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Exposure to Natural Fluoride in Well Water and Hip Fracture: A Cohort Analysis in Finland

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In the retrospective cohort study based on record linkage, the authors studied a cohort of persons born in 1900–1930 (*n* = 144,627), who had lived in the same rural location at least from 1967 to 1980. Estimates for fluoride concentrations (median, 0.1 mg/liter; maximum, 2.4 mg/liter) in well water in each member of the cohort were obtained by a weighted median smoothing method based on ground water measurements. Information on hip fractures was obtained from the Hospital Discharge Registry for 1981–1994. No association was observed between hip fractures and estimated fluoride concentration in the well water in either men or women when all age groups were analyzed together. However, the association was modified by age and sex so that among younger women, those aged 50–64 years, higher fluoride levels increased the risk of hip fractures. Among older men and women and younger men, no consistent association was seen. The adjusted rate ratio was 2.09 (95% confidence interval: 1.16, 3.76) for younger women who were the most exposed (>1.5 mg/liter) when compared with those who were the least exposed (≤0.1 mg/liter). The results suggest that fluoride increases the risk of hip fractures only among women. *Am J Epidemiol* 1999;150:817–24.

fluoride; hip fractures; rural population; water; water pollutants

Fluoride in drinking water originates from natural sources or is added to protect dental health. In Finland, the fluoride concentrations in drinking water in most parts of the country are generally low (<0.1 mg/liter). However, especially in the southeast and southwest parts of the country, fluoride concentrations in well water exceed the drinking water quality guideline value of 1.5 mg/liter because of high fluoride concentrations in soil and bedrock. Fluoride concentrations in drinking water are especially high in rural areas because houses are not connected to municipal drinking water supply systems and well water is used.

Even though fluoride has been used to treat osteoporosis, the actual benefit has been questioned (1, 2). Although fluoride may increase bone mass, the newly formed bone may have reduced strength and decreased mechanical properties (3–6). This is because the fluoride ion can replace the hydroxyl group in the calcium hydroxyapatite crystal to form calcium fluoroapatite. Since fluoroapatite is more stable, it makes the skeletal structure more resistant to osteoblastic resorption and further alters the normal remodeling cycle of bone (7, 8). Therefore, a concern about the effects of excess fluoride exposure on bone fractures, especially hip fractures, has been raised (9–14).

Hip fractures are a major cause of morbidity and mortality in persons aged 65 years and older in many Western nations (15). In Finnish men and women aged 50 years or more, the age-adjusted incidence in 1991 was 194 and 412 per 100,000 persons, respectively (16). The total number of hip fractures seems to increase more than that which could be expected based on the increasing size of elderly population (16).

The results from epidemiologic studies on fluoride concentrations in drinking water and hip fracture rates have been contradictory. The consumption of drinking water containing approximately 1 mg/liter of fluoride has been associated with no (17, 18), lower (19), and higher (9–11) hip fracture risk when compared with drinking water with lower fluoride concentrations. We therefore studied the relation between hip fractures and fluoride concentrations in well water in a cohort of 144,512 elderly rural men and women.

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Abbreviations: CI, confidence interval; RR, rate ratio.

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MATERIALS AND METHODS

Cohort

Data on the type of water source in 1985 and the codes of place of residence were obtained from the Population Census of Statistics Finland. Villages and squares in which more than 90 percent of the population was not provided with a municipal drinking water system were included. Each code of residence was matched with the Population Registry, from which the subjects born in 1900–1930 who had lived at the same address at least from 1967 to 1980 were selected (figure 1). For the cohort, we had information on the birth year, sex, and map coordinates of the residence, residence history, and occupation in 1970, 1975, and 1980 (table 1).

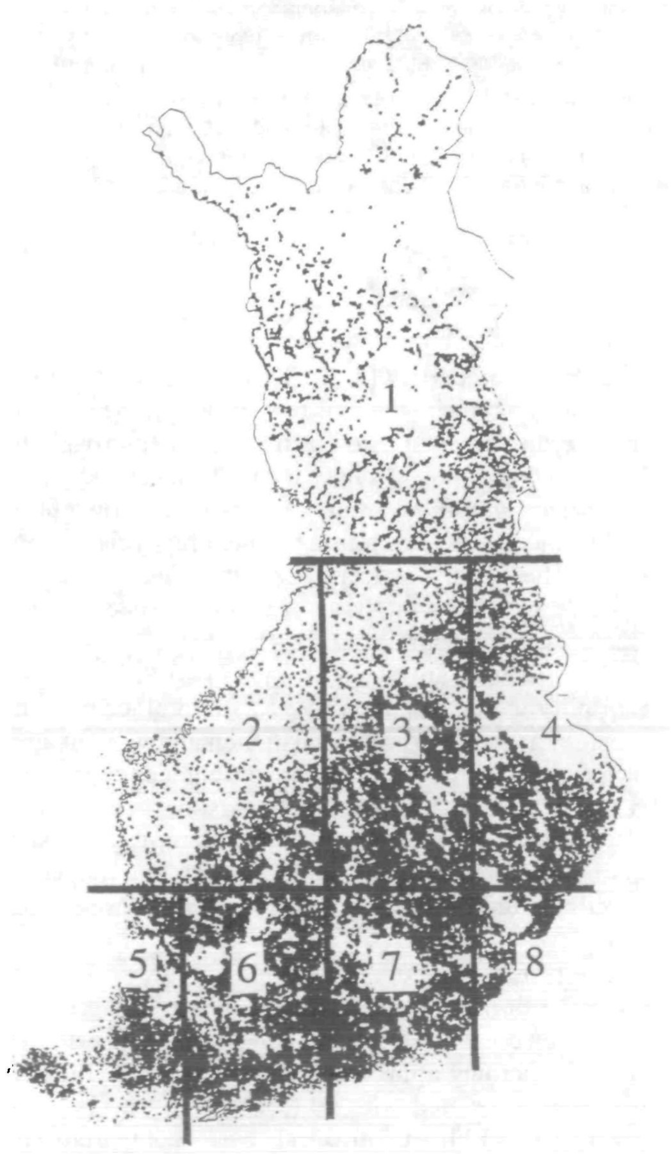

FIGURE 1. Map of the locations in which the study persons had lived at least from 1967 to 1981 outside municipal drinking water sources in Finland (n = 144,627). The lines show the division of the country into eight areas.

Hospital discharge registry

The cohort was linked to the Hospital Discharge Register by using personal identification numbers. All hospital types were included into the study. The cohort was followed-up from January 1, 1981, to December 31, 1994, for diagnosis of hip fracture (*International Classification of Diseases*, Eighth and Ninth Revisions, code 820) (table 1). Those who had had a hip fracture between January 1, 1978, and December 31, 1980 (before the follow-up) were excluded (n = 355,233 women). Only those records in which the main diagnosis was hip fracture were included. Only the first hip fracture was considered for each person.

Exposure assessment

Individual exposure was estimated for each member of the cohort on the basis of the nationwide database on ground water fluoride measurements in 8,927 wells by the Geological Survey of Finland (20). The fluoride concentrations were analyzed potentiometrically from untreated water samples. To obtain a regular grid of estimated fluoride concentrations, we interpolated the concentrations and smoothed using the method of moving weighted median, which has been used earlier for viewing geochemical maps (21). The distribution of concentrations in a circular window centered at a grid node was weighted depending on the distance between individual points and the window center. Here the grid was 2×2 km^2, and the window radius was 42 km. Points less than 5 km from the window center were assigned weights greater than 0.5, while peripheral points were assigned lower weights. Grid points located farther than 15 km from the nearest sample were assigned a missing value. All positive values were accepted, including those below the detection limit of 0.05 mg/liter. For each member of the cohort, the nearest accepted grid value was searched by using the quad-tree algorithm. In general, the moving weighted median is robust against single outliers.

The exposure estimation method was tested by comparing it with the measured fluoride concentrations of the wells (n = 1,411) in the study by Ministry of Social Affairs and Health and National Board of Waters and the Environment carried out in 1990–1991 (22). The wells represented geographically the private wells in all of Finland. Seventy-four were wells with a stone ring, 1,006 had concrete ring, 295 were in bedrock, 25 were springs, and 11 were of other types. The fluo-

TABLE 1. Description of the study subjects who had lived at least from 1967 to 1980 outside municipal drinking water sources in Finland

	Hip fractures observed in 1981–1994					
	Men (*n* = 66,742)			Women (*n* = 77,885)		
	No hip fractures (*n* = 65,493)	Hip fracture (*n* = 1,249)	% of hip fractures (1.9%)	No hip fractures (*n* = 74,685)	Hip fracture (*n* =3,200)	% of hip fractures (4.1%)
Age (years) on January 1, 1981						
50–54	13,825	77	0.6	13,065	100	0.8
55–59	14,752	128	0.9	15,590	217	1.4
60–64	11,466	172	1.5	14,018	354	2.5
65–69	10,502	234	2.2	12,908	635	4.9
70–74	8,771	310	3.5	10,676	906	8.5
75–80	6,177	328	5.3	8,428	988	11.7
Occupation						
Administrative, service, commercial	2,596	25	1.0	5,926	130	2.2
Construction, industrial, transportation	13,858	200	1.4	3,361	55	1.6
Farming, forestry, fishery	41,023	699	1.7	37,698	1,200	3.1
Unknown	8,016	325	3.9	27,700	1,815	6.6
Geographic area						
1	4,170	54	1.3	4,382	142	3.2
2	3,802	74	1.9	4,207	182	4.3
3	10,033	188	1.8	10,978	437	4.0
4	6,780	118	1.7	7,569	290	3.8
5	6,984	162	2.3	8,113	372	4.6
6	16,119	323	2.0	19,009	901	4.7
7	13,572	260	1.9	15,770	687	4.4
8	4,033	70	1.7	4,657	189	4.1

ride was analyzed potentiometrically, and the detection limit was 0.1 mg/liter. The map coordinates of the measured wells were known, and the fluoride value was estimated for those coordinates as described above.

Statistical analysis

We used age at the beginning of follow-up (in January 1, 1981). Some of the analyses were performed separately for persons who were younger than age 65 years ("younger") and 65 years old or older ("older") in 1981. Person-years were calculated from the beginning until the end of the follow-up, which was the date of the diagnosis of hip fracture, the date of death, or December 31, 1994. The country was divided into eight areas along the longitudes 22.5°, 25.5°, and 28.5° and the latitudes 62.2° and 65.0° (figure 1). This was done to achieve a crude adjustment for possible geographic differences in other risk factors for hip fracture. We used Cox's regression to calculate the crude and age-, area-, and occupation-adjusted rate ratios and 95 percent confidence intervals. The risk estimators were similar if the age was continuous or class variable, and a continuous variable was used when age was adjusted for. Adjustment for occupation did not practically influence the estimates, and hence, these results are not shown. Fluoride concentration was analyzed both as a continuous and a stratified variable.

RESULTS

The estimated fluoride concentrations varied from below the detection limit (0.05 mg/liter) to 2.4 mg/liter. Ninety percent of the estimated fluoride concentrations were below 0.63 mg/liter. The highest concentrations are located in southern Finland in areas 5–7. Most of the cohort members were located in areas in which less than 0.1 mg/liter of fluoride concentration in drinking water was estimated (table2). The highest fluoride concentrations are cut down because the exposure estimation is not based on actual measurements from wells, but it is based on smoothed data from a national registry (figure 2). Fluoride estimation correlated with measured well water fluoride concentrations.

The incidences of hip fractures were clearly related to higher age and female gender. Most patients who entered the hospital due to hip fracture were aged

TABLE 2. Rate ratios (RR) and 95% confidence intervals (CI) of hip fractures in the categorized fluoride concentration among the Finnish rural population aged 50–80 years in 1981

Fluoride concentration (mg/liter)	No. of hip fractures in 1981–1994	Person-years in 1981–1994	Incidence/1,000 person-years	Crude RR	95% CI	Age- and area-adjusted RR	95% CI
Men							
≤0.10	735	442,192	1.66	1.0		1.0	
0.11–0.30	318	165,736	1.92	1.15	1.01, 1.32	1.05	0.90, 1.22
0.31–0.50	38	26,820	1.42	0.85	0.61, 1.18	0.72	0.51, 1.02
0.51–1.00	108	51,347	2.10	1.26	1.03, 1.54	1.03	0.81, 1.32
1.10–1.50	32	22,753	1.41	0.85	0.60, 1.21	0.67	0.46, 0.97
>1.50	18	9,522	1.89	1.13	0.71, 1.81	0.98	0.61, 1.60
Women							
≤0.10	1,850	554,621	3.34	1.0		1.0	
0.11–0.30	775	219,627	3.53	1.06	0.97, 1.15	0.93	0.84, 1.02
0.31–0.50	142	34,617	4.10	1.23	1.04, 1.46	1.12	0.93, 1.34
0.51–1.00	268	66,448	4.03	1.21	1.06, 1.38	1.12	0.96, 1.31
1.10–1.50	118	30,497	3.87	1.16	0.97, 1.40	1.08	0.88, 1.32
>1.50	47	11,759	4.00	1.20	0.90, 1.60	1.08	0.80, 1.46

80–85 years. In the basic statistical analysis, no clear dose-response between estimation of fluoride concentration and hip fractures was observed (table 2). When the fluoride estimation was treated as a continuous variable, the age-adjusted rate ratio (RR) for men was 0.97 (95 percent confidence interval (CI): 0.82, 1.15), and that for women was 1.07 (95 percent CI: 0.97, 1.18). The age- and area-adjusted RRs were 0.90 (95 percent CI: 0.73, 1.10) and 1.10 (95 percent 0.98, 1.24), respectively.

When rate ratios were calculated for six age groups separately, crude and adjusted rate ratios for men

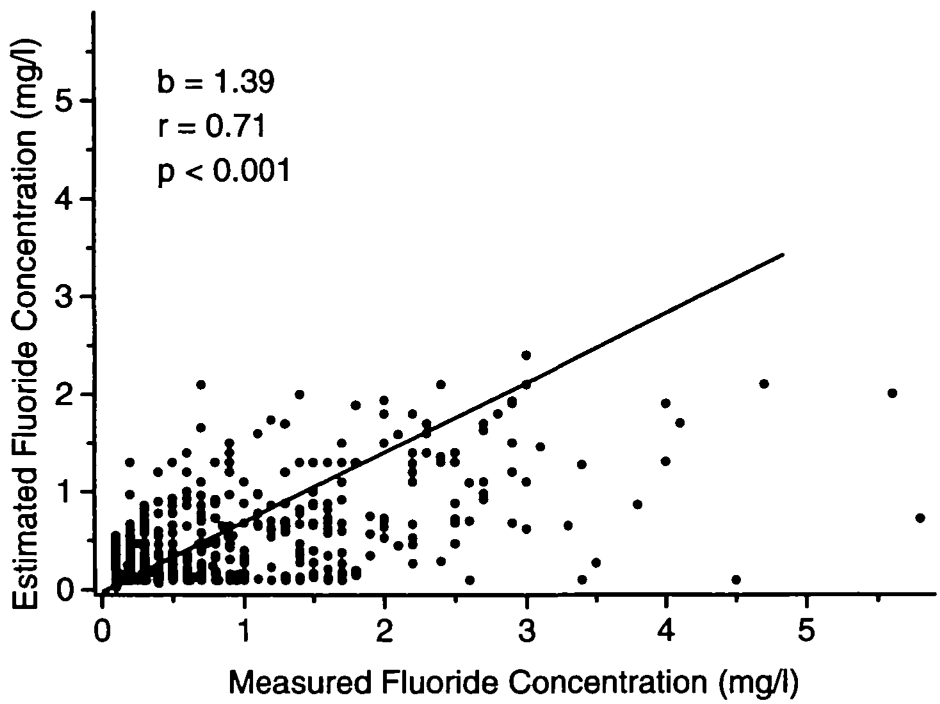

FIGURE 2. Scattergram showing the association between the measured fluoride concentrations in well water (n = 1,411) and the estimated fluoride concentration (by weighted median smoothing method) at the same sites. Linear fit line is shown, r = correlation coefficient, b = slope.)

tended to be below 1.0, and those for women were above 1.0 in the two and three lowest age groups, respectively (figure 3). The effect of fluoride was diluted in older ages. Therefore, the data for those aged 50–64 years were further analyzed. The results suggest a slight protective effect of fluoride against hip fracture among the younger men, but the effect was not statistically significant (table 3). For younger women, an increase in the fluoride concentration was associated with increased hip fracture incidence, suggesting a slight dose-response effect (table 3). Adjustment for occupation did not change the results.

When the estimated fluoride concentration was treated as a continuous variable, the age-adjusted RR for younger men was 0.85 (95 percent CI: 0.61, 1.20), and that for younger women was 1.25 (95 percent CI: 1.01, 1.54). The age- and area-adjusted RRs were 0.75 (95 percent CI: 0.51, 1.12) for younger men and 1.44 (95 percent CI: 1.12, 1.86) for younger women. In the sensitivity analysis among only those with a known occupation (men, n = 33,021; women, n = 26,206), the age- and area-adjusted RRs were 0.93 (95 percent CI: 0.66, 1.32) for younger men and 1.43 (95 percent CI: 1.06, 1.94) for younger women. Further analyses were also performed by dividing the follow-up time into three periods. The age- and area-adjusted RRs for younger women were 1.20 (95 percent CI: 0.62, 2.30; number of hip fractures = 119), 0.82 (95 percent CI: 0.46, 1.48; number of hip fractures = 217), and 1.21 (95 percent CI: 0.88, 1.66; number of hip fractures = 335) for the hip fractures that had occurred in 1981–1985, 1986–1990, and 1990–1994, respectively.

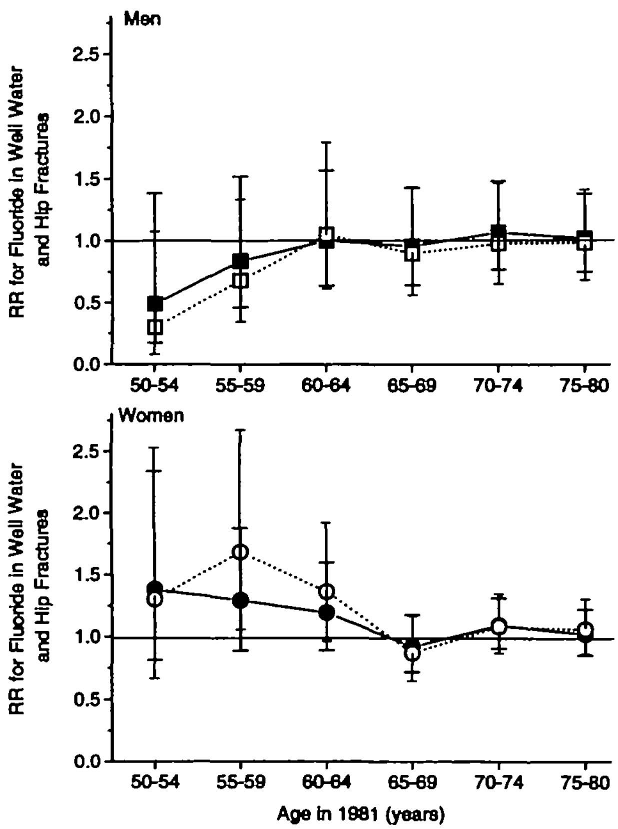

FIGURE 3. Rate ratios and 95 percent confidence intervals of the association of the estimated fluoride concentration in well water (df = 1) and hip fractures in men and women (Cox regression). Age-adjusted (■ and ●) and age- and area-adjusted (□, O, and the narrower cap of 95 percent confidence intervals) are shown.

DISCUSSION

In this retrospective cohort study based on record linkage, we studied the relation between hip fractures observed in 1981–1994 and fluoride exposure among the Finnish persons born in 1900–1930 who had lived without municipal drinking water source for at least the years 1967–1980. Women aged 50–64 years at the beginning of the follow-up with estimated high fluoride exposure had statistically significantly increased hip fracture risk, whereas among men there was a suggestion of a negative association. No association between fluoride exposure and hip fractures was found in older men or women.

The highest concentrations of fluoride are located in the southeast and southwest parts of Finland, in which typical concentrations of fluoride in well water are 1.5–5.0 mg/liter (20). We consider that the exposure estimation is an adequate proxy of the real fluoride exposure through drinking water. This is supported by the correlation of 0.71 between analyzed and estimated fluoride concentrations in well water. The effect of the highest concentrations was diluted, and the estimated fluoride value tended to be 0.7 times less than the measured fluoride concentration in a well. This possible nondifferential misclassification of exposure may have biased the rate ratio estimates toward the null.

In this study, only rural persons were included in the cohort. Urbanization level is important to consider because rural populations tend to have a lower incidence of hip fractures (23–25). We do not know whether the fluoride exposure has changed during the years in the cohort or for how long the consumption of the well water continued after 1980.

According to the Mini-Finland Health Survey (26), certain risk factors for hip fractures and osteoporosis (namely alcohol consumption in men and women, low body weight, and smoking among women) are more common in southern Finland (covering area 7), with high fluoride exposure, but not in southwest Finland (area 5), where there is also high fluoride exposure. Because this study was based on the registry linkages, information on the important covariables, such as nutri-

TABLE 3. Rate ratios (RR) and 95% confidence intervals (CI) of hip fractures in the categorized fluoride concentration among Finnish men and women aged 50–65 years ("younger men and women") in 1981

Fluoride concentration (mg/liter)	No. of hip fractures	Person-years in 1981–1994	Incidence/ 1,000 person-years	Crude RR	95% CI	Age- and area-adjusted RR	95% CI
Men							
≤0.1	228	305,816	0.74	1.0		1.0	
0.1–0.3	103	109,615	0.94	1.04	0.99, 1.58	1.20	0.91, 1.56
0.3–0.5	12	17,698	0.68	0.75	0.50, 1.61	0.81	0.44, 1.49
0.5–1.0	21	34,021	0.62	0.82	0.53, 1.29	0.68	0.41, 1.13
1.1–1.5	8	14,409	0.55	0.90	0.37, 1.51	0.60	0.29, 1.25
>1.5	5	6,426	0.78	1.25	0.43, 2.52	0.87	0.35, 2.16
Women							
≤0.1	388	350,847	1.11	1.0		1.0	
0.1–0.3	165	132,505	1.24	1.12	0.94, 1.35	1.16	0.93, 1.43
0.3–0.5	27	20,667	2.66	1.18	0.80, 1.74	1.31	0.86, 1.99
0.5–1.0	57	39,412	1.45	1.31	0.99, 1.73	1.53	1.08, 2.16
1.1–1.5	21	17,875	1.15	1.06	0.68, 1.65	1.24	0.77, 2.01
>1.5	13	6,908	1.88	1.70	0.98, 2.96	2.09	1.16, 3.76

tion and physical activity, were not available. Therefore, we could not control all of the possible confounders. However, the overall effect of geographic variation in the suggested risk factors in this analyses can be considered small, since the statistical analysis adjusting for area did not change the result significantly.

Everyone in the cohort received individual fluoride exposure estimations. Due to the smoothing method, exposure estimates for persons living close to each other are correlated, which may lead to insufficient control of the areal differences. However, in the areas with the highest estimated fluoride concentrations, low levels of estimated concentrations also exist. In areas 1–8, the estimated fluoride concentration below 0.1 mg/liter were in 100, 88, 86, 100, 14, 43, 43, and 89 percent of the population in the cohort, respectively.

The coverage of the population in the Population Registry is complete for all of Finland. Virtually all persons suffering a hip fracture are hospitalized, and thus, registration in the Hospital Discharge Registry is not dependent on area of residence.

Occupations were used as measures of the socioeconomic status. The proportion of those for whom no data on occupation were available was 59 percent. If a person had retired, no previous occupation was coded. Those with an unknown occupation were older (mean age, 69 years) than rest of the cohort (mean age, 61 years). The sensitivity analysis, in which only those with a definite occupation were included, showed results similar to those of the entire analysis.

The association between bone fractures and fluoride exposure through drinking water has also been studied in Finland previously. Arnala et al. (27) did not find differences in the incidences of hip fractures between persons aged 64–92 years in the low-fluoride, rural Kuopio region (fluoride concentration in drinking water, <0.3 mg/liter), urban Kuopio (providing fluoridated drinking water, 1.0–1.2 mg/liter), and the naturally high-fluoride Kotka region (>1.5 mg/liter). However, gender and urbanization level were not considered in the statistical analyses. Another study among women aged 47–59 years indicated no differences in self-reported bone fracture rates in the low-fluoride, rural and fluoridated, urban Kuopio region (28). In that study, hip fractures were not analyzed separately. In the third study from Finnish towns, Jyväskylä (< 0.1 mg/liter) and Kuopio (1 mg/liter), Simonen and Laitinen (19) concluded that fluoride protected against hip fractures among men and women aged 50 years or more. However, the higher fluoride concentration in drinking water was more clearly associated with increased hip fractures among younger men (aged 50–59 years) than among the older men. Furthermore, among younger women (aged 50–69 years), the hip fractures incidences even tended to be higher in the town with fluoridated drinking water.

Furthermore, consistent with our study, Danielson et al. (9) showed that the rates of hip fracture were higher in the fluoridated areas among the younger women (aged 65–80 years at the time of diagnosis) but not among the older women. The authors suggested that an explanation for this could have been that younger women had been exposed to fluoride as they passed through menopause, a period of increased bone remodeling. Women older than 80 years would have already gone through menopause at the beginning of fluoridation and would have had less bone remodeling and less incorporation of fluoride into the bone. This explanation looks unlikely in our study because the fluoride concentrations in wells have probably remained stable.

Ecologic studies in the United States have found no effect (29) or increase in hip fracture rates (9–11) in the areas with fluoridated drinking water (approximately 1 mg/liter) when compared with nonfluoridated areas for men and women aged 65 years or more. Caùley et al. (30) showed no statistically significant difference in the hip fracture risk and the duration of exposure to fluoridated drinking water (1.01 ± 0.21 mg/liter) among women aged 65 years or more. In prospective studies in Iowa, higher fluoride concentrations in drinking water (4 vs. 1 mg/liter) were associated with an increased rate of osteoporotic fractures, such as fracture in the hip, among postmenopausal women (12, 13). A population-based study among persons aged 65 years or more in southwestern France revealed that the risk of hip fracture was higher when fluoride concentration in water was 0.11–1.83 mg/liter when compared with 0.05–0.11 mg/liter, even when men and women were analyzed together (14).

This study suggests that fluoride is associated with increased hip fracture risk in younger women, but not in older women or men. Possibly because of more prominent risk factors at higher ages, the effect of fluoride could not be seen in very old persons. For example, calcium absorption decreases with age as a result of various possible mechanisms, including decreased vitamin D intake, synthesis, and metabolism (31). Furthermore, kinetics of fluoride may be different at older ages (32). An explanation of the gender differences may be related to an involvement of fluoride in the differences between men and women in bone formation and resorption, hormonal differences (33, 34), prevalence of osteoporosis (16), the way trabecular bone is decreased (35), or differences in the cortical bone density (36). An important risk factor for age-related bone loss in women is low estrogen level and for men (possible) low testosterone level (33, 34). Age-related decrease of the cortical bone density is less in men than in women (36), and width of bars in the trabecular network decreases in men, but the number of bars in the network decreases in women (35). Some of the risk factors for osteoporosis and fractures, such as the use of alcohol and cigarette smoking, are more prominent in men than in women (26), which may mask the association between fluoride and hip fractures among men. Furthermore, some persons may have had hip fractures prior to 1978, which may affect the result, especially among older persons, who may be more likely to have a second fracture during the follow-up of 1981–1994.

Ingested fluoride absorbs rapidly and almost completely in the duodenum (2). Fluoride accumulates into skeletal bone mainly during the age of growth, but the accumulation continues until very old age (37). We do not have data on the beginning of the residency at the address in which the fluoride exposure was estimated, nor do we know the fluoride exposure from drinking water before 1967. This is a limitation of the study if fluoride exposure at younger age is most important.

The fluoride dose from drinking water among the cohort would vary from 0 to 3.6 mg/day (median, 0.2 mg/day) if consumption of 1.5 liters/day drinking water was assumed. The estimated average dietary intake of fluoride in Finland is 0.6 mg/day (38). Plants may concentrate fluoride, and persons who consume locally grown food may be more exposed in the areas with high fluoride concentrations. On the other hand, the smoothing dilutes the peak values of fluoride concentrations in water. The daily dose from toothpaste can be estimated as 0.08 mg (39). The ingestion from air and soil is generally insignificant (40). The total fluoride dose in the cohort would thus amount to between 0.6 and 3.7 mg/day (median, 0.8 mg/day), which is approximately the same as that reported previously in the North America (40, 41).

In conclusion, the results suggest that increase in the estimated fluoride concentrations in well water is associated with elevated risk of hip fracture among women who were age 50–64 years at the beginning of the 14-year follow-up. The association for men of the same age tended to be to in the opposite direction, but the protective effect was not statistically significant. These results suggest that fluoride may be associated with some gender-dependent mechanisms or risk factors for hip fractures. No association was found for older women or men, which may indicate that other risk factors for hip fracture are more prominent in older age. Further research should include studies in which personal fluoride exposure is measured from all sources and age and sex are carefully considered.

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REFERENCES

1. Hillier S, Inskip H, Coggon D, et al. Water fluoridation and osteoporotic fracture. Community Dent Health 1996;13

(Suppl. 2):63–8.
2. Inkovaara JA. Fluoride in the prevention and treatment of osteoporosis. Adv Nutr Res 1994;9:231–43.
3. Guggenheim K, Simkin A, Wolinsky I. The effect of fluoride on bone of rats fed diets deficient in calcium or phosphorus. Calcif Tissue Res 1976;22:9–17.
4. Riggins RS, Rucker RC, Chan MM, et al. The effect of fluoride supplementation on the strength of osteopenic bone. Clin Orthop 1976;January-February:352–7.
5. Riggs BL, Hodgson SF, O'Fallon WM, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 1990;322:802–9.
6. Turner CH, Hasegawa K, Zhang W, et al. Fluoride reduces bone strength in older rats. J Dent Res 1995;74:1475–81.
7. Grynpas MD, Cheng PT. Fluoride reduces the rate of dissolution of bone. Bone Miner 1988;5:1–9.
8. Kleerekoper M. Fluoride and the skeleton. Crit Rev Clin Lab Sci 1996;33:139–61.
9. Danielson C, Lyon JL, Egger M, et al. Hip fractures and fluoridation in Utah's elderly population. JAMA 1992;268:746–8.
10. Jacobsen SJ, Goldberg J, Cooper C, et al. The association between water fluoridation and hip fracture among white women and men aged 65 years and older. A national ecologic study. Ann Epidemiol 1992;2:617–26.
11. Jacobsen SJ, Goldberg J, Miles TP, et al. Regional variation in the incidence of hip fracture. US white women aged 65 years and older. JAMA 1990;264:500–2.
12. Sowers MR, Wallace RB, Lemke JH. The relationship of bone mass and fracture history to fluoride and calcium intake: a study of three communities. Am J Clin Nutr 1986;44:889–98.
13. Sowers MR, Clark MK, Jannausch ML, et al. A prospective study of bone mineral content and fracture in communities with differential fluoride exposure. Am J Epidemiol 1991; 133:649–60.
14. Jacqmin-Gadda H, Commenges D, Dartigues JF. Fluorine concentration in drinking water and fractures in the elderly. JAMA 1995;273:775–6.
15. Cooper C, Campion G, Melton LJ 3rd. Hip fractures in the elderly: a world-wide projection. Osteoporos Int 1992;2: 285–9.
16. Kannus P, Parkkari J, Niemi S, et al. Epidemiology of osteoporotic ankle fractures in elderly persons in Finland. Ann Intern Med 1996;125:975–8.
17. Madans J, Kleinman JC, Cornoni-Huntley J. The relationship between hip fracture and water fluoridation: an analysis of national data. Am J Public Health 1983;73:296–8.
18. Suarez-Almazor ME, Flowerdew G, Saunders, LD, et al. The fluoridation of drinking water and hip fracture hospitalization rates in two Canadian communities. Am J Public Health 1993; 83:689–93.
19. Simonen O, Laitinen O. Does fluoridation of drinking-water prevent bone fragility and osteoporosis? Lancet 1985;2:432–4.
20. Lahermo P, Ilmasti M, Juntunen R, et al. Suomen Geokemian Atlas, osa 1. Suomen pohjavesien hydrogeokemiallinen kartoitus. (In Finnish). [Geochemical Atlas of Finland. Part 1. Hydrogeochemical survey of the Finnish ground waters]. Helsinki, Finland: Geological Survey of Finland, 1990.
21. Gustavsson N, Lampio E, Tarvainen T. Visualization of geochemical data on maps at the Geological Survey of Finland. J Geochem Explor 1997;59:197–207.
22. Korkka-Niemi K, Sipilä A, Hatva T, et al. Valtakunnallinen kaivovesitutkimus. Talousveden laatu ja siihen vaikuttavat tekijät. (In Finnish). [Nationwide well water study. Quality of drinking water and factors affecting the quality]. Publications of Water and Environment Board, Series A 146. Research of Ministry of Social Affairs and Health February 1993. Helsinki, Finland: Water and Environment Board and Ministry of Social Affairs and Health, 1993.
23. Falch JA, Kaastad TS, Bohler G, et al. Secular increase and geographical differences in hip fracture incidence in Norway. Bone 1993;14:643–5.
24. Ray WA, Griffin MR, West R, et al. Incidence of hip fracture in Saskatchewan, Canada, 1976–1985. Am J Epidemiol 1990; 131:502–9.
25. Madhok R, Melton LJ 3rd, Atkinson EJ, et al. Urban vs rural increase in hip fracture incidence. Age and sex of 901 cases 1980–89 in Olmsted County, U.S.A. Acta Orthop Scand 1993; 64:543–8.
26. Aromaa A, Heliövaara M, Impivaara O, et al. Terveys, tomintakyky ja hoidontarve Suomessa. Mini-Suomi-terveystutkimuksen perustulokset. (In Finnish). [Health, functional limitations and need for care in Finland. Basic results from the Mini-Finland Health Survey]. Publications of the Social Insurance Institution, AL:32. Helsinki, Finland: Social Insurance Institution, 1989.
27. Arnala I, Alhava EM, Kivivuori R, et al. Hip fracture incidence not affected by fluoridation. Osteofluorosis studied in Finland. Acta Orthop Scand 1986;57:344–8.
28. Kröger H, Alhava E, Honkanen R, et al. The effect of fluoridated drinking water on axial bone mineral density—a population-based study. Bone Miner 1994;27:33–41.
29. Karagas MR, Baron JA, Barrett JA, et al. Patterns of fracture among the United States elderly: geographic and fluoride effects. Ann Epidemiol 1996;6:209–16.
30. Caùley JA, Murphy PA, Riley TJ, et al. Effects of fluoridated drinking water on bone mass and fractures: the study of osteoporotic fractures. J Bone Miner Res 1995;10:1076–86.
31. Riggs BL, Melton LJ 3rd. Involutional osteoporosis. N Engl J Med 1986;314:1676–86.
32. Rao HV, Beliles RP, Whitford GM, et al. A physiologically based pharmacokinetic model for fluoride uptake by bone. Regul Toxicol Pharmacol 1995;22:30–42.
33. Jackson JA, Kleerekoper M. Osteoporosis in men: diagnosis, pathophysiology, and prevention. Medicine 1990;69:137–52.
34. Rudman D, Drinka PJ, Wilson CR, et al. Relations of endogenous anabolic hormones and physical activity to bone mineral density and lean body mass in elderly men. Clin Endocrinol 1994;40:653–61.
35. Aaron JE, Makins NB, Sagreiya K. The microanatomy of trabecular bone loss in normal aging men and women. Clin Orthop 1987;February:260–71.
36. Ruff CB, Hayes WC. Sex differences in age-related remodeling of the femur and tibia. J Orthop 1988;6:886–96.
37. Alhava EM, Olkkonen H, Kauranen P, et al. The effect of drinking water fluoridation on the fluoride content, strength and mineral density of human bone. Acta Orthop Scand 1980; 51:413–20.
38. Varo P, Koivistoinen P. Mineral element composition of Finnish foods. XII. General discussion and nutritional evaluation. Acta Agric Scand 1980;(Suppl. 22):165–71.
39. Levy SM. Review of fluoride exposures and ingestion. Commun Dent Oral Epidemiol 1994;22:173–80.
40. Liteplo RG, Meek ME, Gomes R, et al. Inorganic fluoride: evaluation of risks to health from environmental exposure in Canada. Environ Carcinog Ecotoxicol Rev 1994;C12:327–44.
41. Burt BA. The changing patterns of systemic fluoride intake. J Dent Res 1992;71:1228–37.