest) in 12-year olds

![Graph 1](image-url)
5.2.1.2 Prevalence of any D3MFT
The prevalence of any D3MFT was 30% (95% CI 28%, 32%) in fluoridated compared to 33% (95% CI 32%, 34%) in non-fluoridated areas; weighted for the population (12-year olds) the prevalence of any D3MFT was 31% (95% CI 30%, 33%) in fluoridated compared to 34% (95% CI 33%, 35%) in non-fluoridated areas. The weighted prevalence of any D3MFT was 11% lower* (95% CI -20%, -0.1%; p=0.03) in fluoridated compared to non-fluoridated areas; adjusted for deprivation and ethnicity there was strong evidence that the prevalence of any D3MFT was lower in fluoridated compared to non-fluoridated areas (21% lower*; 95% CI -29%, -12%; p<0.001).

No formal statistical test for interaction between fluoridation status and deprivation could be performed with robust standard errors in the models used; stratum-specific estimated demonstrated that the prevalence of any D3MFT was 9% lower (95% CI -21%, 5%; p=0.21) in fluoridated areas in the combined four least deprived quintiles compared to 26% lower (95% CI -40%, -8%; p<0.01) in the most deprived quintile.

5.2.2 Five-year olds
There are 326 lower-tier local authorities in the dataset: Hartlepool and Bedford Borough Council were excluded from this analysis. Allerdale, as previously described, was regarded as non-fluoridated, leaving 324 lower tier local authorities in this analysis.

The total number of five-year old children resident in the 324 lower-tier local authorities was 632,850. The mean proportion of children sampled in each lower-tier local authority was 24% (s.d. 18%; range 0.9% - 79%).

Of the 324 lower-tier local authorities 32 (10%) were fluoridated, representing a population of 71,101 (11%).

5.2.2.1 Mean d3mft
Mean d3mft data was missing from of 0/32 fluoridated and 16/292 (5.5%) non-fluoridated areas (Fisher’s exact test p=0.38). Of the 308 lower tier local authorities with indicator data 265 (86%) were entirely non-fluoridated; 11 (3.6%) had some but less than 50% of constituent LSOAs fluoridated; 7 (2.3%) had greater than 50% but not universal fluoridation; and 25 (8.1%) were entirely fluoridated.

The mean d3mft was 0.89 (95% CI 0.84, 0.94) in non-fluoridated areas compared to 0.67 (95% CI 0.58, 0.76) in fluoridated areas; weighted for population (five-year olds) the mean d3mft was 1.01 (0.95, 1.07) in non-fluoridated areas compared to 0.81 (95% CI 0.71, 0.90) in fluoridated areas. The weighted mean d3mft was 0.20 lower (95% CI -0.36, -0.04; p=0.01) in fluoridated compared to non-fluoridated areas. Adjusted for deprivation and ethnicity there was strong evidence that mean d3mft was lower in fluoridated compared to non-fluoridated areas (0.37 lower; 95% CI -0.48, -0.27; p<0.001).

There was no evidence of an interaction between fluoridation status and deprivation across all quintiles (p=0.15 using test for interaction). In an exploratory analysis the difference between d3mft in fluoridated compared to non-fluoridated areas appears to
be greater in the most deprived quintile compared to the combined four least deprived quintiles (graph 2). There was good evidence that the association between fluoridation and mean d3mft was different in the most deprived quintile of deprivation compared to the combined four least deprived quintiles (p<0.01 using test for interaction). Stratum-specific estimates demonstrate that mean d3mft was 0.16 lower (95% CI -0.32, -0.01; p=0.04) in fluoridated areas in the combined four least deprived quintiles compared to 0.51 lower (95% CI -0.75, -0.27; p<0.001) in the most deprived quintile.

Graph 2. Mean d3mft (2012) score in non-fluoridated and fluoridated areas subdivided by the combined four least deprived quintiles (lowest four) compared to the most deprived quintile (highest) in in five-year olds.

5.2.2.2 Prevalence of any d3mft
Five-year old prevalence of any d3mft data was missing for 16/292 (5.5%) non-fluoridated and 0/32 fluoridated lower tier local authorities (p=0.38; Fisher’s exact test).

The mean prevalence of any d3mft in fluoridated areas was 23% (21, 25%) compared to 27% (95% CI 26%, 28%) in non-fluoridated areas; the weighted prevalence of any d3mft was 26% (24%, 28%) in fluoridated compared to 29% (28%, 30%) in non-fluoridated areas. The crude weighted prevalence of any d3mft was 15% lower* (95% CI -29%, 2.5%; p=0.09) in fluoridated areas; adjusted for deprivation and ethnicity there was strong evidence of a negative association between fluoridation status and prevalence of any d3mft (28% lower*; 95% CI -35%, -21%, -21%; p<0.001).

No formal statistical test for interaction between fluoridation status and deprivation could be performed in the robust standard error models used; stratum-specific estimates
demonstrated that the prevalence of any d3mft was in fluoridated areas in the combined four least deprived quintiles was 17% lower (95% CI -28%, -3.9%; p<0.01) compared to non-fluoridated areas; in the most deprived quintile the prevalence of any d3mft was 32% lower (-42%, -19%; p<0.001) in fluoridated areas.

5.2.3 Dental admissions

Of the 152 upper-tier local authorities in the dataset, Hartlepool was excluded from the analysis and 17 areas, including Bedford Borough Council, had missing data, leaving 134 local authorities with indicator data. There was no evidence that missing data was associated with fluoridation status; there were no indicator data for 2/15 (13%) of fluoridated areas compared to 15/136 (11%) in non-fluoridated areas (p=0.68 Fisher’s exact test).

Of the 134 upper-tier local authorities in the analysis: 112 (84%) received no fluoridation; 9 (6.0%) had some but less than 50% of constituent LSOAs fluoridated; 2 (1.5%) received more than 50% but incomplete coverage; 11 (8.2%) had complete coverage.

The median rate of admission in non-fluoridated areas was 370 per 100,000 person years at risk (pyar) compared to 42 per 100 000 pyar in fluoridated areas (table 3). The rate of admission in fluoridated areas was 45% lower than in non-fluoridated areas (95% CI -68%, -6%; p=0.03); following adjustment for deprivation there was strong evidence that the rate of admission was lower in fluoridated compared to non-fluoridated areas (55% lower; 95% CI -73, -27%; p=0.001). Ethnicity did not fulfil criteria for inclusion in final models as outlined in section 4.2.1.4.3.

Table 3. Rate of admission for fluoridated versus non-fluoridated areas

<table>
<thead>
<tr>
<th>Rate of admission mean (median; range; standard deviation)</th>
<th>Fluoridated</th>
<th>Non-fluoridated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>221(42; 13 – 773; 257)</td>
<td>400 (370; 7 – 1550; 311)</td>
<td>0.01b</td>
<td></td>
</tr>
</tbody>
</table>

*per 100 000 pyar *(Ranksum test)

There was some evidence of an interaction between fluoridation status and deprivation across all quintiles (p=0.05 using test for interaction). In an exploratory analysis the negative association between fluoridation status and admission rates appears to be greater in the most deprived compared to the combined four least deprived quintiles (graph 3). There was weak statistical evidence of an interaction (p<0.1) between fluoridation status and deprivation – i.e., the effect of fluoride was greater in the most deprived quintile compared to the combined four least deprived quintiles. The rate of admission was 27% lower (95% CI -62%, 39%; p=0.34) in fluoridated areas compared to non-fluoridated areas in the combined four least deprived quintiles; when examining only the most deprived quintile the rate of admission was 76% lower (95% CI -89%, -45%; p=0.001).
Graph 3. Dental admissions in 1-4-year old children in non-fluoridated and fluoridated areas subdivided by the combined four least deprived quintiles (lowest four) compared to the most deprived quintile (highest) in 2009-2012.

5.2.4 Fluorosis

The mean age of the children was 12.4 years (±0.6) and 56% were male. The overall consent rate for examination was 63.1%. Data from an examination using the TF index were available for 906 children in the fluoridated city (Newcastle) and 869 in the non-fluoridated city (Manchester).

Questionnaire data revealed that there were no significant differences between the two populations studied with respect to oral hygiene practices, sugar consumption, gender, age, or IMD scores.

Table 4 presents the TF scores for subjects by city. There was strong evidence of a higher prevalence any positive fluorosis score in the fluoridated city. Explanatory variables for city (fluoridation status) and quintile of IMD were entered into a logistic regression model with the presence or absence of fluorosis as the dependent variable. The odds ratio for developing any fluorosis (TF score greater than 0) was 3.4 (95% CI 2.8, 4.2) times greater in the fluoridated city compared to the non-fluoridated city. Fluorosis recorded at a level of TF3, considered to be mild or mild to moderate, was 6% in the fluoridated city and 1% in the non-fluoridated city. However, the prevalence of higher scores (TF4 or greater) was very low at less than 1% in both areas.
Table 4. Descriptive data for fluorosis TF scores by city

<table>
<thead>
<tr>
<th>Fluorosis TF Score</th>
<th>Newcastle (fluoridated)</th>
<th>Manchester (non-fluoridated)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td>0</td>
<td>410</td>
<td>45%</td>
<td>638</td>
</tr>
<tr>
<td>1</td>
<td>355</td>
<td>39%</td>
<td>209</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>9%</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>6%</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0.1%</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>906</td>
<td></td>
<td>869</td>
</tr>
</tbody>
</table>

5.3 Non-dental health indicators – hip fracture, kidney stones and all-cause mortality

The population denominator, counts, crude and adjusted rates of hip fracture, kidney stones and all-cause mortality by fluoridation status are presented in table 5.

5.3.1 Hip fracture

The crude rate of emergency consultant in-patient episodes with hip fracture between 2007 and 2013 was 119 per 100,000 person-years at risk (pyar) in fluoridated compared to 111 per 100,000 pyar in non-fluoridated LSOAs; the crude rate of hip fracture episodes was 7.2% higher (95% CI 4.9%, 9.6%; p<0.001) in fluoridated compared to non-fluoridated LSOAs. There was no evidence that rate of hip fracture was different in fluoridated areas compared to non-fluoridated areas following adjustment for age, gender and deprivation (0.9% higher; 95% CI -0.8%, 2.6%; p=0.29) and following adjustment for age, gender, deprivation and ethnicity (0.7% higher; 95% CI -1.0%; 2.4%; p=0.42).

5.3.2 Kidney stones

The crude rate of emergency in-patient consultant episodes with kidney stones between 2007 and 2013 was 48.9 per 100,000 pyar in fluoridated compared to 51.6 per 100,000 pyar in non-fluoridated LSOAs; the crude rate of kidney stones episodes was 5.3% lower (95% CI -7.1%, -3.5%; p<0.001) in fluoridated compared to non-fluoridated LSOAs. There was strong evidence that the rate of kidney stones was lower in fluoridated areas compared to non-fluoridated areas following adjustment for age, gender and deprivation (8.4% lower; 95% CI -10%, -6.7%; p<0.001) and following additional adjustment for ethnicity (7.9% lower; 95% CI -9.6%, -6.2%; p<0.001).

5.3.3 All-cause mortality

The crude rate of all-cause mortality between 2009 and 2012 was 924 per 100,000 pyar in fluoridated compared to 874 per 100,000 pyar in non-fluoridated LSOAs. The crude
rate of all-cause mortality was 5.2% higher (95% CI 3.4%, 7.0%; p<0.001) in fluoridated LSOAs. There was some evidence that all-cause mortality was lower in fluoridated compared to non-fluoridated LSOAs (1.4% lower; 95% CI -2.6%, -0.3%; p=0.02) following adjustment for age, gender and deprivation; and also some evidence that it was lower following additional adjustment for ethnicity (1.3% lower; 95% CI -2.5%, -0.1%; p=0.04).

Table 5. Incidence of hip fracture, kidney stones, and all-cause mortality – crude rates by fluoridation status, and results of univariate and multivariable analysis

<table>
<thead>
<tr>
<th>indicator</th>
<th>Fluoridation</th>
<th>Population</th>
<th>Number of cases</th>
<th>Crude rate per 100 000 pyar</th>
<th>Crude Incidence rate ratio (IRR) (%)</th>
<th>IRR Adjusted for age, gender, IMD (%) n=32424</th>
<th>IRR Adjusted for age, gender, IMD, ethnicity (%) n=31619</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Fracture 2007-2013</td>
<td>F</td>
<td>37,971,918</td>
<td>45,219</td>
<td>119</td>
<td>7.2 (4.9, 9.6)</td>
<td>0.9 (-0.8, 2.6)</td>
<td>0.7 (-1.0, 2.4)</td>
</tr>
<tr>
<td>(six years)</td>
<td>Non-F</td>
<td>274,884,530</td>
<td>303,848</td>
<td>111</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney stones 2007-2013</td>
<td>F</td>
<td>37,971,918</td>
<td>18,579</td>
<td>48.9</td>
<td>-5.3 (-7.1, -3.5)</td>
<td>-8.4 (-10, -6.7)</td>
<td>-7.9 (-9.6, -6.2)</td>
</tr>
<tr>
<td>(six years)</td>
<td>Non-F</td>
<td>274,884,530</td>
<td>141,963</td>
<td>51.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality 2009-2012</td>
<td>F</td>
<td>25,314,612</td>
<td>233,922</td>
<td>924</td>
<td>5.2 (3.4, 7.0)</td>
<td>-1.4 (-2.6, -0.3)</td>
<td>-1.3 (-2.5, -0.1)</td>
</tr>
<tr>
<td>(four years)</td>
<td>Non-F</td>
<td>183,256,350</td>
<td>1,602,206</td>
<td>874</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.3.4 Down’s syndrome

There were 324 lower-tier local authorities in this analysis: Hartlepool and Bedford Borough Council were not included. Allerdale was considered to be non-fluoridated. There were 6,619 cases of Down’s syndrome out of 2,727,300 live births in England between 2009-2012; a prevalence of 24.3 per 10,000 live births (95% CI: 23.7, 24.9). The prevalence was 21.7 (95% CI: 20.0, 23.4) per 10,000 live births in fluoridated local authorities (658/303818) compared with 24.6 (95% CI: 24.0, 25.2) per 10,000 live births in non-fluoridated local authorities (5961/2423482). The average maternal age was higher in the non-fluoridated local authorities (29.3 years; 95% CI: 29.30-29.31) compared with the fluoridated local authorities (28.4 years; 95% CI: 28.37-28.41).

In the Poisson regression model adjusting for the total number of births but not including any adjustment for maternal age the incidence rate in fluoridated local authorities compared to non-fluoridated was 12% lower (95% CI -19%, -4%; p<0.01); whereas in the model fitted with expected births as a measure of the exposure, ie, adjusting for maternal age, there was no evidence of an association between fluoridation and Down’s syndrome (2% higher; 95% CI -6%, 10%; p=0.68).
5.3.5 Cancer

The number of cases, population, crude and age-standardised rates and results of univariate and multivariable analysis for bladder cancer and all cancer indicators are presented in table 6; osteosarcoma results are presented in table 7.

5.3.5.1 Bladder cancer

The crude rate of bladder cancer between 2000 and 2010 was 16.7 per 100,000 in fluoridated areas compared to 17.4 in non-fluoridated areas; the age-standardised rate was 12.4 (95% CI 12.2, 12.6) in fluoridated compared to 13.0 (95% CI 12.9, 13.1) in non-fluoridated areas. The crude incidence rate was 4.4% lower (95% CI -6.7, -2.1; p<0.001) in fluoridated areas. Following adjustment for age, gender and deprivation there was strong evidence that the rate of bladder cancer was lower in fluoridated areas (8.6% lower; 95% CI -11%, -6.7%; p<0.001); this negative association was maintained after additional adjustment for ethnicity (8.0% lower; 95% CI -9.9%, -6.0%; p<0.001).

Table 6. Incidence of bladder cancer and all-cancer; crude and age-standardised rates by fluoridation status, and results of univariate and multivariable analysis

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Fluoridation</th>
<th>Population</th>
<th>Number of cases</th>
<th>Crude rate per 100 000 pyar</th>
<th>Age-standardised rate</th>
<th>Crude Incidence rate ratio (IRR) (%)</th>
<th>IRR Adjusted for age, gender, IMD (%)</th>
<th>IRR Adjusted for age, gender, IMD, ethnicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder cancer</td>
<td>F</td>
<td>67,978,298</td>
<td>11,327</td>
<td>16.7</td>
<td>12.4 (12.2, 12.6)</td>
<td>-4.4 (-6.7, -2.1)</td>
<td>-8.6 (-11, -6.7)</td>
<td>-8.0 (-9.9, -6.0)</td>
</tr>
<tr>
<td>2000-2010</td>
<td>Non-F</td>
<td>487,149,150</td>
<td>84,780</td>
<td>17.4</td>
<td>13.0 (12.9, 13.1)</td>
<td>4.0 (1.4, 0.0)</td>
<td>-1.1 (-1.9, -0.3)</td>
<td>-0.4 (-1.2, 0.4)</td>
</tr>
<tr>
<td>All-cancer</td>
<td>F</td>
<td>25,314,612</td>
<td>131,288</td>
<td>519</td>
<td>402 (399, 404)</td>
<td>2.7 (1.4, 0.0)</td>
<td>-1.1 (-1.9, -0.3)</td>
<td>-0.4 (-1.2, 0.4)</td>
</tr>
<tr>
<td>2007-2010</td>
<td>Non-F</td>
<td>183,256,350</td>
<td>921,583</td>
<td>503</td>
<td>396 (395, 397)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
</tr>
</tbody>
</table>

5.3.5.2 Osteosarcoma

5.3.5.2.1 Osteosarcoma under 25 years old (table 7)

For those aged under 25 years at age of diagnosis the crude rate of osteosarcoma between 1995 and 2010 was 0.47 per 100,000 pyar in fluoridated compared to 0.44 per 100,000 pyar in non-fluoridated areas; the age-standardised rate was 0.45 (95% CI 0.38, 0.52) per 100,000 pyar in fluoridated compared to 0.42 (95% CI 0.40, 0.45) per 100,000 pyar in non-fluoridated areas. For all those aged under 25 years the crude rate of osteosarcoma was 8.0% higher (95% CI -9.3%, 29%; p=0.39) in fluoridated areas. Following adjustment for age, gender and deprivation there was no evidence of a difference in osteosarcoma rates in those aged under 25 years in fluoridated compared to non-fluoridated areas (6.6% higher; 95% CI -11%, 27%; p=0.48); and similarly following additional adjustment for ethnicity (8.2% higher; 95% CI -9.3%, 29%; p=0.38).
For males under 25 years the crude rate of osteosarcoma was 18% higher (95% CI -5.4%, 48%; p=0.14) in fluoridated compared to non-fluoridated areas. Following adjustment for age and deprivation there was no evidence of an association between fluoridation and osteosarcoma in males (16% higher; 95% CI -11%, 27%; p=0.20), likewise following additional adjustment for ethnicity (17% higher; 95% CI -7.1%, 46%; p=0.19).

For females under 25 the crude rate of osteosarcoma was 5.3% lower (95% CI -29%, 26%; p=0.70) in fluoridated compared to non-fluoridated areas. Following adjustment for age and deprivation there was no evidence of an association between fluoridation and osteosarcoma in females (4.7% lower; 95% CI -28%, 27%; p=0.74), likewise following additional adjustment for ethnicity (2.5% lower; 95% CI -27%, 30%; p=0.86).

### 5.3.5.2.2 Osteosarcoma aged 50 years and over
For those aged 50 years and over at the time of diagnosis the crude rate of osteosarcoma was 0.22 per 100,000 pyar in fluoridated compared to 0.25 per 100,000 pyar in non-fluoridated areas; the age-standardised rate was 0.20 (95% CI 0.15, 0.25) in fluoridated compared to 0.23 (95% CI 0.21, 0.25) in non-fluoridated areas. The crude rate was 12% lower (95% CI -31%, 13%; p=0.32) in fluoridated areas; following adjustment for age, gender and deprivation there was no evidence of a difference in osteosarcoma incidence between fluoridated compared to non-fluoridated areas (10% lower; 95% CI -30%, 15%; p=0.38); and similarly following additional adjustment for ethnicity (15% lower; 95% CI -34%, 9.6%; p=0.21).

Table 7. Incidence of osteosarcoma; crude and age-standardised rates by fluoridation status, and results of univariate and multivariable analysis

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Fluoridation</th>
<th>Population</th>
<th>cases</th>
<th>Crude rate per 100 000 pyar</th>
<th>Crude incidence rate ratio (IRR) (%)</th>
<th>IRR Adjusted for age, gender, IMD (%)</th>
<th>IRR Adjusted for age, gender, IMD, ethnicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma under 25 years - all</td>
<td>F</td>
<td>31,313,151</td>
<td>148</td>
<td>0.47</td>
<td>0.45 (0.38, 0.52)</td>
<td>8.0 (-9.3, 29)</td>
<td>8.2 (-9.3, 29)</td>
</tr>
<tr>
<td>F</td>
<td>216,921,400</td>
<td>949</td>
<td>0.44</td>
<td>0.4</td>
<td>0.42 (0.40, 0.45)</td>
<td>8.0 (-9.3, 29)</td>
<td>8.2 (-9.3, 29)</td>
</tr>
<tr>
<td>Non-F</td>
<td>15,981,438</td>
<td>92</td>
<td>0.58</td>
<td>0.55 (0.45, 0.68)</td>
<td>18 (-5.4, 48)</td>
<td>16 (-11, 27)</td>
<td>17 (-7.1, 46)</td>
</tr>
<tr>
<td>F</td>
<td>110,831,320</td>
<td>540</td>
<td>0.49</td>
<td>0.47 (0.43, 0.51)</td>
<td>18 (-5.4, 48)</td>
<td>16 (-11, 27)</td>
<td>17 (-7.1, 46)</td>
</tr>
<tr>
<td>Non-F</td>
<td>15,331,713</td>
<td>56</td>
<td>0.37</td>
<td>0.35 (0.26, 0.46)</td>
<td>-5.3 (-29, 26)</td>
<td>-4.7 (-28, 27)</td>
<td>-2.5 (-27, 30)</td>
</tr>
<tr>
<td>F</td>
<td>106,090,080</td>
<td>409</td>
<td>0.39</td>
<td>0.37 (0.34, 0.41)</td>
<td>-5.3 (-29, 26)</td>
<td>-4.7 (-28, 27)</td>
<td>-2.5 (-27, 30)</td>
</tr>
<tr>
<td>Osteosarcoma under 25 years - male</td>
<td>F</td>
<td>33,080,465</td>
<td>73</td>
<td>0.22</td>
<td>0.20 (0.15, 0.25)</td>
<td>-12 (-31, 13)</td>
<td>-15% (-34, 9.6)</td>
</tr>
<tr>
<td>F</td>
<td>232,282,090</td>
<td>587</td>
<td>0.25</td>
<td>0.23 (0.21, 0.25)</td>
<td>-12 (-31, 13)</td>
<td>-10 (-30, 15)</td>
<td>-15% (-34, 9.6)</td>
</tr>
<tr>
<td>Non-F</td>
<td>106,090,080</td>
<td>409</td>
<td>0.39</td>
<td>0.37 (0.34, 0.41)</td>
<td>-5.3 (-29, 26)</td>
<td>-4.7 (-28, 27)</td>
<td>-2.5 (-27, 30)</td>
</tr>
<tr>
<td>F</td>
<td>33,080,465</td>
<td>73</td>
<td>0.22</td>
<td>0.20 (0.15, 0.25)</td>
<td>-12 (-31, 13)</td>
<td>-10 (-30, 15)</td>
<td>-15% (-34, 9.6)</td>
</tr>
<tr>
<td>Non-F</td>
<td>232,282,090</td>
<td>587</td>
<td>0.25</td>
<td>0.23 (0.21, 0.25)</td>
<td>-12 (-31, 13)</td>
<td>-10 (-30, 15)</td>
<td>-15% (-34, 9.6)</td>
</tr>
</tbody>
</table>
5.3.5.3 All cancer (table 6)
The crude rate for all cancers excluding non-melanoma skin cancer between 2007 and 2010 was 519 per 100,000 pyar in fluoridated areas compared to 503 in non-fluoridated areas; the age-standardised rate was 402 (95% CI 399, 404) per 100 000 pyar in fluoridated compared to 396 (395, 397) per 100 000 pyar in non-fluoridated areas. The crude incidence rate was 2.7% higher (95% CI 1.4, 4.0%; p<0.001) in fluoridated compared to non-fluoridated areas; following adjustment for age, gender and deprivation there was good evidence that all cancer incidence was lower in fluoridated areas (-1.1% lower; 95% CI -1.9%, -0.3%; p<0.01); following adjustment for age, gender, deprivation and ethnicity there was no evidence of any association between fluoridation status and all cancer incidence (0.4% lower ; 95% CI -1.2%, 0.4%; p=0.29).

6 Discussion

6.1 Dental data

6.1.1 Dental caries
The analyses in this report show a reduction in caries prevalence associated with water fluoridation. Currently available research suggests that water fluoridation is associated with reduced levels of dental caries in populations served by this public health measure, therefore the results of this surveillance, within the confines of the data used, are in keeping with the evidence.1-3 The analysis of caries data was at lower tier local authority and not at LSOA level as data was available at lower tier local authority level only. The binary classification of the fluoridation status of local authorities is likely to have diluted the effect of water fluoridation on dental caries prevalence. Despite this the analysis showed a 28% reduction in the prevalence of dental caries in primary teeth at age five years and a 21% reduction in permanent teeth at age 12 years. Such reductions are significant from a public health perspective.

Although this was an exploratory analysis, the findings were consistent with a greater effect – that is a greater reduction in caries – in the most deprived communities with a 32% reduction at age five years and a 26% reduction at age 12 years compared to the combined four least deprived quintiles.

6.1.2 Dental admissions
As with the analysis of dental caries data, the binary classification of local authorities may have diluted the effect of fluoridation. Despite this, there was a marked 45% difference in rates of admission between fluoridated and non-fluoridated local authorities. This is likely to have significant effects on the relative costs of dental services provision due to the high costs associated with hospital admission.

There are potential problems with data quality that mean that this observation should be treated with caution. 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; 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. Although 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, further work to improve data quality and analysis is recommended.

### 6.1.3 Fluorosis

In the study by McGrady et al. (2012) the prevalence of any positive score for fluorosis was greater in the fluoridated city (Newcastle) compared to the non-fluoridated (Manchester) city. However, the prevalence of TF scores greater than 3 was less than 1% in both areas. Although an Irish study demonstrated that adolescents aged 14-15 years rated the appearance of TF3 less favourably than lower grades, they still preferred the appearance to that of teeth affected by caries; moreover, in the same study the less severe forms of fluorosis were not distinguishable from the absence of the condition. In this context, the increase in fluorosis prevalence in fluoridated Newcastle in the study by McGrady et al. (2000) was accompanied by a statistically significant decrease in caries.

It should be noted that fluorosis may reflect fluoride consumption from any source, not of water fluoridation per se. Other sources of fluoride include toothpaste, foodstuffs and fluoride supplements. This is evident in data from non-water fluoridated communities worldwide where mild fluorosis is present among some lifetime residents.

The methodology employed by McGrady et al. (2012) has been further developed and enhanced. PHE has commissioned new research to allow this methodology to be used to study fluorosis in additional populations in England.

### 6.2 Non-dental health indicators

#### 6.2.1 Hip Fracture

This monitoring report demonstrated no association between exposure to fluoridation and in-patient hip fracture episodes in multivariate analysis. The York report reviewed 18 studies examining the relationship between fluoridation and hip fractures, finding inconsistency in the results but effect sizes were evenly distributed around a relative risk of 1.0. The MRC (2002) suggests a worse case estimate for relative risk of 1.2 for the effect of fluoridation on the incidence of hip fractures, but stated that it was most likely that there was no impact on risk, and there could even be a protective effect. A further systematic review did not suggest any evidence of increase risk of hip fracture with exposure to fluoridation. More recent ecological level research has demonstrated no association between drinking water fluoride levels up to 2.7mg per litre and in-patient hip fracture episodes in Sweden. Age-standardised rates of hospitalisation of over 65s with hip fracture have been demonstrated to be similar between fluoridated and non-fluoridated cities in South Korea. A multivariable individual level study in China suggested a U-shaped pattern in the relationship between drinking water fluoride level
and bone fractures, with the lowest prevalence at 1.00-1.06ppm; the prevalence of bone fracture from age 20 years was highest in those with water fluoride levels of 4.32-7.97ppm (7.4%) and 0.25-0.34ppm (7.4%) compared to 5.1% in the 1.00-1.06ppm group.\textsuperscript{15}

\section*{6.2.2 Kidney stones}

This monitoring report demonstrated strong statistical evidence of a negative association between fluoridation and hospital episodes with kidney stones, although the effect size was small, the adjusted incidence rate being 7.9% lower (95% CI -9.6%, -6.2%). This negative association is consistent with some previous ecological level research, but 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. 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 \(\leq 0.49\) 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.\textsuperscript{16}

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 4.9 mg/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. Malnutrition among the study population probably increased the risk of kidney stones formation.\textsuperscript{17}

Risk factors for kidney stones include age, male gender, genetic susceptibility, dehydration, a diet rich in protein and obesity;\textsuperscript{18} 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 and obesity rates could potentially reflect urban versus rural lifestyles. Attempts were made to control for age, gender, deprivation and ethnicity differences between LSOAs 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, although unlikely, 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;\textsuperscript{18} the presence of chronic illness may lead to migration to, or less emigration from, urban areas, so potentially increasing the association with fluoridation status.
Overall, this finding of a lower rate of kidney stones in fluoridated areas is of interest, but simply raises the possibility of a relationship; further research would be required to investigate a potentially protective association.

6.2.3 All-cause mortality
This report showed some evidence of lower all-cause mortality in fluoridated versus non-fluoridated areas; the overall effect size was very small, and this is likely to have occurred as a result of chance, or possibly confounding as previously discussed in section 6.2.2.

The York Review appraised five studies that looked at the relationship between all-cause mortality and water fluoride exposure. Three of the studies reported more deaths in areas with water fluoridation; one found fewer deaths in fluoridated areas and the other reported no association. None of these studies reported measures of statistical significance of these associations. However, for two of the studies that reported more deaths the point estimate [adjusted rate ratio] was 1.01, which the report authors concluded was unlikely to have reflected a statistically significant effect.

6.2.4 Down’s syndrome
Following adjustment for maternal-age there was no evidence of an association between water fluoridation and Down’s syndrome.

A systematic review by Whiting et al. (2001) identified six ecological studies investigating any association between drinking water fluoride levels and Down’s syndrome; all were considered to be of low validity. Two of the six 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.

6.2.5 Bladder cancer
This report demonstrated a lower incidence of bladder cancer in fluoridated compared to non-fluoridated areas, but again the effect size was small. As previously described in section 6.2.2, possible explanations include confounding, bias and reverse causation.

The risk of bladder cancer was higher in males, and increases dramatically with age; 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, and was not adjusted for in this report.

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 natural fluoridation. 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.\textsuperscript{20}

\subsection*{6.2.6 Osteosarcoma – under 25 years and 50 years and over}
This monitoring report demonstrated no evidence of an association between fluoridation and osteosarcoma in both age groups studied, 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.\textsuperscript{1} Fluoride is taken up preferentially in bones, leading to the suggestion that effects on this tissue, including carcinogenesis, are biologically plausible.

When the analysis was restricted to look specifically at only males less than 25 years this monitoring report did not provide any evidence of an increased risk of osteosarcoma. 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 100ppm and higher,\textsuperscript{21} 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.\textsuperscript{9} In their study the strongest association was at ages 6-8 years, the authors suggesting biological plausibility related to timing of a growth spurt;\textsuperscript{9} 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.\textsuperscript{22} In contrast Gelberg et al. (1995) demonstrated no increased risk of osteosarcoma related to fluoride exposure, and demonstrated a negative association in males.\textsuperscript{23} Further case-control studies have demonstrated no association between fluoridation and osteosarcoma.\textsuperscript{24-26}

The majority of previous ecological level research has not demonstrated any association between fluoridation and osteosarcoma incidence in: Ireland;\textsuperscript{27} The United States;\textsuperscript{28-30} and international studies using multiple cancer registries.\textsuperscript{31} 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.\textsuperscript{32}

A recent ward-level ecological study using data from Great Britain population-based cancer registries (1980-2005) found no association between measured fluoride levels in drinking water (2004-6) 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.\textsuperscript{33}

This monitoring report is therefore consistent with the majority of previous ecological level studies and the York report which concluded there was no clear association between fluoridation and osteosarcoma.\textsuperscript{1}
6.2.7 All cancer
This monitoring report did not show any association between fluoridation and all cancer. The York report demonstrated mixed findings from studies looking at fluoridation and overall cancer incidence and mortality, but the findings were small variations on either side of no effect. The majority of studies were deemed to have a high risk of bias. An additional systematic review performed in 2006 did not find any association between fluoridation and overall cancer incidence or mortality.

6.3 Limitations
The main limitations of this report relate to the use of an ecological level analysis and observational data. Additionally, there was potential for considerable misclassification of exposure status.

Use of an ecological level measurement of fluoridation, in essence reflecting the nature of the intervention, does not take into account individual consumption of fluoride. In addition to that measured in this report, personal intake of fluoride depends on levels of tap water consumption – the predominate source of fluoride, dietary factors such as tea and soft drink consumption, and use of dentifrices (eg, toothpaste, mouthwash). Given this report was looking for possible differences between areas where fluoride has been added to water and areas where it has not (a binary variable), the presence of varied levels of natural fluoridation in non-fluoridated tap water also introduces misclassification bias to some extent. The exposure status at local authority level was considered as a binary variable, although many such areas were only partially fluoridated again introducing the potential to dilute any associations.

The relative risk of disease from environmental exposures tends to be low, and therefore any effects can be negated and dominated by more strongly associated independent variables such as age, diet, smoking, gender and deprivation. Failure to control for these variables in analyses will lead to confounding of estimates, thereby raising uncertainty in both the presence and lack of associations found. Additionally, routine statistics used, such as population denominator data, contain some inaccuracies that may lead to biased rate estimates.

The majority of non-dental health indicator data in this monitoring report came from robust sources, including the National Cancer Registration Service, death certification, and HES. Although there remains some theoretical potential for systematic differences in data collection between fluoridated and non-fluoridated areas, this is unlikely.

The ecological level associations in this report may not reflect the true relationship between fluoridation and health at an individual level and thereby represent ecological fallacy: for example, the lower rate of bladder cancer in fluoridated areas cannot be taken to mean a lower individual risk of bladder cancer with increased personal fluoride consumption.

The method used to assign an exposure status – resident in an area with fluoridation – in this report was based on LSOA of residence at the time of diagnosis. This approach has the potential to introduce misclassification bias, through migration, and temporal changes.
in fluoridation and water supply boundaries. In the absence of any clear biological mechanism for putative adverse health effects of fluoridation the effect of migration is uncertain, but residence at time of diagnosis does not provide any robust information regarding exposure to fluoridation prior to this date. The likely effect of migration would be to bias any measured effect of fluoridation on health towards no effect. In addition to personal migration, the geographical distribution of water quality zones has changed over time, with sub-optimal fluoridation in some places and the effect of plants having to be taken out of commission for essential repairs or upgrading. This monitoring report used fluoridation data from 2012 only. Blakey et al. (2014) similarly only assessed fluoridation for three out of 35 years studied but did demonstrate only relatively minor changes in fluoridation levels over time.\textsuperscript{33} The majority of English fluoridation schemes have been in place for over thirty years, but there are more recent programmes. This monitoring report did not stratify by the duration of the fluoridation scheme, which would represent an exploratory analysis in the absence of clear biological mechanisms of effect.

Although clear geographical demarcation of water quality zones is available, there are likely to be “halo” effects, whereby residents of a non-fluoridated LSOA travel to work or attend school in a neighbouring fluoridated area and vice versa.\textsuperscript{35} The low total number of cases of osteosarcoma in this analysis limited the statistical power to detect associations with fluoridation; the time period chosen was intended to allow a reasonable lag time following the introduction of the majority of schemes. Nevertheless, a recent UK-wide study that included 2,566 cases similarly found no evidence of an increased risk with fluoridation.\textsuperscript{33} The methodology in this monitoring report did not take into account the use of private water supplies, although this represents only approximately 1\% of the population.\textsuperscript{33} Despite these limitations, the use of GIS in this monitoring report to determine fluoridation of tap water from WQZ data at a small area represents a considerable improvement on previous ecological studies, for example those comparing entire cities, additionally allowing more accurate adjustment for confounders. The routine data used to measure health indicators used were comprehensive, covering all of England.

7. Conclusion

This monitoring report provides evidence of lower dental caries rates in children living in fluoridated compared to non-fluoridated areas. Similarly, infant dental admission rates were substantially lower. 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.
References


### Appendix

**Classification of local authorities**

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.

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

A list of local authorities where some of the population receive a water supply with adjusted fluoride levels.

<table>
<thead>
<tr>
<th>County and unitary</th>
<th>“Fluoridated” for report purposes</th>
</tr>
</thead>
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Notes: Fluoridation status by local authority was only relevant for a limited number of indicators where data were not available at LSOA level. Bedford Borough and Allerdale were regarded as non fluoridated or excluded from some analyses, see main report for details.