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Population data on calcium in drinking water and hip fracture: An association may depend on other minerals in water. A NOREPOS[1] study

Cecilie Dahl [a,*], Anne Johanne Søgaard [a], Grethe S. Tell [b,h], Lisa Forsén [a,g], Trond Peder Flaten [c], Dag Hongve [d], Tone Kristin Omsland [a,e], Kristin Holvik [a], Haakon E. Meyer [a,e], Geir Aamodt [f]

[a] Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway
[b] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[c] Department of Chemistry, Norwegian University of Science and Technology, Trondheim, Norway
[d] Division of Environmental Medicine, Norwegian Institute of Public Health, Oslo, Norway
[e] Department of Community Medicine (Institute of Health and Society), University of Oslo, Oslo, Norway
[f] Department of Landscape Architecture and Spatial Planning (ILP), Norwegian University of Life Sciences, Ås, Norway
[g] Women and Children's Division, Norwegian Resource Centre for Women's Health, Oslo University Hospital, Norway
[h] Department of Health Registries, Norwegian Institute of Public Health, Bergen, Norway

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ABSTRACT

Background: The Norwegian population has among the highest hip fracture rates in the world. The incidence varies geographically, also within Norway. Calcium in drinking water has been found to be beneficially associated with bone health in some studies, but not in all. In most previous studies, other minerals in water have not been taken into account. Trace minerals, for which drinking water can be an important source and even fulfill the daily nutritional requirement, could act as effect-modifiers in the association between calcium and hip fracture risk. The aim of the present study was to investigate the association between calcium in drinking water and hip fracture, and whether other water minerals modified this association.

Materials and methods: A survey of trace metals in 429 waterworks, supplying 64% of the population in Norway, was linked geographically to the home addresses of patients with incident hip fractures (1994–2000). Drinking water mineral concentrations were divided into "low" (below and equal waterworks average) and "high" (above waterworks average). Poisson regression models were fitted, and all incidence rate ratios (IRRs) were adjusted for age, geographic region, urbanization degree, type of water source, and pH of the water. Effect modifications were examined by stratification, and interactions between calcium and magnesium, copper, zinc, iron and manganese were tested both on the multiplicative and the additive scale. Analyses were stratified on gender.

Results: Among those supplied from the 429 waterworks (2,110,916 person-years in men and 2,397,217 person-years in women), 5433 men and 13,493 women aged 50–85 years suffered a hip fracture during 1994–2000. Compared to low calcium in drinking water, a high level was associated with a 15% lower hip fracture risk in men (IRR = 0.85, 95% CI: 0.78, 0.91) but no significant difference was found in women (IRR = 0.98, 95%CI: 0.93–1.02). There was interaction between calcium and copper on hip fracture risk in men ($p = 0.051$); the association between calcium and hip fracture risk was stronger when the copper concentration in water was high (IRR = 0.52, 95% CI: 0.35, 0.78) as opposed to when it was low (IRR = 0.88, 95% CI: 0.81, 0.94). This pattern persisted also after including potential confounding factors and other minerals in the model. No similar variation in risk was found in women.

Conclusion: In this large, prospective population study covering two thirds of the Norwegian population and comprising 19,000 hip fractures, we found an inverse association between calcium in drinking water and hip fracture risk in men. The association was stronger when the copper concentration in the water was high.

1. Introduction

Hip fracture is a serious event; one out of every four patients die within one year from experiencing a hip fracture [1], and survivors often report severe pain and loss of physical function [2]. With such severe consequences, preventing fractures at the population level is crucial. The Norwegian population has among the highest rates of hip

* Corresponding author at: Norwegian Institute of Public Health, Division of Epidemiology, P.O. Box 4404 Nydalen, 0403 Oslo, Norway.
E-mail address: Cecilie.Dahl@fhi.no (C. Dahl).

1 Norwegian Epidemiologic Osteoporosis Studies.

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fracture in the world [3,4]. The incidence has been found to vary considerably within Norway, with a higher incidence in urban compared to rural areas [5]. The reasons for the high incidence and geographic variations are poorly understood. The protective factors high bone mineral density (BMD) and high body mass index (BMI) are more prevalent in rural areas of Norway, but this cannot entirely explain the variation in fracture risk [6].

Adequate diet and physical activity throughout life could help achieve one's full genetic potential in peak bone mass, and reduce the risk of developing osteoporosis later in life [7–9]. Calcium and other minerals, such as magnesium, copper, zinc, iron and manganese are important components of an adequate diet. A high calcium intake has been found to be beneficial to bone mass [10], and randomized controlled trials have shown that dietary supplements with calcium and vitamin D in the elderly have a moderate effect on preventing fractures [11]. Calcium is considered an important component in bone health, however nutrients are usually co-dependent, and the effect of calcium intake on bone may be influenced by varying intakes of trace minerals [12–14]. The essential trace minerals copper, zinc and manganese, as well as magnesium and iron, have been suggested to be protective for bone health in several studies [5,8,14–20], but their relative contribution to bone health in combination with calcium is less clear [8,14,15].

Drinking water provides small daily doses of calcium and other essential minerals, and may be an important source throughout the entire lifespan [8,21,22]. Minerals in water are present mostly as free ions. As a result, they are more readily absorbed from water than from food, where they are more commonly bound in compounds [22,23]. Studies conducted in Southern Europe have reported that drinking water high in calcium could reduce bone mineral loss and increase BMD, but the potential influence of other minerals on the effect of calcium were not considered in these studies. Norwegian drinking water has low concentrations of many minerals compared with drinking water in other European countries [24–26]. In our previous study of Norwegian drinking water, we found that water low in magnesium was associated with a higher incidence of hip fracture in both men and women, while the association between calcium in the water and hip fracture was less clear [5].

The aim of the present study was to further explore the possible association between calcium in municipal drinking water and the risk of hip fracture in Norwegian men and women 50–85 years, taking into account possible effect modification by other minerals that have previously been found to be important to bone health.

2. Materials and methods

2.1. Data sources

2.1.1. Survey of trace metals in municipal drinking water

During 1986–1991 a survey of 30 physicochemical parameters was conducted in waterworks throughout Norway, selected to represent the general population [27]. Personnel at the waterworks were asked to collect samples of raw and treated water. All together 566 waterworks, supplying 64% of the population, provided samples. Over time, several smaller waterworks were incorporated into larger ones, resulting in a total of 429 waterworks included in this study. The sampling and analysis procedures are described elsewhere [27].

2.1.2. The NOREPOS Hip fracture database (NORHip)

A database consisting of all hip fractures treated in Norwegian hospitals from 1994 through 2008 has been established by the Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) research collaboration (www.norepos.no). This database, "NORHip", includes almost 140,000 incident hip fractures. The validity of the database has been assessed by comparisons to local hip fracture registries (verified by hospital records and radiographic archives) in the cities of Oslo and Tromsø. More information on the data quality assurance is found in Omsland et al. [28].

2.1.3. Drinking water criteria

Drinking water criteria considered in this study are those of the World Health Organization (WHO) [22], the United States Environmental Protection Agency (EPA) [29], and Norwegian authorities [30,31]. Both required (law-enforceable) and recommended criteria were considered. All these criteria primarily serve to protect public health, but also take into account operational and environmental aspects of drinking water.

2.2. Data Linkage

In assigning exposure to individuals, we used geographic information systems (ArcGIS 9.3) to create a map of the areas supplied by each waterworks. Using this waterworks map and the participants' numerical addresses based on the National Registry, we were able to categorize which waterworks area the inhabitants resided in for each year in the observation period (1994–2000). These data were combined with data from the trace metal survey, and subsequently linked to the fracture outcome in the NORHip database.

2.3. Subjects

We restricted the sample to men and women 50–85 years old during 1994–2000, supplied by waterworks with complete information on calcium and other minerals in their drinking water. The observation period was between 3 and 14 years. To calculate the person-years (py) we used the total population residing in the areas served by the waterworks, as provided by the National Registry. Within waterworks and 1-year age classes we added the person-time per calendar year. Relocation was taken into account by including those who changed residence into their new waterworks area the following year. The person-time contributed was weighted according to a detailed matrix developed by Carstensen [32]. In short, within each one-year age group (50–85 years) we counted the total number of individuals served by each waterworks for every calendar year in the period 1994–2000 (2,110,916 person-years in men and 2,397,217 person-years in women), and the number of hip fractures within the same groups (5,433 in men and 13,493 in women).

2.4. Variables

2.4.1. Outcome

Employing the NORHip database [28,33], information on incident hip fractures was retrieved from all hospitalizations with a diagnosis code for hip fracture, ICD-9: 820 with all subgroups, ICD-10: S72.0, S72.1 and S72.2. Surgical procedure codes and additional diagnosis codes during hospital admissions with hip fracture were used for fracture assessment. Up to two hip fractures were included per subject.

2.4.2. Drinking water exposure

Minerals were included based on literature search indicating a potential relation with bone health and/or calcium. Tap water concentrations of calcium, magnesium, copper, zinc, iron and manganese were measured at the Norwegian Institute of Public Health using automated colorimetric analysis for iron and electrothermal atomic absorption spectrometry techniques for other minerals. The average of the mineral concentrations in two or four samples (collected at different seasons) from each waterworks was used in the statistical analyses.

2.4.3. Covariates

Potential confounding variables (age, gender, urbanization degree, geographic region, water source type and pH of the water) were chosen based on previous studies on their relations with hip fracture and drinking water quality [24]. The urbanization degree of each municipality, which was assigned to each inhabitant, was provided by Statistics Norway and represents the proportion of inhabitants in each municipality living in a cluster of houses with at least 200 people, and where the distance between the buildings does not exceed 50 m. The degree of urbanization for each individual was specified by a number on a continuous scale between 0 and 1, where 0 indicated "no urbanization", and close to 1 indicated "city". For waterworks that supplied more than one municipality, a population-weighted average of the urbanization degree was calculated. To take into account variations in sampling and underlying geographic differences, the waterworks were categorized into five regions based on their county of location: South, East, West, Middle and North (map shown in [5,34]). The trace metal survey also provided data on the type of water source (ground or surface water). More information can be found in: Hongve et al. [27].

2.5. Statistics

Concentrations of minerals below or equal the waterworks average were defined as “low”, whereas concentrations above the waterworks average were defined as “high”. The percent of person-years exposed to high concentrations of minerals was determined, along with the percent of person-years in accordance with drinking water criteria (Section 2.1.3). Correlations between continuous calcium concentrations, pH and other minerals were calculated as Spearman's correlation coefficients (rho). Poisson regression models provided incidence rate ratios with 95% confidence intervals (IRR, 95% CI), comparing hip fracture incidence rates across high and low levels of minerals in water with the low concentration group as reference. Non-parametric functions were used to visualize hip fracture risk across the concentration range of calcium with low and high levels of other minerals in water. Extreme values were removed before running the Poisson models and the non-parametric functions. To find potential extreme values the data were log-transformed and single measurements more than 1.5 Inter Quartile Range (IQR) away from the lowest and highest quartiles on box plots were identified. All measurements identified as extreme values were included in a sensitivity analysis. P-values ≤ 0.05 were considered as statistically significant; tests were two-sided.

The presence of effect modification was assessed by comparing the calcium and hip fracture association across strata of age, gender, urbanization degree, geographic region, water source type, pH and minerals, and by formally testing interaction terms. All variables were dichotomized, age: 50–65 vs. 66–85; geographic region: South, East, West and Middle vs. North; pH: 4.5–6.63, 6.64-10.2; and water minerals into categories below and above waterworks average. In accordance with recommendations by Knol and Vanderweele [35], the category with the lowest hip fracture risk was set as reference in tests of interaction terms. Interactions were considered on both the multiplicative scale, defined as the Interaction Contrast Ratio (ICR) and 95% confidence interval, and on the additive scale by the Relative Excess Risk of Interaction (RERI) and 95% confidence interval. RERI with 95% confidence interval was calculated using an Excel spreadsheet provided by Knol and VanderWeele [35]. We defined an ICR or RERI of $p \leq 0.05$ (two-sided) as significant statistical interaction. All models in this study were adjusted for urbanization degree (continuous), geographic region (five categories), type of water source (dichotomous) and pH (continuous), and stratified on gender. The analyses were done in STATA 13 (StataCorp LP, Texas, United States) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

2.6. Ethics

The study was approved by the Norwegian Data Protection Authority, the Regional Committee for Medical and Health Research Ethics (2009/1521/REK), the Norwegian Directorate of Health and the owners of the registries and databases, all in accordance with the Declaration of Helsinki.

3. Results

3.1. Concentrations of minerals, required and recommended criteria

Table 1 gives the average concentrations of minerals in drinking water provided by the waterworks. Only 10–30% of the subjects in the present study received water with above average mineral concentrations (Table 1). Table 1 also gives the drinking water criteria given by the WHO, with additional criteria from the EPA and Norwegian authorities noted below. Most subjects received drinking water with mineral concentrations in accordance with international and national criteria; however, calcium and magnesium concentrations were much lower than recommended by the WHO (Table 1).

3.2. Correlations with other minerals and pH

Calcium in drinking water was positively correlated with pH (rho = 0.60) and magnesium (rho = 0.32), and negatively correlated with copper (rho = −0.44), zinc (rho = −0.31), iron (rho = −0.25) and manganese (rho = −0.20). All correlations were statistically significant ($p < 0.01$).

3.3. Risk of hip fracture

The mean age at hip fracture was 74.7 years in men, and 76.7 in women. The overall incidence of hip fracture (first or subsequent, 50–85 years) was 26 per 10,000 person years in men and 56 per 10,000 person years in women.

Table 2 shows IRRs of hip fracture according to the different minerals in drinking water included in this study. Compared to low calcium, a high calcium level in drinking water was associated with a 15% lower hip fracture risk in men (IRR = 0.85, 95% CI: 0.78, 0.91), after adjusting for covariates (Table 2). The IRR in women was no longer significant after adjustment (Table 2). High magnesium was associated with a 10% lower risk in men and women (Table 2). Other included minerals (copper, zinc, iron and manganese) were not associated with hip fracture risk after adjustment.

3.4. Effect modification

3.4.1. Calcium and covariates

As tested by interaction terms, the association between calcium in drinking water and hip fracture risk varied significantly according to gender ($p = 0.008$) and geographical region ($p = 0.007$, men only). Comparing within the same geographical region, men living in region South and receiving water with high calcium had 14% lower risk of hip fracture compared to those receiving water with low calcium (IRR = 0.86, 95% CI: 0.79, 0.93), whereas men living in region North did not have a lower risk of hip fracture with high calcium compared to low (IRR = 1.02, 95% CI: 0.83, 1.25). There was no effect modification by age, urbanization degree, water source type, or pH of the water.

3.4.2. Calcium and other water minerals

The inverse association between calcium and hip fracture risk in men was significantly stronger at high compared to low concentrations of copper (Table 3), p interaction = 0.051. Men receiving water high in calcium and low in copper had a 12% lower rate of hip fracture, whereas men receiving water high in both calcium and copper had a 48% lower rate. The interaction withstood inclusion of other minerals from water (magnesium, zinc, iron and manganese) in the model (data not shown). No similar variation in risk with high compared to low calcium across levels of copper was seen in women, and no significant interaction was seen between calcium and other minerals from water, however for zinc and iron the association between calcium and hip fracture seemed stronger in the high-mineral group (Table 3).

Table 1
Concentrations of calcium and other minerals in Norwegian drinking water (1988–1991), the percentage of persons supplied with high mineral levels[a], and drinking water criteria.[b]

Water mineral	Range	Waterworks average	Percentage > average[a]	Criterion[b]	Percentage in accordance with criterion
Calcium	0.22–112 mg/l	5.39 mg/l	30.5	>20 mg/l[c]	9.1
Magnesium	0.08–31.5 mg/l	1.03 mg/l	18.6	>10 mg/l[d]	0.3
Copper	1.0–1500 μg/l	56.0 μg/l	14.7	<2000 μg/l[e]	100.0
Zinc	1.0–1137 μg/l	30.7 μg/l	10.8	<3000 μg/l[f]	100.0
Iron	10–1730 μg/l	70.0 μg/l	29.7	<300 μg/l[g]	97.7
Manganese	1.0–730 μg/l	20.0 μg/l	31.4	<50 μg/l[h]	87.5

[a] Above waterworks average.
[b] Required or recommended drinking water criterion by the World Health Organization (WHO) [22]. Criteria from the United States Environmental Protection Agency (EPA) [29] and Norwegian authorities [30,31] are listed in footnotes.
[c] WHO recommendation. Norwegian recommendation [31]: 15–25 mg/l. No criterion given by the EPA.
[d] WHO recommendation. Norwegian recommendation [31]: <10 mg/l. No criterion given by the EPA.
[e] WHO requirement. Norwegian requirement [30]: <1000 μg/l. EPA: requirement: <1300 μg/l, recommendation: <1000 μg/l.
[f] WHO requirement. EPA recommendation <5000, no recommendations given by Norwegian authorities.
[g] WHO requirement. Norwegian requirement [30] <200 μg/l. EPA recommendation <300 μg/l.
[h] Recommended by the WHO and the EPA, but required by Norwegian authorities [30].

Supplementary Table S1 gives the association of the joint exposure of calcium and other minerals with hip fracture risk, using the group with lowest risk as reference. The Interaction Contrast Ratio (ICR, 95% CI) and Relative Excess Risk due to Interaction (RERI, 95% CI) give the estimates of interaction on the multiplicative and additive scale, respectively. A RERI (95% CI) of −0.27 (−0.59, 0.04) for the interaction between calcium and copper on hip fracture risk in men was calculated.

Fig. 1 shows hip fracture risk in men and women across concentrations of calcium in drinking water, according to low and high levels of copper. At low copper concentrations, there was a linear decline in hip fracture risk in men with increasing calcium concentrations (Fig. 1a). At high copper concentration, the decline in risk seemed to start at a higher calcium concentration, and declined faster than with low copper (Fig. 1b). For women, no clear trend in risk was seen across calcium concentrations (Fig. 1c and d).

3.5. Sensitivity analysis

There were large variations in concentrations of minerals in drinking water, also after log transformation. Seven waterworks had extreme values according to our definition, but only one of these values influenced the effect measures. This waterworks used a ground water source situated close to old mining industry. Its location made it at risk of occasional runoff from the closed mine, especially with heavy rainfall in the spring, resulting in sporadic high measurements of copper (1400 μg/l copper in May). When including this measurement in the multivariate analysis, the interaction between calcium and copper became slightly attenuated, i.e. the ICR (95% CI) changed from 0.79 (0.62, 1.00) to 0.81 (0.64, 1.01).

4. Discussion

In this large, prospective cohort study covering two thirds of the Norwegian population and comprising 19,000 hip fractures, we saw an inverse association between calcium in drinking water and hip fracture risk in men. The association was modified according to different levels of copper in the water, and the variation persisted when adjusting for potential confounders, including other minerals in the water.

4.1. Comparison with previous studies

A lower risk of hip fracture was found for men with high drinking water calcium (above 5.39 mg/l), independent of other minerals in the water. These results are in agreement with studies from Italy and France showing lower serum PTH, lower urinary biochemical markers of bone remodeling and higher femoral BMD with consumption of water with much higher calcium concentrations (100–596 mg/l) [36–39]. The observed variation in the association between calcium and hip fracture risk in men across low and high levels of copper indicates that a protective effect of calcium may not only depend on the concentration of calcium, but also on the levels of other minerals in water. Saltman and Strause [20] found that rats given a diet deprived of copper and manganese had elevated calcium concentrations in serum compared to the group given a diet sufficient in these minerals. Serum calcium was significantly and inversely correlated with femur calcium content [20], indicating that suboptimal levels of trace minerals in the diet could result in an efflux of calcium from bone, resulting in a lower BMD. Our results in men are also in accordance with Strause et al. [14], which found that bone loss in calcium supplemented

Table 2
Risk of hip fracture according to mineral levels in drinking water[a]. A NOREPOS study.

		Calcium		Magnesium		Copper		Zinc		Iron		Manganese	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Men	IR/10,000 py	26.9	23.2	26.3	23.4	25.2	28.9	25.8	25.2	25.2	26.8	26.1	24.7
N hip fractures = 5,433	IRR (95% CI)[b]	Ref	0.86 (0.81, 0.91)***	Ref	0.89 (0.82, 0.95)***	Ref	1.15 (1.07.1.23)***	Ref	0.98 (0.90, 1.07)	Ref	1.06 (1.00, 1.12)*	Ref	0.95 (0.89, 1.00)
	IRR (95% CI)[c]	Ref	0.85 (0.78, 0.91)***	Ref	0.90 (0.83, 0.98)***	Ref	1.05 (0.96, 1.14)	Ref	0.97 (0.88, 1.08)	Ref	1.03 (0.97, 1.11)	Ref	0.94 (0.88, 1.00)
Women	IR/10,000 py	57.7	53.0	57.7	50.2	55.3	60.7	56.4	54.8	55.6	58.0	57.4	53.9
N hip fractures = 13,493	IRR (95% CI)[b]	Ref	0.92 (0.88,0.95)***	Ref	0.87 (0.83,0.91)***	Ref	1.09 (1.04,1.15)***	Ref	0.97 (0.92, 1.03)	Ref	1.04 (1.00, 1.08)*	Ref	0.94 (0.90, 0.97)**
	IRR (95% CI)[c]	Ref	0.98 (0.93, 1.02)	Ref	0.90 (0.85, 0.95)***	Ref	1.01 (0.96, 1.07)	Ref	0.96 (0.90, 1.02)	Ref	1.00 (0.95, 1.04)	Ref	0.98 (0.94, 1.02)

ref = reference category, Significance level: ***p ≤ 0.001, **p ≤ 0.01, *p ≤ 0.05
[a] Incidence rates (IR/10,000 py) and incidence rate ratios with 95 percent confidence interval (IRRs, 95% CI) of hip fractures in men and women 50–85 years according to low and high levels of water minerals. Poisson regression.
[b] Unadjusted.
[c] Adjusted for age, urbanization degree, geographic region, water source type (ground or surface) and pH of the water.

Table 3
Association between calcium in drinking water and hip fracture risk across levels of other minerals in drinking water[a,b]. A NOREPOS study.

		Men		Women	
		Low calcium IRR (95% CI)	High calcium IRR (95% CI)	Low calcium IRR (95% CI)	High calcium IRR (95% CI)
Magnesium	Low	Ref	0.85 (0.77, 0.93)***	Ref	0.97 (0.91, 1.02)
	High	Ref	0.89 (0.74, 1.06)	Ref	1.04 (0.93, 1.16)
Copper	Low	Ref	0.88 (0.81, 0.94)***	Ref	0.97 (0.93, 1.02)
	High	Ref	0.52 (0.35, 0.78)**	Ref	1.12 (0.87, 1.42)
Zinc	Low	Ref	0.88 (0.81, 0.95)***	Ref	0.98 (0.93, 1.03)
	High	Ref	0.58 (0.37, 0.91)*	Ref	0.72 (0.53 0.98)*
Iron	Low	Ref	0.89 (0.82, 0.97)**	Ref	0.99 (0.94, 1.04)
	High	Ref	0.76 (0.65, 0.91)**	Ref	0.92 (0.84, 1.05)
Manganese	Low	Ref	0.84 (0.76, 0.91)***	Ref	0.94 (0.89, 1.00)*
	High	Ref	0.90 (0.76, 1.07)**	Ref	1.00 (0.90, 1.11)

Significance level: ***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$.
[a] Incidence rate ratios of hip fracture with 95 percent confidence interval (IRRs, 95% CI).
[b] Adjusted for: age, urbanization degree, geographic region, water source type (ground or surface) and pH of the water. Poisson regression. Ages 50–85 years.

postmenopausal women could be further reduced by concomitant increases in trace mineral (zinc, copper and manganese) intake. The effect of calcium and copper alone could however not be assessed in these studies. Copper-supplementation by itself has been reported to be beneficially associated with bone health. Eaton-Evans et al. [17] reported a reduced rate of vertebral trabecular BMD loss over a 2 year period in middle-aged women (45–56 years) given copper supplements, compared to placebo. In copper deficiency, the activity of lysyl oxidase is greatly reduced, which could cause a reduction in enzymatic collagen crosslinking that may influence the synthesis and stability of bone collagen, possibly leading to decreased bone strength [19]. In the current study the association between copper in water and hip fracture risk was no longer significant after adjustment for covariates.

4.2. Possible explanations

The results in our study must be seen in light of the levels of calcium and trace minerals ingested from sources other than drinking water. Dietary calcium intake is considered to be generally high in the Norwegian population due to high consumption of dairy foods. Results from a nationwide dietary survey in adults show that Norwegians consume on average above or around the recommended intake of 800 mg calcium per day [40]. People already receiving adequate amounts of calcium through the diet may not have much added benefit from calcium in drinking water [41], especially when the water concentrations are as low as those found in the current study. On the other hand, the additional benefit of increased calcium concentrations in drinking water may be higher in those not consuming dairy products, or in those with reduced intestinal calcium absorption, e.g. older persons [42]. A meta-analysis concluded that the bioavailability of calcium from drinking water seemed to be at least comparable to, and possibly better than from

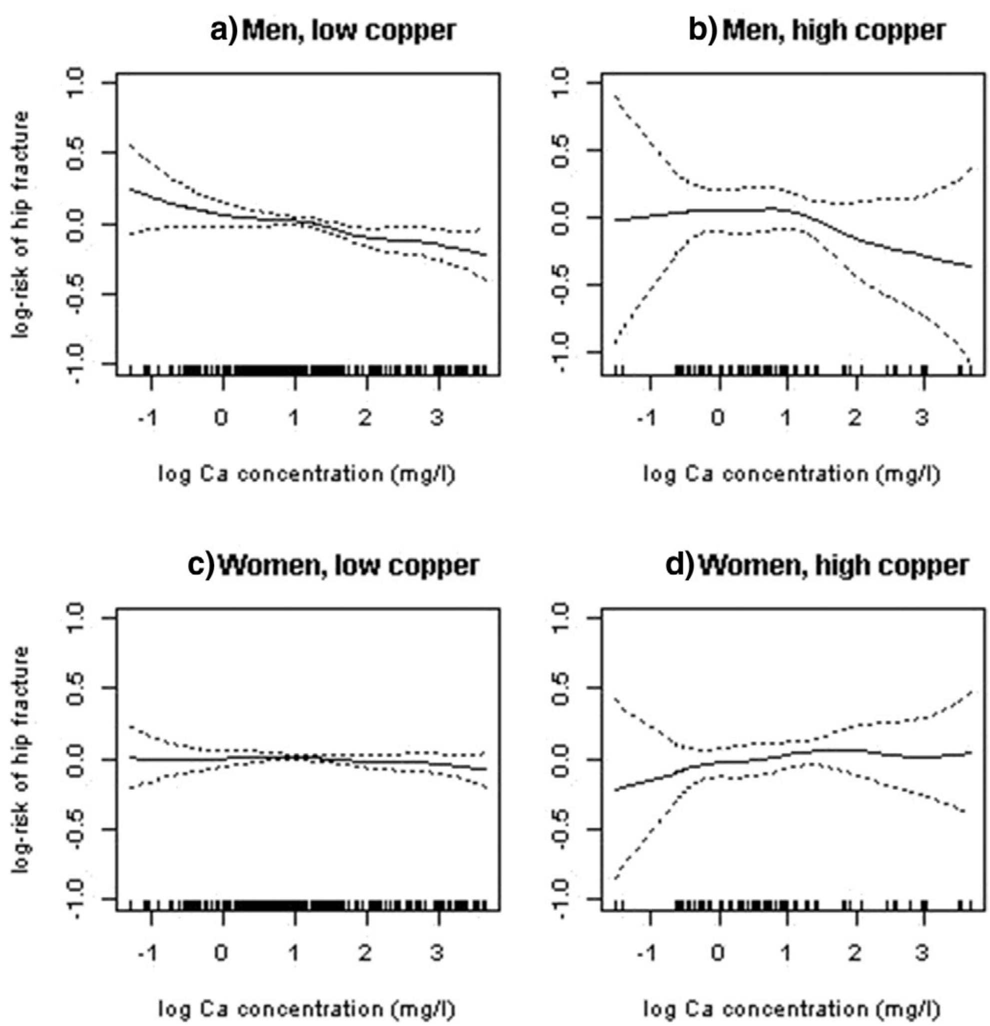

Fig. 1. Hip fracture risk in men and women across concentrations of calcium, according to low and high levels of copper in drinking water.

dairy products [23], hence regular consumption of water with high calcium may be an option for improving calcium status in some population subgroups whose consumption of dairy products is low [23,43]. Still, data only exist from few studies with relatively few participants [23].

Indications of reduced bone loss with high calcium in drinking water have previously been seen both in men [38] and women [14,36,37,39], however in our present study the inverse association between calcium and hip fracture in women was weaker and no longer significant after adjustment for covariates. A significant interaction was also found between gender and calcium on hip fracture risk, even after adjusting for urbanization degree, geographic region, water source type and pH of the water. It is possible that men and women differ with respect to bodily background levels of calcium and other minerals due to different intakes and different rates of excretion [44]. Men and women may also differ in other important factors such as physical activity, BMI, smoking and hormonal levels, which may influence hip fracture risk [7,44]. In women, the most important water mineral seemed to be magnesium [5]. To our knowledge, only one other study dealing primarily with magnesium in water and bone health has previously been performed, and the results on bone biomarkers were unclear, probably due to a short follow-up period [45].

Drinking water usually contributes less than 1 mg of copper per day [46], but consumption of standing or partially flushed water from a distribution system that includes copper pipes or fittings can considerably increase total daily exposure [31,46]. Generally, food is the principal source of copper, but the daily allowance (0.9 mg/day in adults) can occasionally be fulfilled solely through drinking water. All waterworks in the current study supplied water with copper levels below the WHO permissible limit of 2 mg per liter, and the large majority supplied levels below the Norwegian limit of 1 mg/l.

4.3. Public health implications

Due to weathering resistant bedrock and a cold climate, Norway has low levels of calcium and other minerals in municipal drinking water compared with other countries in Europe [24–26]. The country has among the highest rates of hip fractures in the world: in the Norwegian population of 5.1 million, about 9000 people fracture their hip every year [28]. Within one year after a hip fracture one out of every four patients has died, and the average costs for each survivor has been calculated to be 67,000 Euro (approximately 580,000 NOK) within the first year [47]. Much can be done for the prevention of fractures at the individual level, such as proper medications and fall-prevention for the elderly [48], but measures for prevention at the population level should also be considered. To achieve peak bone mass in children and adolescents, and to maintain bone mass in adults and the elderly, a sufficient mineral intake must be emphasized throughout life. In this instance, increasing mineral concentrations in municipal water to recommended levels is one possible measure. In our study, only 9% of individuals received drinking water with calcium concentrations above the WHO recommended level, i.e. over 90% had less than optimal water supply. The level of magnesium was also very low, only 0.3% received water meeting the recommendation. Calcium and magnesium (in the form of calcium carbonate or dolomite) are already being added by some Norwegian waterworks with the purpose of controlling corrosion in the water distribution network. An important question is whether some households, based on their current level of trace minerals in water, would receive a greater public health benefit from supplementing calcium to water? In the current study we found negative additive interaction (RERI less than zero) between copper and calcium. It is therefore possible that adding calcium to drinking water with high copper concentration would give an even greater benefit (fewer hip fractures in men) than adding calcium to drinking water with low copper. Yet, all chemical aspects need to be taken into account when adding a mineral to drinking water. Some studies have shown that a balance between calcium and magnesium may be important [15,24]. Achieving an optimal water composition, with balanced mineral concentrations, may be more beneficial than simply increasing calcium alone.

4.4. Interaction

The primary concern of the current study was with effect modification of the association between calcium and hip fracture, and in this process interactions were tested. Significant statistical interaction between calcium and copper on the risk of hip fracture could signify mechanistic (biologic) interaction. Vanderweele [49] argues that if effects are not confounded, are monotonic (always operate in the same direction), or if RERI is sufficiently large (<1 or >1 rather than <0 or >0), there would be evidence of mechanistic interaction. In the current study we calculated a RERI of -0.27 for the interaction between calcium and copper, which is not sufficient evidence of mechanistic interaction. Furthermore, harmful effects from very high levels of calcium or copper cannot be ruled out [8]. More research is clearly needed to be able to evaluate the relations between calcium and trace elements on fracture risk.

4.5. Strengths and limitations

Major strengths of our study include the large population, covering representative geographic regions with variations in exposure. Due to high statistical power we were able to detect even small relative differences in fracture rates, and we were able to assess interactions, which typically require four times the sample size than that of main effect analyses. Unlike most previous studies of environmental effects on hip fracture risk we were able to adjust for individual factors including gender and age by linking water quality information to individuals in a geographic information system. All drinking water analyses were performed in the same laboratory within a relatively short time span, reducing the risk of systematic errors in the exposure data. In addition, we had high quality data ascertainment of hip fractures.

Several possible limitations exist in the study. The exposure was determined by the geographic location of the home address, and not by the actual individual intakes. Within a waterworks area the exposure to municipal drinking water will vary depending on the amount of water consumed. The exposure could also vary depending on whether the water was consumed at the workplace or at home. Tap water is the main source of water in Norway, with a consumption of approximately 1.1 l per day, more than milk and soft drinks [40]. At the time of the current study (1994–2003), the average annual consumption of bottled water in Norway was only 18 l per capita per year [50]. However, some individuals may have consumed more bottled water if the tap water was conceived to be of low quality. In addition, dietary intakes of calcium and trace minerals, vitamin D status (from diet and sun exposure), socioeconomic and lifestyle factors including tobacco use and alcohol intake vary between individuals. If these factors are associated with the water intake and with hip fracture risk, they may confound the observed effects, and they may also work as effect modifiers if associated only with hip fracture risk. Moreover, since no individual dietary intakes or excretion of calcium and trace minerals were measured, the accurate intake of minerals from water and the accurate contribution of minerals in drinking water to total intake in diet are not known.

We were not able to examine whether changes in water composition over time may have influenced our results, as we had measurements only at one short time period (which were combined into one average measurement) for each waterworks. The observed associations may have been subject to non-differential misclassification when the time period between the exposure and the fracture was long. This could possibly have led to a dilution of the true effect. To account for the change in concentrations of minerals within waterworks over time, we limited the outcome to fractures occurring between 1994 and 2000. Each participant was registered in a new waterworks area the following year if he or she moved to a new location. However, since we expect the effect of mineral composition in drinking water on the bone to be long-term, some misclassification could also have occurred if a participant with a fracture had just recently moved to an area with a different concentration of minerals in the water, perhaps attenuating the results. Lifetime exposure to minerals from drinking water (especially in the attainment of one's genetically predisposed peak bone mass) may also be of importance, which means that relocations between waterworks areas in early life could have randomly misclassified the exposure. Not all households in Norway were registered with numerical addresses in Statistics Norway at the time of the study; therefore we were not able to assign addresses to all individuals, especially among those residing in rural areas. We do not know in which way this could have affected our results.

4.6. Conclusion

The purpose of this study was to evaluate the association between calcium in drinking water and hip fracture risk, and whether it could be modified by different levels of trace minerals in the water. In conclusion, we found a lower hip fracture risk in men (50–85 years) that were supplied water with relatively high calcium, and the association between calcium and hip fracture was stronger when also the copper level in the water was high. Thus, our results showed effect modification by copper on the association between calcium and hip fracture risk. These results, along with previous findings of us and others, clearly warrant further research on the possible effects of low mineral concentrations in drinking water. With the enormous public health impact of hip fractures in the Norwegian population, identifying the underlying cause(s) of the geographic disparity may give clues to important fracture-preventive actions.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bone.2015.07.020.

Disclosures

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