ABSTRACT
The cariostatic benefit from water fluoridation is indisputable, but the knowledge of possible adverse effects on bone and fracture risk due to fluoride exposure is ambiguous. The association between long-term (chronic) drinking water fluoride exposure and hip fracture (ICD-7-9: ‘820’ and ICD-10: ‘S72.0-S72.2’) was assessed in Sweden using nationwide registers. All individuals born in Sweden between January 1, 1900 and December 31, 1919, alive and living in their municipality of birth at the time of start of follow-up, were eligible for this study. Information on the study population (n = 473,277) was linked among the Swedish National In-Patient Register (IPR), the Swedish Cause of Death Register, and the Register of Population and Population Changes. Estimated individual drinking water fluoride exposure was stratified into 4 categories: very low, < 0.3 mg/L; low, 0.3 to 0.69 mg/L; medium, 0.7 to 1.49 mg/L; and high, ≥ 1.5 mg/L. Overall, we found no association between chronic fluoride exposure and the occurrence of hip fracture. The risk estimates did not change in analyses restricted to only low-trauma osteoporotic hip fractures. Chronic fluoride exposure from drinking water does not seem to have any important effects on the risk of hip fracture, in the investigated exposure range.

KEY WORDS: chronic exposure, nationwide cohort study, epidemiology, relative risk, Sweden.

INTRODUCTION
All people are exposed daily to fluoride through food and water. During the past 60 years, there has been a debate on possible adverse effects from fluoride on human health. The cariostatic benefit from water fluoridation is indisputable, but the knowledge of possible adverse effects on bone tissue and associated fracture risk is ambiguous (NHS CRD, 2000; The EFSA, 2006; NRC, 2006; NHMRC, 2007).

Fluoride is a bone-seeker and has potent effects on bone cell function, bone structure, and bone strength (Whitford, 1996). In infants, the retention of fluoride can be as high as 90% of the amount ingested (Fomon et al., 1993; Ekstrand et al., 1994). In adults, a steady state is reached where 50% is retained and 50% is excreted (Fomon et al., 1993; Whitford, 1996). This retention results in a lifetime accumulation of fluoride in hard tissues. Although extensive research has investigated possible side-effects from water-borne fluoride exposure, the question of whether long-term consumption of drinking water containing lower fluoride levels (< 2 mg/L) influences the risk of bone fracture remains unresolved (NRC, 2006; NHMRC, 2007).

In this study, we investigated possible adverse health effects from drinking-water fluoride exposure on bone tissue in a large cohort of Swedish residents chronically exposed to various fluoride levels, with the hypothesis of a possible association between fluoride level in the drinking water and the risk of hip fracture.

MATERIALS & METHODS
Setting
Unique personal identifiers, national registration numbers (NRN) assigned to each Swedish resident since 1947, allowed for the linkage of individual records in register data. Swedish health care is public and population based, and hospital referrals are based on geographic residency rather than financial capacity or health insurance, ensuring an unbiased and complete ascertainment of patients receiving hospital care. The study was approved by the Stockholm regional ethical vetting board. This study conforms to the STROBE guidelines for reporting observational studies (http://www.strobe-statement.org).

Study Cohort
Individuals born in Sweden between January 1, 1900 and December 31, 1919, alive and living in their municipality of birth at the time of start of follow-up, were identified in the Swedish Register of Population (n = 474,217). In total, 940 (0.2 %) individuals in the baseline cohort were excluded because of hip fracture before start of follow-up; thus the number of eligible individuals was
473,277. For each individual included in the study, follow-up started from the date the county of residence had full coverage in the Swedish National In-Patient Register (IPR). The IPR, which was initiated in 1964, covered 83% of the Swedish population in 1972 and all inpatient care in Sweden since 1987. Those in the study population were linked to the Register of Population and Population Changes to ascertain domestic movement, emigration, or death during follow-up.

Hazard ratios for fluoride exposure and hip fracture were calculated with the PHREG procedures in the Statistical Analysis System (SAS®) package, version 9.3. We also tested whether the effect of fluoride was modified by age attained (< 70 yrs, 70-79 yrs, and ≥ 80 yrs) and gender, using Wald’s heterogeneity test.

Relative risk estimates are given as hazard ratios (HRs) with 95% confidence intervals (CI). Person-years were calculated for each individual in the cohort. All analyses were performed with PHREG procedures in the Statistical Analysis System (SAS®) package, version 9.3.

RESULTS
Information on the study cohort of 473,277 is presented in Table 2. In total, 60,773 hip fractures were identified, the incidence among women being twice the incidence among men (Fig.). The vast majority (97.0%) of all hip fractures occurred at ages older than 65 yrs.

Fluoride Exposure and Hip Fracture
Hazard ratios for fluoride exposure and hip fracture were calculated with the PHREG procedures in the Statistical Analysis System (SAS®) package, version 9.3. We also tested whether the effect of fluoride was modified by age attained (< 70 yrs, 70-79 yrs, and ≥ 80 yrs) and gender, using Wald’s heterogeneity test.

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Hazard ratios were additionally calculated for 3 age groups separately (< 70, 70 - < 80, ≥ 80) (Table 3). Adjusted relative risk estimates in the 2 lowest age groups tended to be below 1.0. The effect was not seen in the oldest age group. The risk estimates for hip fracture were statistically different among age groups (heterogeneity test, \( p < .001 \)). The results suggest a protective effect of fluoride among the younger (age younger than 80 yrs); however, the majority of fractures occurred above the age of 80 yrs (median age at time of fracture, 82.0).

The fracture incidence was about 70% higher for women, HR = 1.72 (95% CI: 1.69-1.75). We found no difference in risk estimates of hip fracture between men and women (heterogeneity test: \( p = .54 \)).

**Fluoride Exposure and Low-trauma Osteoporotic Hip Fracture**

To restrict our analyses to only low-trauma osteoporotic fracture of the hip, we identified all first-recorded low-trauma osteoporotic hip fractures in our study population, regardless of any prior hip fracture. In total, 50,923 low-trauma osteoporotic hip fractures were identified. As with hip fractures in general, low-trauma osteoporotic hip fracture incidence among women was twice the incidence among men (data not shown), and the vast majority (97.3%) occurred at ages older than 65 yrs. The adjusted HRs for low-trauma osteoporotic fracture did not differ from the overall adjusted relative risk estimates above, with adjusted HR estimates ranging from 0.95 to 1.00 (Table 3).

Additional analysis on the 3 different age groups did not differ from the results above (data not shown). Also, the risk estimates for low-trauma osteoporotic hip fracture differed significantly among the age groups (heterogeneity test: \( p < .001 \)), and no difference was found in risk estimates of low-trauma osteoporotic hip fracture between men and women (heterogeneity test: \( p = .0937 \)).

**DISCUSSION**

We studied the relation between hip fractures observed in 1964 to 2006 and estimated long-term fluoride exposure among individuals
In low-fluoride areas (< 4 mg/L), fluoride content in food does not exceed 0.2 mg/kg, with the exception of fish and tea (The EFSA, 2006), though fluoride intake from sources other than drinking water can be substantial.

In our study design, we reduced the potential confounding influences of age, gender, calendar period, and geographic area, but we were not able to consider a number of other potential confounders, such as body mass index, physical activity, nutrition, smoking, alcohol use, and the use of bisphosphonates or hormone-replacement therapy. Low body mass index is an important risk factor for fractures in the elderly (Cummings et al., 1995; Farahmand et al., 2000; van der Voort et al., 2001). However, in a case-control study (Hillier et al., 2000), adjustments for potential confounders such as physical inactivity and low body mass index had a negligible effect on risk estimates and were not significantly associated with exposure to fluoride in the water. Smoking is a risk factor for hip fractures in both men and women (Law and Hackshaw, 1997; Olofsson et al., 2000), and we cannot exclude the possibility that inclusion of smoking in our model would have affected our risk estimates. Whether our results would have been modified if we were able to account for the use of alcohol, bisphosphonates, and hormone replacement therapy is uncertain.

The follow-up in this study did not cover the entire lifespan of those in the study population. Their median age at study entry was 62.8 yrs, with a range of 44.0-87.0 (Table 2), and for those born in 1919, the follow-up stopped at the age of 87 yrs. However, hip fractures are rare in individuals under the age of 50 yrs and constitute only 2% of the total (Berglund-Rödén et al., 1994); thus, a few “first” fractures were missed. Furthermore, the possible difference in having a fracture prior to study start was minimized, since the analytical method implies that we compared persons with different exposure levels given that they belonged to the same age group, and started their follow-up at the same calendar year.

Several ecological studies linking fluoride content in drinking water to the incidence of hip fracture have shown conflicting results (McDonagh et al., 2000). The interpretation of ecological studies is difficult because of the inability to control for confounding factors. Only a few studies have individually related fluoride ingestion to the risk of hip fracture. Our results suggest that fluoride concentration up to about 2 mg/L in drink-
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REFERENCES


