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Effect of Long-Term Exposure to Fluoride in Drinking Water on Risks of Bone Fractures

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ABSTRACT

Findings on the risk of bone fractures associated with long-term fluoride exposure from drinking water have been contradictory. The purpose of this study was to determine the prevalence of bone fracture, including hip fracture, in six Chinese populations with water fluoride concentrations ranging from 0.25 to 7.97 parts per million (ppm). A total of 8266 male and female subjects ≥50 years of age were enrolled. Parameters evaluated included fluoride exposure, prevalence of bone fractures, demographics, medical history, physical activity, cigarette smoking, and alcohol consumption. The results confirmed that drinking water was the only major source of fluoride exposure in the study populations. A U-shaped pattern was detected for the relationship between the prevalence of bone fracture and water fluoride level. The prevalence of overall bone fracture was lowest in the population of 1.00–1.06 ppm fluoride in drinking water, which was significantly lower ($p < 0.05$) than that of the groups exposed to water fluoride levels ≥4.32 and ≤0.34 ppm. The prevalence of hip fractures was highest in the group with the highest water fluoride (4.32–7.97 ppm). The value is significantly higher than the population with 1.00–1.06 ppm water fluoride, which had the lowest prevalence rate. It is concluded that long-term fluoride exposure from drinking water containing ≥4.32 ppm increases the risk of overall fractures as well as hip fractures. Water fluoride levels at 1.00–1.06 ppm decrease the risk of overall fractures relative to negligible fluoride in water; however, there does not appear to be similar protective benefits for the risk of hip fractures. (J Bone Miner Res 2001;16:932–939)

Key words: fluoride, fluoridation, bone, fracture

INTRODUCTION

FLUORIDE IS ubiquitous in our environment, and it is the most electronegative and reactive of all elements.(1) Historically, the association between fluoride and prevention of dental caries was first recognized in the 1930s in studies on chronic endemic dental fluorosis. It was noted that people living in communities with a natural fluoride content of 1 part per million (ppm) or more in drinking water had about 50% fewer dental caries than those with water containing 0.1–0.3 ppm fluoride.(2,3) Subsequently, several independently conducted studies in the 1940s confirmed the cariostatic efficacy of fluoride.(4–7) Based on these findings, it was suggested that drinking water be fluoridated to an

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"optimal" level, which ranges from 0.7 to 1.2 ppm in the United States depending on the ambient air temperature in the area.[8,9] The fluoridation of drinking water supplies has proceeded at a steady rate since its introduction in the late 1940s. Currently, a significant portion of the U.S. population is exposed to drinking water that has been fluoridated artificially or naturally. In 1992, the U.S. population supplied with drinking water of 0.7–1.2 ppm fluoride was 62%, and the target was to reach 75% by the year 2000.[10] The rest of the U.S. population has at least some fluoride exposure through the use of toothpaste, mouthrinse, pediatric supplements, and various dental materials. Water fluoridation also has been practiced in most other developed countries, and many people in developing countries are exposed to drinking water with natural fluoride.[11]

Although its cariostatic benefits have been well documented, the safety of fluoridated drinking water has been controversial since its introduction.[12] So far extensive research has investigated the most potentially negative side effects. Other than fluorosis in populations of long-term, excessive fluoride intake, studies have uncovered little evidence to suggest any important health problems associated with the consumption of drinking water containing approximately 1 ppm fluoride. However, the question of effects of fluoride exposure from drinking water on fracture risk remains unresolved. Generally, it is accepted that excessive fluoride exposure conveys an increased risk for bone fractures.[13] Less is understood regarding fracture risk at lower exposure.[14] Available information in the literature is limited and often contradictory. Reported results varied from an increased risk,[15–18] to no effect,[19–22] to a decreased risk[23,24] of fractures associated with exposure to fluoridated water.

The question of whether the exposure to fluoride in drinking water for cariostatic purposes increases the risk of fractures is both scientifically and politically important. With a significant portion of the population exposed to fluoride, even small increases in the risk will yield large increases in the number of fractures, which will have a significant impact on public health. On the other hand, unlike most potential risk factors that depend on an individual's personal choices, fluoride exposure from drinking water is determined largely by public health policy. Clearly, it is imperative that any potential risks associated with such exposure be well understood.

The purpose of this study was to determine the prevalence of bone fractures in Chinese populations residing in rural communities of various fluoride concentrations in drinking water. Fluoride exposure in most populations in rural China is limited to drinking water and diet, and there is virtually no fluoride exposure from other sources such as fluoride supplements and fluoride-containing dentifrice, mouthrinse, or infant formula. Most Chinese still reside in the community in which they were born, and mobility in the countryside is practically nonexistent. Consequently, determination of the history of fluoride exposure in individuals is relatively easy and reliable.

MATERIALS AND METHODS

Before the conduct of the study, protocols and pertinent documents were submitted to and approved by the Indiana University Institutional Review Board (IRB). In addition, an IRB was established at the collaborating institution in China, the Institute of Environmental Health and Engineering, Chinese Academy of Preventive Medicine, and the Single Project Assurance was approved by the Office for Protection from Research Risks, National Institutes of Health, Bethesda, MD. An informed consent letter was provided to and signed by all participants before the initiation of the project at each study site.

TABLE 1. DEMOGRAPHIC DATA OF SIX CHINESE POPULATIONS RESIDING IN COMMUNITIES OF VARYING FLUORIDE CONCENTRATION IN DRINKING WATER

Group	*Water F (ppm)*	n	*Age (year)*	*Male (%)*
1	0.25–0.34	1363	62.6 ± 9.3[a]	41.8
2	0.58–0.73	1407	62.7 ± 9.1	47.0
3	1.00–1.06	1370	62.5 ± 9.0	43.7
4	1.45–2.19	1574	63.6 ± 8.8	44.5
5	2.62–3.56	1051	64.0 ± 9.0	43.3
6	4.32–7.97	1501	61.3 ± 8.4	52.4

[a] Mean ± SD.

Six groups of subjects ≥50 years of age were recruited randomly from communities of water fluoride concentrations ranging from 0.25 to 7.97 ppm (Table 1). A minimum of 25 years of continuous residence in the study communities and a lifelong exposure to the specified fluoride level in drinking water was required for each participant. The residency of each subject was determined by the following three measures: (1) objective assessment by checking the Family Registry Book, an official document issued by the government; (2) a subject survey questionnaire; and (3) confirmation by village officials who were familiar with the subject.

For each study site, samples of drinking water were collected and analyzed for fluoride using the direct method with a combination fluoride-specific electrode (no. 96-909-00; Orion Research, Inc., Boston, MA, USA)). Eight additional elements in drinking water also were analyzed, including calcium, aluminum, selenium, lead, cadmium, iron, zinc, and arsenic. A modified International Organization for Standardization ISO method[25] was used to determine the fluoride content in ambient air. Surveys also were conducted to ensure no other potential sources of fluoride exposure (e.g., pollution, dentifrice, etc.) in the study populations.

Data collected from each subject included medical history and demographic information, bone fractures, physical activity as determined using the Chinese standard,[26] tea drinking, cigarette smoking, and alcohol consumption. For subjects reporting bone fractures, additional information associated with each fracture was collected. The subjects were questioned for the site (22 sites using an illustrative drawing of the human body), age, and frequency of each fracture as well as circumstances associated with the fracture, including cause (eight categories), location (six categories), ground condition, and fall or without fall. If the fracture received medical attention, efforts were made to obtain the original records and X-ray film. For those without medical records, an X-ray of the bone with the reported fracture was taken to verify the self-reported bone fracture. In addition, each subject reporting fracture was questioned for the information on falls within the last year, if any, and the family history of hip fractures (parents, grandparents, and siblings). Although the information on the number of fractures per person was collected, the analysis defined subjects as to whether they had the fracture or not and did not use the count of multiple fractures in the same subject.

In addition, a 3-day dietary survey and analysis for dietary intake of calcium, protein, and fluoride were conducted in a randomly selected 10% of subjects to ensure that all study populations had adequate nutrition and to determine fluoride exposure from diet. The dietary fluoride and brewed tea samples were analyzed using a modified method of Taves,[27,28] and calcium and protein were determined using Chinese National Standard procedures. [29]

For each class of fractures, the bivariate relationship was first examined between the fracture rate and several demographic and lifestyle variables including gender, current cigarette smoking status, consumption of alcohol, physical activity level on the job, age, and body mass index (BMI). Comparisons were made using χ^2 tests for categorical variables and *t*-tests for continuous variables. Dose-dependent analyses were performed using a multiple logistic regression model, which was used to compare fracture rates across fluoride levels, while adjusting for demographic and lifestyle variables, which were significant in the bivariate analysis. Adjusted odds ratios (ORs) were calculated based on the coefficients in the multiple logistic regression models.

RESULTS

The demographic data collected from the six study populations are summarized in Table 1. A total of 8266 male and female Chinese subjects participated in the study. The age distribution was comparable among the groups. The gender composition also was similar except for the group of the highest fluoride concentration (4.32–7.97 ppm) in drinking water, which had more male participants than the other five groups. The residency of all the subjects was verifiable, and the majority of the subjects had been living in the same community since they were born. For subjects who changed residency, mainly because of marriage, water fluoride within the specified range was verified for the previous community in which they resided. Surveys indicated that the environment, culture, ethnic background, social structure, and economic conditions of these populations had not changed significantly during the past several decades. There were no ethnic differences among the six study populations. The level of physical activities was found similar among the six populations, and over 90% of the participants in each population were either farmers or housewives. The estimated nutrition levels were adequate for all six populations as determined by the dietary survey and laboratory analysis of daily intake of protein, calcium, and calories, which was performed in 10% of the subjects.

The analysis of water samples collected from water supplies for the study populations confirmed the specified fluoride concentrations in drinking water. None of the study subjects used fluoride-containing toothpaste or mouthwashes, and the use of packaged beverages and canned food was minimal. Surveys and analysis of meals found no unusual sources of fluoride. Tea drinking was reported by 13.5% of subjects. The analysis of the brewed tea samples showed that their fluoride concentration was largely determined by the fluoride concentration of water used. The fluoride content in ambient air was negligible ($<3\ \mu g/m^3$) in all populations. The calculated average total daily fluoride intake was proportional to the water fluoride concentration (Fig. 1).

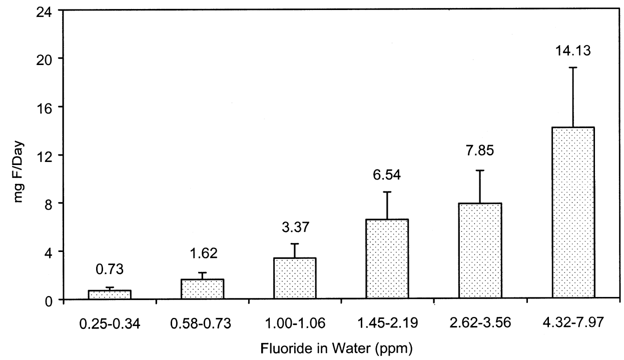

FIG. 1. Total daily fluoride intake in relation to fluoride concentration in drinking water in six Chinese populations.

The initial analysis of bone fracture data included overall, spinal, and hip fractures since the age 20 years. There were 531 subjects reporting fractures; so, the prevalence of overall bone fracture in the entire study population was 6.42%. Among these 531 subjects, 526 were confirmed fractures by X-ray; so, the reliability of the reported fracture was 99.1%. The mean ages of subjects with fracture were 63.4, 64.2, 63.5, 66.1, 64.6, and 62.1 years for groups 1–6 (Table 1), respectively. Statistical analysis of the data showed that only group 4 (1.45–2.19 ppm fluoride) and group 6 (4.32–7.97 ppm fluoride) differed significantly, indicating that subjects of fractures were slightly younger in the population of the highest fluoride in drinking water. However, the effect was not dose dependent.

The prevalence of overall bone fracture for each fluoride level is presented in Table 2. Bivariate analysis of the data showed that age, gender, alcohol consumption, and the level of physical activity were significant factors for the risk of overall bone fractures. Subjects with fractures were significantly older ($p < 0.01$) than those without fractures. More males suffered fractures compared with females ($p < 0.01$), and subjects who consumed alcohol had more fractures ($p < 0.01$) than nondrinkers (Table 3). Gender and alcohol consumption were highly correlated, with 46.9% of males reported drinking alcohol and only 4.3% of females reported drinking alcohol. The level of physical activity also had a significant effect ($p = 0.05$); it appeared that either excessively strenuous activity or the lack of activity increased the risk of fractures. No significant effect of cigarette smoking ($p = 0.15$) or BMI ($p = 0.80$) on overall fracture rates was detected. For the results of water calcium, aluminum, sele-

TABLE 2. EFFECT OF FLUORIDE EXPOSURE FROM DRINKING WATER ON PREVALENCE OF OVERALL FRACTURE SINCE THE AGE OF 20 YEARS IN SIX CHINESE POPULATIONS

Water F (ppm)	n *(surveyed)*	n *(fracture)*	*Prevalence (%)*	*OR*[a]	p *Value*[a]
0.25–0.34	1363	101	7.41	1.50	0.01
0.58–0.73	1407	90	6.40	1.25	0.17
1.00–1.06	1370	70	5.11	1.00	—
1.45–2.19	1574	95	6.04	1.17	0.33
2.62–3.56	1051	64	6.09	1.18	0.35
4.32–7.97	1501	111	7.40	1.47	0.01

[a] Values relative to the 1.00- to 1.06-ppm fluoride group, adjusted for age and gender using multiple logistic regression.

TABLE 3. BIVARIATE ASSOCIATIONS OF OVERALL BONE FRACTURE RISKS SINCE THE AGE OF 20 YEARS WITH CATEGORICAL FACTORS

Variable	*Category*	*Subjects*	*Fracture (%)*	p *Value*
Gender	Male	3771	7.48	
	Female	4495	5.54	<0.01
Cigarette smoking	Yes	3100	6.94	
	No	5166	6.12	0.15
Alcohol consumption	Yes	1960	8.52	
	No	6299	5.76	<0.01
Physical activity	Very little	652	7.98	
	Light	2532	5.53	
	Moderate	4157	6.54	
	Heavy	912	7.13	
	Extremely strenuous	11	18.18	0.05

nium, lead, cadmium, iron, zinc, and arsenic, the data analyses were adjusted for each of these elements by including them individually in the logistic regression model for overall fractures. Only calcium ($p = 0.044$) and iron ($p = 0.032$) showed a significant relationship with fracture but neither one (nor any of the other elements) altered the results concerning the six fluoride groups.

Table 2 also presents the ORs and *p* values from the multiple logistic regression model adjusted for age and gender. Alcohol consumption was not included in the model because it was highly correlated with gender. Physical activity was not included because it was no longer significant when the small number of people with strenuous activity was combined with the heavy activity group. Both the populations with the lowest (0.25–0.34 ppm) and the highest (4.32–7.97 ppm) fluoride in drinking water showed a significantly higher prevalence of overall fractures ($p = 0.01$) than those residing in areas where the fluoride in water was 1.00–1.06 ppm. The prevalence of overall fractures was lowest in subjects with 1.00–1.06 ppm of fluoride in water; however, it was not significantly different from the values for the groups in which water contained 0.58–0.73 ppm, 1.45–2.19 ppm, and 2.62–3.56 ppm of fluoride. In general, the trend of the fracture prevalence in relation to the water fluoride concentration approximates a U-shaped pattern (Fig. 2).

Table 4 presents the prevalence of hip fractures since age 20 years in the six populations and the results of the multiple logistic regression model. Among the 8266 subjects surveyed, 56 suffered hip fractures, resulting in a prevalence of 0.68%. Bivariate analysis of the data showed that subjects with hip fractures were significantly older (mean age, 68.5 years vs. 62.7 years) and thinner (mean BMI, 21.2 vs. 22.6) than those without fractures ($p < 0.01$ for both). However, no significant effects were detected for gender, cigarette smoking, alcohol consumption, and the level of physical activity. After adjusting for age and BMI, the risk of hip fracture was significantly higher in the highest fluoride group (4.32–7.97) than the population with 1.00–1.06

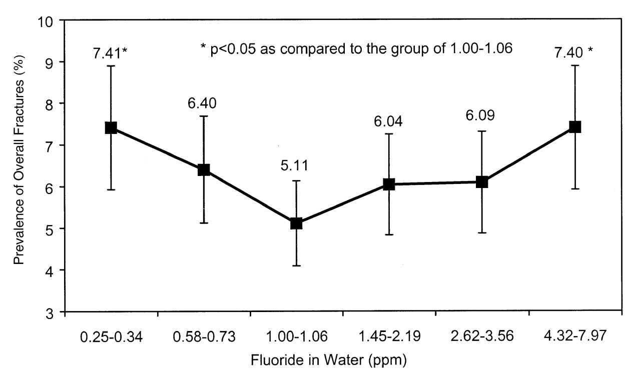

FIG. 2. Prevalence of overall fractures and fluoride concentration in drinking water in six Chinese populations since the age of 20 years.

TABLE 4. EFFECT OF FLUORIDE EXPOSURE FROM DRINKING WATER ON PREVALENCE OF HIP FRACTURES IN SIX CHINESE POPULATIONS SINCE THE AGE OF 20 YEARS

Water F (ppm)	n *(surveyed)*	n *(fracture)*	*Prevalence (%)*	*OR*[a]	p *Value*[a]
0.25–0.34	1363	5	0.37	0.99	0.99
0.58–0.73	1407	6	0.43	1.12	0.85
1.00–1.06	1370	5	0.37	1.00	—
1.45–2.19	1574	14	0.89	2.13	0.15
2.62–3.56	1051	8	0.76	1.73	0.34
4.32–7.97	1501	18	1.20	3.26	0.02

[a] Values relative to the 1.00- to 1.06-ppm fluoride group, adjusted for age and BMI using multiple logistic regression.

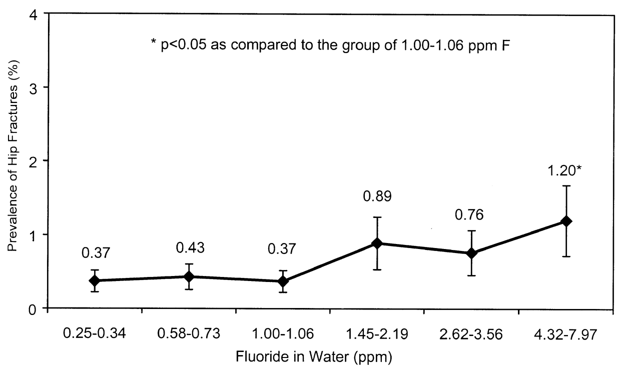

FIG. 3. Prevalence of hip fractures and fluoride concentration in drinking water in six Chinese populations since the age of 20 years.

ppm of water fluoride, which had the lowest prevalence. In general, the hip fracture prevalence was stable up to 1.06 ppm of fluoride and then appeared to rise, although it did not attain statistical significance until the water fluoride concentration reached 4.32–7.97 ppm (Fig. 3).

Only 49 subjects in the entire study population reported spinal fractures. None of the demographic factors examined appeared to be related to spinal fracture. In the logistic regression analysis, none of the fluoride groups differed significantly from the group that had 1.00–1.06 ppm of fluoride in drinking water.

The data were further analyzed for overall bone fractures since the age of 50 years, and the results are summarized in Table 5. In the bivariate analyses, age remained a risk factor; subjects with fractures were significantly older than subjects without fractures. The level of physical activity also was significant ($p = 0.03$) in relation to fractures (Table 6). However, no significant effects were detected for gender, cigarette smoking, alcohol consumption, and BMI. There were 311 people with fractures, and the overall prevalence was 3.76%. The relationship between water fluoride level and overall fractures showed a similar trend to the overall fractures since the age of 20 years (Table 2); however, only the group with the highest level of fluoride in the water (4.32–7.97 ppm) had a significantly higher risk for fractures, after adjusting for age, than the group that had 1.00–1.06 ppm of fluoride in the water. The pattern is similar to overall fractures since the age of 20 years but less pronounced.

There were only 79 subjects who suffered fractures as a result of a fall from less than standing height since the age of 50 years, and the prevalence was small in all of the populations. Therefore, no further analyses were performed.

DISCUSSION

Each year in the United States there are approximately 1.5 million fractures associated with osteoporosis. The annual number of hip fractures is estimated to be around 250,000, with the vast majority occurring in women over the age of 60 years. Although osteoporotic fractures generally are viewed as affecting primarily developed nations, the rapidly increasing population of elderly people in developing, particularly Asian, countries dictates that the problem of osteoporotic fractures will soon place major burdens on health care systems in other parts of the world. Recently published projections suggest that by the year 2020, Asian countries may bear the majority of the world's hip fracture burden.[30] In China, the rates of hip fracture are low but have been predicted to rise rapidly.[31] The identification of preventable factors that increase risk for fractures is clearly an important issue. Because of the increasing use of water fluoridation for the prevention of dental caries in general populations, it is imperative to understand the potential impact of fluoride levels used on the risk of bone fractures.

A major factor that may have caused controversial findings on water fluoridation and bone fracture is the difficulty in locating study populations with definable fluoride exposure. Average water consumption from an "optimally" fluoridated water supply (approximately 1 ppm) would result in an adult exposure of approximately 1–4 mg of fluoride daily, of which 60–70% would come from beverages.[32] However, for the United States and other developed countries as well as many developing countries, the use of fluoride in various delivery systems other than water fluoridation, such as toothpaste, mouthrinse, supplements, etc., has become increasingly extensive since the 1970s.[12] Thus, it is erroneous to use the community water fluoride level as the sole indicator for long-term fluoride exposure. The relatively high mobility of the population in the United States further increases the difficulty in accurately estimating the history of individual fluoride exposure. Consequently, a reliable and accurate estimation of long-term

TABLE 5. EFFECT OF FLUORIDE EXPOSURE FROM DRINKING WATER ON PREVALENCE OF OVERALL FRACTURES IN SIX CHINESE POPULATIONS SINCE THE AGE OF 50 YEARS

Water F (ppm)	n *(surveyed)*	n *(fracture)*	*Prevalence (%)*	*OR*[a]	p *Value*[a]
0.25–0.34	1363	59	4.33	1.33	0.16
0.58–0.73	1407	45	3.20	0.97	0.87
1.00–1.06	1370	45	3.28	1.00	—
1.45–2.19	1574	52	3.30	0.96	0.85
2.62–3.56	1051	38	3.62	1.04	0.87
4.32–7.97	1501	72	4.80	1.59	0.02

[a] Values relative to the 1.00- to 1.06-ppm fluoride group, adjusted for age using multiple logistic regression.

TABLE 6. BIVARIATE ASSOCIATION OF OVERALL BONE FRACTURE RISKS SINCE THE AGE OF 50 YEARS WITH CATEGORICAL FACTORS

Variable	*Category*	*Subjects*	*Fracture (%)*	p *Value*
Gender	Male	3771	3.61	
	Female	4495	3.89	0.52
Cigarette smoking	Yes	3100	3.29	
	No	5166	4.05	0.08
Alcohol consumption	Yes	1960	3.98	
	No	6299	3.70	0.59
Physical activity	Very little	652	5.21	
	Light	2532	3.71	
	Moderate	4157	3.58	
	Heavy	912	3.51	
	Extremely strenuous	11	18.18	0.03

fluoride exposure in such populations has become extremely difficult, if not impossible.

In contrast to the U.S. population, residents of rural China rarely change residences, and most have been using the same water supply throughout their life. Because of its unique environmental and cultural conditions, such as virtually no residential mobility and a relatively consistent lifestyle, rural China has been considered a perfect "living laboratory" for studying the relationship between various factors and diseases.[33] The survey results of our study sites and data from individual subjects show that fluoride exposure in rural Chinese communities is still limited to water and diet.

The potential association between fluoride exposure and fractures derives from the incorporation of ingested fluoride into the bone crystal. Fluoride can replace hydroxyl groups in the hydroxyapatite crystal with uncertain effects on the strength of such bone. Studies reported an increase in bone density in populations with fluoridated water[34,35] and in individuals receiving therapeutic fluoride doses for the treatment of osteoporosis.[36,37] However, the decrease in fracture risk that might be expected to accompany such an increase in bone mass may not occur. Moreover, there may be an increase in fracture risk at nonspine sites.[36] The results of the present study indicate that long-term consumption of water with excessive fluoride significantly increases the risk of overall bone fractures as well as hip fractures. However, the association between fluoride exposure and the risk of fracture is not linear. The prevalence of overall bone fractures is the lowest for populations living in areas of approximately 1 ppm of fluoride (Table 2), indicating that the fluoride concentrations used for cariostatic purposes also may be beneficial in reducing the risk of overall bone fractures. The data appear to suggest that there may be a "beneficial window" of fluoride intake for bone health, because an increased risk of overall bone fractures was detected in both the populations with deficient and excessive fluoride in drinking water. This finding is in agreement with the results reported by a study in Germany, which found that 1 ppm of fluoride in drinking water did not influence peak bone density but may reduce the incidence of osteoporotic hip fractures in older individuals.[38] A recent study in osteoporosis patients also suggested that low fluoride doses resulting in a moderate increase in bone mineral density (BMD) may be advantageous in terms of fracture-reducing potency.[39] Further investigations are warranted to confirm our findings and to define the possible beneficial window of fluoride exposure observed in the present study.

As compared with the results on overall bone fractures, the data show a somewhat different pattern for hip fractures in relation to the water fluoride levels. The U-shaped effect of water fluoride levels observed in overall fractures (Fig. 2) was not observed in the hip fracture data. Instead, the prevalence of hip fractures was stable until the water concentration reached 1.45–2.19 ppm (Fig. 3). The OR was 2.13 for the population with 1.45–2.19 ppm in water compared with the group of about 1 ppm (Table 4), although the increased risk was not statistically significant. Different ORs for fractures of different locations also were observed by Feskanich et al.,[35] who found an OR of 0.8 for hip fractures and 1.6 for forearm fractures in women with a similar toenail fluoride level. However, it may not be appropriate to conclude that the risk of hip fracture is more sensitive to the water fluoride concentration as compared with overall fractures, because the number of hip fractures in the present study is relatively small. In addition, fractures are influenced by a number of other factors, such as the age, gender, alcohol consumption, and physical activity, as confirmed in the present study. However, our results on hip fractures support previous findings that fluoride around 1 ppm in drinking water does not increase the risk of hip fracture.[19–24,38]

It is important to recognize potential confounding factors and the inherent limitations associated with ecological studies. The populations used in the present study had a definable history of fluoride exposure, which minimizes the potential error for the most important variable in the study. However, the total number of people with fractures was still relatively small, and it is impossible to sort out all potential confounding factors individually. Attempts were made to address this issue statistically by adjusting for factors related to fracture but it is not possible to measure or adjust for all possible differences among the populations. It has been estimated that appropriately designed cohort studies to resolve the problem of bone fracture and water fluoride concentration would require a sample size of more than 400,000 subjects.[40]

The bone fracture prevalence in this study was determined based on self-reported fractures, which would tend to be traumatic fractures, and osteoporotic fractures may be underreported. The low number of spinal fractures in this study appears to support such an assumption. Although such a possibility was recognized, it was determined not feasible to have an X-ray examination of the spine (or whole body) for each of the 8266 subjects. On the other hand, severe accidents (such as those caused by motor vehicles) were rare because all study participants were rural residents with similar environment and lifestyles, and the risk for traumatic fractures was comparable among the six study populations. In addition, there do not appear to be any reasons to believe that populations with high fluoride concentrations in water would be more likely to report their fractures. Therefore, the underreported spinal fractures, if any, should not significantly affect the importance of the findings of this study.

Fluoride contents in blood plasma and urine were not measured in this study. Although the analysis would be helpful in evaluating fluoride metabolism, the lack of plasma and urine fluoride data in this study would not constitute concerns with possible environmental factors that might influence fluoride absorption and excretion in the six study populations. Our previous studies[41–43] on similar populations indicate that blood plasma and urine fluoride contents correlate well with water fluoride concentration in populations that do not have other sources of significant fluoride exposure (e.g., air pollution, fluoride-containing toothpaste and mouthrinse, etc.). The data on fluoride exposure showed that the six study populations did not have other sources of fluoride exposure, other than fluoride in drinking water (Fig. 1).

Fluoride is a bone-seeking element, and there has been circumstantial evidence that fractures associated with fluoride exposure may be related to bone fluoride content.[36–38] This study was an epidemiological investigation and the objective was to determine the prevalence of bone fractures in Chinese populations residing in rural communities of various fluoride concentrations in drinking water. It was determined unfeasible to collect bone samples from the Chinese elderly subjects for bone fluoride analysis; so that bone fluoride content of the study populations was not measured. Because the data have shown that the fluoride exposure of the study populations is limited to drinking water, the findings on the effect of long-term exposure to fluoride in drinking water on the risk of bone fractures are well founded. However, bone fluoride content would provide useful evidence in evaluating the risk of fractures associated with water fluoridation, particularly in populations with uncertain history and source of fluoride exposure. Future studies need to consider the inclusion of the bone fluoride measurement, including feasible appropriate approaches for the sample collection.

Based on the data collected from this investigation, it is concluded that long-term fluoride exposure from drinking water containing 4.32 ppm or more increases the risk of overall fracture as well as hip fracture. Water fluoride levels of 1.00–1.06 ppm decrease the risk of overall fractures relative to negligible fluoride in water; however, there does not appear to be a similar protective benefit for the risk of hip fractures. Because of the limitations of ecological studies, future research on the long-term effects of consuming fluoridated drinking water on bone fractures needs to determine individuals' bone fluoride, bone mass, and bone strength in relation to bone fractures in populations with defined fluoride exposure.

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