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Fluoride in drinking water and risk of hip fracture in the UK: a case-control study

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Summary

Background Although the benefits of water fluoridation for dental health are widely accepted, concerns remain about possible adverse effects, particularly effects on bone. Several investigators have suggested increased rates of hip fracture in places with high concentrations of fluoride in drinking water, but this finding has not been consistent, possibly because of unrecognised confounding effects.

Methods We did a case-control study of men and women aged 50 years and older from the English county of Cleveland, and compared patients with hip fracture with community controls. Current addresses were ascertained for all participants; for those who agreed to an interview and who passed a mental test, more detailed information was obtained about lifetime residential history and exposure to other known and suspected risk factors for hip fracture. Exposures to fluoride in water were estimated from the residential histories and from information provided by water suppliers. Analysis was by logistic regression.

Findings 914 cases and 1196 controls were identified, of whom 514 and 527, respectively, were interviewed. Among those interviewed, hip fracture was strongly associated with low body-mass index (p for trend <0·001) and physical inactivity (p for trend <0·001). Estimated average lifetime exposure to fluoride in drinking water ranged from 0·15 to 1·79 ppm. Current residence in Hartlepool was a good indicator for high lifetime exposure to fluoride. After adjustment for potential confounders, the odds ratio associated with an average lifetime exposure to fluoride ⩾0·9 ppm was 1·0 [95% CI 0·7–1·5].

Interpretation There is a low risk of hip fracture for people ingesting fluoride in drinking water at concentrations of about 1 ppm. This low risk should not be a reason for withholding fluoridation of water supplies.

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Introduction

Fluoride has been added to drinking-water supplies in some areas of the UK since 1955 in an attempt to reduce the frequency of dental caries.[1] Although this benefit of fluoridation of water supplies is widely accepted, concerns remain about possible adverse health effects, particularly on bone.[2] About 50% of ingested fluoride is taken up by bone, and fluoridation of water can increase normal dietary intake by about 50%.[3] Fluoride affects bone in at least two ways—fluoride ions can replace hydroxyl ions in the hydroxyapatite lattice, and increased fluoride concentrations in plasma directly increase osteoblastic differentiation and activity. Such changes could have an important effect on risk of fracture.

Trials have shown that high doses of sodium fluoride substantially increase bone density at axial sites, but this effect was not associated with lower rates of spinal fractures.[4,5] However, at peripheral sites, bone density was decreased, which suggests that fluoride might increase the risk of some fractures. This effect has only been seen when intake has been substantially higher than would be expected from fluoridation of water, however, and the implications of lower exposure for risk of fracture are not certain.

Most epidemiological evidence comes from ecological studies of hip fracture,[6–16] but the results of such investigations have not been consistent. Some studies have suggested a positive association between the concentration of fluoride in water and incidence of fractures,[11–14,16] but others have found no association[7,8,10,15] or even an inverse relation.[6,9] Only two studies have related the risk of hip fracture to fluoride ingestion in individuals rather than populations,[17,18] and for one of these only a brief preliminary analysis has been published.[18]

The limited scope in ecological studies to adjust for the effects of potential confounding variables (such as

	Hartlepool				Elsewhere			
	Cases		Controls		Cases		Controls	
	Eligible	Interviewed	Eligible	Interviewed	Eligible	Interviewed	Eligible	Interviewed
Men								
<70 years old	7	5 (71%)	12	4 (33%)	44	29 (66%)	53	31 (59%)
70–79 years old	18	15 (83%)	10	6 (60%)	56	33 (59%)	71	40 (56%)
≥80 years old	12	4 (33%)	8	3 (38%)	57	22 (39%)	49	22 (45%)
Women								
<70 year old	14	11 (79%)	26	20 (77%)	77	65 (84%)	113	61 (54%)
70–79 years old	38	28 (74%)	55	30 (55%)	167	109 (65%)	248	125 (50%)
≥80 years old	80	37 (46%)	103	34 (33%)	344	156 (45%)	448	151 (34%)
Total	169	100 (59%)	214	97 (45%)	745	414 (56%)	982	430 (44%)

All data are numbers of people.

Table 1: **Proportions of eligible cases and controls interviewed by age, sex, and current residence**

physical activity, body build, cigarette smoking, dietary calcium intake, and reproductive variables) makes interpretation of their conflicting findings difficult. To address this uncertainty, we did a population-based case-control study in which the exposure of patients with a hip fracture to fluoride in drinking water was compared with that of controls after adjustment for possible confounding by other risk factors. We did this investigation in the county of Cleveland in northeast England. The Hartlepool area of Cleveland had always been supplied with water naturally high in fluoride (>1 ppm), whereas the rest of the county received water with a low fluoride concentration.

Methods

The study population consisted of residents of Cleveland aged 50 years and older. Virtually all cases of hip fracture in the county are treated at three hospitals—Hartlepool General Hospital, North Tees General Hospital (Stockton), and Middlesbrough General Hospital. By regularly searching ward admission books, we identified all members of the study population who were admitted to these hospitals during a 17-month period with newly diagnosed fractures of the femoral neck that were through or above the lesser trochanter and not caused by cancer. These patients were then visited in hospital by a trained research nurse who invited them to take part in the study. Those who agreed and who achieved a score of six or higher on a Hodkinson abbreviated mental test[19] were interviewed with a structured questionnaire.

The questionnaire asked about demographic variables, height, weight, lifetime residential history, usual physical activities, age at menopause, alcohol consumption, smoking history, recent medication, and dietary sources of calcium and fluoride. From the reported height and weight we calculated the body-mass index. The measures of physical activity (eg, walking speed, time spent walking outside, and time spent gardening) were highly intercorrelated, and were combined to give a summary physical-activity score that was grouped into three categories. The questions on dietary calcium were identical to those used in an earlier study,[20] and were used to classify intake as low, medium, or high.

The control group was randomly selected from a list of all members of the study population registered with National Health Service (NHS) general practitioners, and controls were frequency matched to the cases for age (in 5-year bands) and sex. In England almost everyone is registered with an NHS general practitioner. The control group was matched only by age and sex, and not by area of residence within Cleveland. With permission from their general practitioners, we wrote to the controls and asked if a nurse could visit them at home. Those people who agreed and who scored 6 or more on the Hodkinson abbreviated mental test were interviewed. The same questionnaire was used for both cases and controls.

The residential histories of cases and controls were reviewed by one of us (SH) who was not aware of their case/control status, and information provided by water suppliers was used to assign a water fluoride concentration for each year of the person's life. When this information was acquired for at least 90% of years, it was collated to obtain estimates of the average fluoride concentrations to which the person had been exposed throughout life, up to age 20 years, and in the 20 years before entry to the study. In some areas, including Cleveland, measurements of fluoride in water had been done from before 1960. In other areas, measurement did not begin until the early 1980s. However, concentrations of fluoride before the start of monitoring could be estimated with reasonable confidence when sources of supply had not changed. The associations of hip fracture with exposure to fluoride and other risk factors were analysed by logistic regression with adjustment throughout for age and sex.

To test whether estimates of exposure to fluoride in drinking water were linked to the amount of fluoride in femoral bone, we collected the excised femoral heads from a subset of 105 cases (25 in Hartlepool, 80 in Stockton and Middlesbrough) who were treated by arthroplasty. The femoral heads were stored in clean plastic containers and frozen to −20°C within 24 h of collection before transport in batches on dry ice to the Royal Hallamshire Hospital, Sheffield. The samples were analysed without knowledge of the fluoride exposure of the patient, according to a previously described method.[21] A 1 cm slice of trabecular bone was cut from the femoral head, and if the exercised bone included part of the femoral neck, a piece of cortical bone was also obtained. The samples were freeze-dried and treated with ether to remove fat. Slivers of about 50 mg were dissolved in 1 mol/L perchloric acid, and the fluoride concentration was measured

	Number of cases	Number of controls	Odds ratio (95% CI)
Body-mass index			
>25 kg/m²	102	183	1·0*
22–25 kg/m²	113	173	1·5 (1·0–2·2)
<22 kg/m²	183	102	4·3 (2·9–6·3)
Physical-activity score			
High	69	171	1·0*
Medium	141	181	2·2 (1·5–3·2)
Low	188	106	6·4 (4·1–10·0)
Age at menopause			
<50 years	165	198	1·0*
≥50 years	135	163	1·1 (0·8–1·6)
Current alcohol consumption			
None	215	222	1·0*
Some	183	236	0·9 (0·8–1·2)
Ever smoked			
No	148	188	1·0*
Yes	250	270	1·0 (0·7–1·4)
Current treatment with oral corticosteroids			
No	377	451	1·0*
Yes	21	7	2·2 (0·9–5·4)
Dietary intake of calcium			
Low	131	130	1·0*
Medium	137	156	1·1 (0·8–1·6)
High	130	172	0·9 (0·6–1·3)

*Reference category.
All risk estimates are mutually adjusted and adjusted for age (in 5-year bands) and sex.

Table 2: **Association of hip fracture with potentially confounding variables**

Average concentration of fluoride in drinking water	Current residence	
	Hartlepool	Elsewhere
<0·9 ppm	20 (12%)	706 (99%)
⩾0·9 ppm	150 (88%)	7 (1%)
Total	170 (100%)	713 (100%)

The mean fluoride concentrations in the two exposure categories (for all areas of current residence combined) were 0·2 ppm and 1·5 ppm.

Table 3: **Lifetime exposure of study participants (cases and controls combined) to fluoride in drinking water according to current residence**

with a fluoride electrode. The amount of fluoride in the bone was given as μmol/g dry weight and was linked to the patient's estimated average lifetime exposure to fluoride in drinking water.

Results

914 cases were identified during the study period, of whom 514 (56%) had an interview. There were 1196 controls, of whom 527 (44%) were interviewed (table 1). The main reason for cases not completing interviews was a low score on the mental test (295 patients)—such low scores were more common at older ages. The main reasons for the incomplete response from controls were because general practitioners advised that they should not be approached (108); they could not be contacted at the address given (125); or the control declined to participate (377). Interview rates were somewhat higher in Hartlepool than elsewhere, both in cases and controls.

Table 2 summarises the relation of hip fracture to variables that might confound an association with fluoride. Strong associations were recorded with low body-mass index (p for trend <0·001) and low degrees of physical activity (p for trend <0·001). There was an increased risk in patients who were being treated with oral corticosteroids, although this increase was not significant. By contrast, no clear associations were seen with age at menopause, alcohol consumption, smoking, or dietary calcium intake (p for trend 0·5).

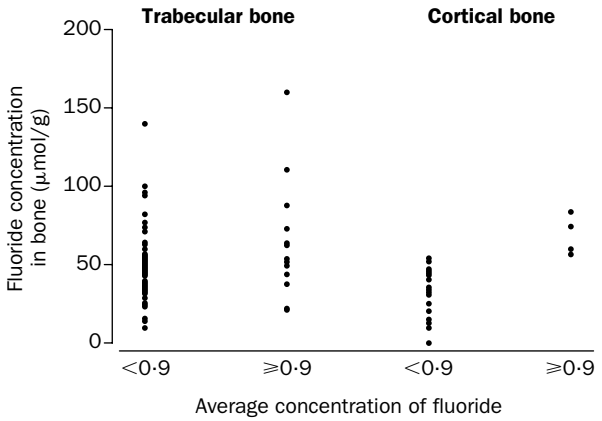
Data on lifetime exposure to fluoride in drinking water were at least 90% complete for 460 cases and 423 controls. The average lifetime concentrations that cases and controls had been exposed to ranged from 0·15 ppm to 1·79 ppm. Most values were either less than 0·2 ppm (76% of participants) or 0·9 ppm and higher (18%), reflecting the large difference between Hartlepool and elsewhere in Cleveland and the low rate of migration between different parts of the county (table 3). Current residence in Hartlepool was a good indicator of lifetime exposure to fluoride in water.

Table 4 shows the associations of hip fracture with lifetime exposure to fluoride in drinking water, and also

Period of exposure and fluoride concentration (ppm)	Number of cases	Number of controls	Odds ratio (95% CI)	
			Adjusted for age and sex	Adjusted for all potential confounders†
Lifetime exposure				
<0·9	380	346	1·0*	1·0*
⩾0·9	80	77	0·9 (0·7–1·3)	1·0 (0·7–1·5)
Exposure to age 20 years				
<0·9	397	393	1·0*	1·0*
⩾0·9	77	67	1·1 (0·8–1·6)	1·1 (0·7–1·7)
Exposure in previous 20 years				
<0·9	402	391	1·0*	1·0*
⩾0·9	85	87	0·9 (0·7–1·3)	0·9 (0·6–1·4)

*Reference category. †Includes age, sex, and the potentially confounding variable listed in table 2.

Table 4: **Associations of hip fracture with exposure to fluoride in drinking water**



Fluoride concentrations in femoral heads according to lifetime exposure to fluoride in drinking water

with exposures early in life and more recently. Risk estimates were all close to unity, and were virtually unchanged by adjustment for potential confounders. Thus, the adjusted odds ratio associated with an average lifetime exposure to fluoride in drinking water of 0·9 ppm or higher was 1·0 (95% CI 0·7–1·5). There was no indication that fluoride was associated with a higher risk of hip fracture than normal in people with low intakes of dietary calcium.

We also calculated the risk of fracture, adjusted for age and sex, by current place of residence, and in this analysis we included all cases and controls, whether or not they were interviewed. By comparison with those living elsewhere, the odds ratio for residents of Hartlepool was 1·0 (0·8–1·3).

The main dietary source of fluoride in the UK is tea (tea leaves contain high concentrations of fluoride). After adjustment for the potential confounding factors listed in table 2, no significant association was seen between hip fracture and higher reported tea consumption (odds ratio 1·3 [95% CI 0·9–2·0]).

Fluoride content was analysed in 79 samples of trabecular bone and 30 samples of cortical bone from patients for whom data on lifetime exposure to fluoride in drinking water were at least 90% complete. The figure summarises the relation of these measures to the lifetime average concentration of fluoride in drinking water. For trabecular bone there was no clear association between exposure to fluoride and the amount of fluoride in the bone. In all four samples of cortical bone from patients exposed to high concentrations of fluoride in water, however, there was an increased amount of fluoride in the bone.

Discussion

We found no evidence of any increase in the risk of hip fracture from fluoride in drinking water at concentrations of about 1 ppm. The association was examined in two ways. First, in the subset of people who underwent interview, we looked at risk of fracture in relation to estimates of exposure to fluoride in water during different periods of life. This analysis had the advantage that it allowed for possible confounding by various known and suspected causes of fracture. Furthermore, since fluoride tends to accumulate in bone progressively,[2] average exposures during extended periods should be more relevant to risk than exposures assessed only at a single point in time. Against this advantage, however, was the limitation of the low participation rate in interviews

(about 50%). For practical and ethical reasons this loss was unavoidable, but it may have introduced a response bias. Such bias would occur if the link between fluoride and risk of hip fracture differed between people who were not interviewed and those who were.

Second, we explored the association between the risk of hip fracture and current residence in Hartlepool in an analysis that included all participants whether or not they were interviewed. Problems of response bias were thereby avoided, but the index of exposure to fluoride was cruder, and no adjustment could be made for potential confounders other than age and sex. This approach was justified by the evidence that, among people who were interviewed, current residence in Hartlepool was a good marker for lifetime average exposure to fluoride in water (table 3), and adjustment for potential confounders had a negligible effect on risk estimates (table 4). This observation suggests that although variables such as physical inactivity and low body-mass index are strong risk factors for hip fracture, they were not significantly associated with exposure to fluoride in water in our study.

Neither of these complementary analyses showed any association between risk of hip fracture and exposure to fluoride in drinking water, and we conclude that any effect of such exposure in our study population is small. The alternative explanation that there is an important but currently unrecognised cause of hip fracture with a lower prevalence in Hartlepool than in other parts of Cleveland seems unlikely.

Most of the epidemiological evidence that links fluoride in drinking water with the incidence of hip fracture comes from comparisons of geographic regions with different water supplies. In one study, Simonen and Laitinen[9] found a 50% lower hip-fracture rate among men and women in Kuopio, a town in Finland with a concentration of fluoride in drinking water of 1 mg/L, compared with another town (Jyvaskyla) with unfluoridated water. However, a follow-up study covering a later period[10,22] suggested that after adjustment for age and sex rates of hip fracture were similar in the two towns. This finding is consistent with the observation that hip-fracture rates were similar in three Swedish communities with different concentrations of fluoride in drinking water.[6]

In the USA, two ecological studies[7,8] reported no significant effect of water fluoride concentration on hip-fracture rates, but a national analysis of data from the health-care financing administration between 1984 and 1987 indicated a significant positive correlation between county-specific, age-adjusted incidence of hip fracture in white women aged 65 years or older, and the proportions of the counties' populations served with fluoridated water.[11] This result is supported by another study in which a higher hip-fracture rate was recorded in a community with fluoridated water than in a nearby population without.[13]

A study in France[16] showed that the risk of hip fracture was significantly increased in places where water fluoride was higher than 0·11 ppm (odds ratio 1·86 [95% CI 1·02–3·06]). However, a survey in China[18] indicated a different relation, with the lowest rates of fracture in populations exposed to fluoride in drinking water at concentrations of 1·02–1·06 ppm, and higher risks above and below this range.

In the UK, hip-fracture rates during 1978–82 were derived from hospital activity analysis data for 39 county districts of England and Wales.[12,23] A significant positive correlation (R=0·41, p=0·009) was seen between concentrations of fluoride in water and rates of hospital discharge for hip fracture in each district.

The conflicting findings of these geographic comparisons are difficult to interpret because of the potential for uncontrolled confounding in such analyses. In a different approach, two North American studies have examined time trends in hip fracture before and after the introduction of water fluoridation for a population.[24,25] One study showed no alteration in rates,[24] whereas the other found a decline after fluoridation.[25] Although such studies are more robust than simple geographic correlations, the possibility of confounding by temporal changes in other risk factors must be taken into account. Steep secular trends in hip-fracture incidence have been noted in various parts of the world during the past 50 years.[26] Also, if the risk of fracture depends on cumulative exposure to fluoride throughout life, the full effects of fluoridation may not be apparent for many years.

By contrast with the large number of ecological studies, ours is one of the few investigations that have related fluoride ingestion to the risk of hip fracture in individuals. In the only North American study of this type,[17] current and historical residential exposures to fluoridated water were ascertained for a cohort of 2076 women, who were then followed up for an average of 6·1 years. After adjustment for potential confounding variables, fluoride exposures in the higher part of the range were, if anything, associated with a decreased risk of hip fracture and other non-spinal fractures. This result accords with our finding that fluoride in drinking water at a concentration of about 1 ppm carries no important increase in the risk of hip fracture.

The effects of fluoride on bone have also been examined in a randomised controlled trial of high-dose sodium fluoride (75 mg daily) as a treatment for osteoporosis.[4] During a 4-year period, the intervention led to a substantial increase in bone density in the spine. However, this increase did not translate into a decreased risk of fracture, and rates of hip fracture were doubled in treated patients. Although this finding suggests a hazard from high doses of fluoride in people with established osteoporosis, the risk cannot necessarily be extrapolated to the much lower doses that are received by the general population from fluoride in water supplies. In assessment of the potential risks from fluoridation of drinking water, greater weight should be given to direct epidemiological observations.

One explanation for an absence of risk at lower doses may be that a concentration of 1 ppm fluoride in water has a negligible effect on people's uptake of the ion. The average daily intake of fluoride in the UK is estimated to be 1·82 mg, of which about 70% is derived from beverages, most notably tea.[27] The other major dietary source is whole fish, for example sardines and pilchards, a typical helping of which contains 1–2 mg fluoride. The main non-dietary source of exposure is fluoridated toothpaste. To test whether water fluoride had a measurable effect on bone within our study sample, we analysed the fluoride content of the femoral heads from a subset of cases. The investigation was limited by the small number of samples that could be analysed; nevertheless, the fluoride content of cortical bone was increased in patients with higher exposures. This finding supports not only the relevance of water fluoride to bone metabolism but also the validity of our exposure estimates derived

from residential histories. The absence of a corresponding excess of fluoride in trabecular bone may have been related to its higher rate of turnover compared with cortical bone.

Within our study population, the main exposure to fluoride in drinking water was from supplies that were naturally high in fluoride. We designed the investigation in this way because it allowed us to study the effects of exposure over the longest possible periods. Unlike many of the places where water is or may be artificially fluoridated. Hartlepool has hard water that is high in calcium. However, this factor would be unlikely to influence the bioavailability of fluoride in the water, either through buffering of gastric acidity (fluoride is absorbed from the stomach as non-ionised hydrogen fluoride) or through complexing of fluoride ions in solution. Our findings should, therefore, be generalisable to other places, and we conclude that fluoridation of water to 1 ppm is not likely to have any important effect on the risk of hip fracture, and that concerns about this potential hazard should not be a reason for withholding the measure.

Contributors

David Coggon and Cyrus Cooper wrote the protocol, supervised the study, and wrote the paper. Sharon Hillier contributed to the protocol, oversaw the day-to-day running of the study and the management and coding of data, did part of the preliminary statistical analysis, and contributed to editing of the paper. Sam Kellingray did the main statistical analysis. Graham Russell contributed to the protocol, supervised the measurements of fluoride in bone, and contributed to editing of the paper. Herbert Hughes planned and carried out the measurements of fluoride in bone and contributed to editing of the paper.

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