







REVIEW

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The association of fluoride exposure with bone density and fracture risk: a dose-response meta-analysis

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Abstract

Background Fluoride exposure and its effects on human health are controversial and highly debated. While beneficial in preventing dental caries, fluoride has been linked to skeletal and dental fluorosis at high levels, as well as other adverse health endpoints in children and adults. However, the safe range of exposure for bone health remains poorly defined. We used existing literature to quantify the dose-response relation between fluoride exposure and bone health, focusing on fracture risk and bone mineral density (BMD).

Methods We conducted a systematic review and dose-response meta-analysis by searching literature in online databases (MEDLINE/PubMed, Embase and Web of Science) up to August 26, 2025, and by pooling results of studies examining fluoride exposure and its associations with bone health outcomes, namely fracture risk and BMD. We also conducted stratified analyses by sex, age, and fracture site. This study is registered in PROSPERO (CRD42022321899).

Results We included 37 studies published between 1945 and 2024. 10 pertained to bone density only; 19 to bone fractures only; and eight to both outcomes. We found a non-linear, positive relation between fluoride exposure and fracture risk, with an indication of an approximate threshold around 1.5 mg/L of fluoride in drinking water and a nearly linear increasing fracture risk above that concentration (risk ratios of 1.06, 1.19 and 1.35 at 2.0, 3.0 and 4.0 mg/L, respectively, compared to null exposure). Sex-specific dose-response analyses, available only for fragility fractures, indicated an effect in females but little or nothing in males. The association between fluoride and BMD was inconsistent, showing opposite trends for different bone sites (hip and spine) and amounts of exposure, and by sex. Among females aged over 50 years, an association of drinking water fluoride with fragility fracture risk started as early as around 0.5 mg/L (risk ratio of 1.26 at 1.0 mg/L).

Conclusions This study indicates increased risk of fractures with fluoride exposure > 1.5 mg/L in drinking water, with an enhanced susceptibility in postmenopausal females. These findings, which appear consistent with those yielded by recent pooled analysis related to other endpoints in children, may be helpful in assessing the risk-benefit profile for fluoride exposure.

Clinical trial registration not applicable.

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Keywords Bone density, Bone fracture, Fluoride, Frailty fracture, Water fluoridation

Background

Bone health is important to both quality of life and independence. Risk of fracture increases with age, along with low bone mineral density, osteopenia and osteoporosis [1]. One of the many environmental factors influencing bone health is fluoride (F), a widespread halogen commonly found in drinking water, but also in diet and dietary supplements, toothpaste, mouthwash, and ambient air [2]. Soil and groundwater fluoride content may be considerably affected by anthropogenic activities [3].

Drinking water is the most abundant source of fluoride for many individuals and populations [2, 4]. Fluoride is added to municipal water supplies in many areas, at concentrations ranging from 0.7 to 1.2 mg/L. The guideline in the USA was lowered to 0.7 mg/L in 2015 [5]. Fluoride from most dietary sources and drinking water is rapidly absorbed into the bloodstream, and deposited in calcified tissues, predominantly in bone and dental enamel [6]. Topical application of fluoride, through fluoride-containing dental products such as toothpaste and mouthrinse, and by direct application of a concentrated solution, is an alternative method of delivering fluoride to tooth enamel, and can be effective for dental caries prevention [2, 7].

Although water fluoridation has long been advocated for oral health promotion, evidence regarding caries prevention is still debated [2, 7, 8], with a recent review finding little benefit of community water fluoridation in caries prevention after the introduction of fluoridated toothpaste [9]. A number of adverse health issues due to excess fluoride intake, particularly in areas with high levels of fluoride in drinking water, have been documented or suspected [2, 4, 10–14]. They include altered cognitive neurodevelopment [11, 14, 15], dental and skeletal fluorosis [13], impaired thyroid function [10], altered bone mineral density and increased risk of fractures [16]. However, the occurrence of such effects and the levels of exposure involved have been debated [17], particularly for the neurodevelopmental effects [2, 12, 18–23]. Given the absence of any dose-response analysis on fluoride and bone health, we conducted a meta-analysis to assess the overall relation between fluoride exposure and bone health, focusing on potential critical thresholds.

Methods

Study protocol and registration

We registered the protocol of this systematic review in the PROSPERO database (registration no. CRD42022321899) and carried it out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [24].

Search strategy and study selection

We conducted two independent comprehensive literature searches according to the PECOS criteria (population, exposure, comparison, outcome, study type) [25], driven by the questions: “What is the effect of fluoride exposure on bone strength and density?” and “What is the effect of fluoride exposure on risk of fractures?”. We included all studies with: (P) substantially healthy population of any age; (E) assessment of long-term fluoride exposure by determination of drinking water fluoride content or dietary intake and/or using biomarkers of exposure; (C) reporting of health indicators within two or more categories of fluoride exposure; (O) assessment indicators of bone density or strength (e.g., bone mineral density-BMD, bone mineral content-BMC), and/or diagnosis of bone fractures; (S) any study type, including trial, cohort or case-control study. When multiple studies examined the same population, we included only the most complete one (e.g. with the longest follow-up).

To find the eligible studies, we searched the PubMed/MEDLINE, Embase, and Web of Science databases from inception up to August 26, 2025, using MeSH terms and keywords linked to “bone”, “density”, “fracture” and “fluoride” (Supplementary Table S1), deleting duplicate studies. Three authors (RM, II, LDP) independently screened titles, abstracts, and full texts of the retrieved studies to exclude those that did not meet the eligibility criteria. Any disagreements were resolved by the intervention of two other authors (TF and MV), or until a consensus was reached. Additionally, we checked the reference lists of included studies and previous reviews, and employed backward and forward citation retrieval techniques to identify potentially relevant additional articles [26].

We included studies reporting different types of effect and risk measures, such as relative risk (RR), hazard ratio (HR), odds ratio (OR), or mean difference (MD), along with the corresponding 95% confidence interval (95% CI), standard error (SE), standard deviation (SD), or interquartile range (IQR), or data to calculate them as per Cochrane Handbook for Systematic Reviews of Interventions [27]. This included calculating standard errors from reported confidence intervals, converting interquartile ranges to standard deviations using established conversions (e.g., $SD = IQR/1.35$), and estimating standard deviations from p-values using standard normal approximations when applicable. We did not apply statistical transformations to convert between effect estimates, which were pooled only when directly comparable.

Data extraction

Three authors (RM, II, LDP) independently conducted data extraction from the selected articles, with a fourth author (TF) verifying the process. We employed two distinct standardized spreadsheets for collecting data relating to the two outcomes. For each article, we compiled the following details: (1) the first author's name; (2) study details (title, publication year, study design, country); (3) population characteristics (sex, age, sample size); (4) exposure characteristics (definition, assessment method, categories of exposure); (5) outcome (definition, assessment method, number of cases); (6) effect estimates (RRs, HRs, ORs, MDs) with their 95% CIs, SE, SD from the most adjusted model; (7) potential confounders accounted for in the multivariable analysis.

Risk of bias assessment

Three authors (RM, II, LDP) independently assessed the risk of bias (RoB) of the included studies based on the Risk of Bias for Non-randomized Studies of Exposures (ROBINS-E) criteria [28]. Any discrepancies were resolved with input from two other authors (MV and TF). We categorized the studies into low, moderate, or high risk of bias based on seven domains: (1) confounding bias; (2) participant selection bias; (3) exposure classification bias; (4) departures from intended exposures bias; (5) missing data bias; (6) outcome measurement bias; and (7) bias in the selection of reported results. In (Supplementary Table S2), we detailed the criteria for risk of bias evaluation. We deemed a study to have a moderate or high risk of bias if at least one domain was judged as moderate or high risk, respectively; else, it was classified as having a low risk of bias.

Data analysis

We quantitatively compared fracture risks and BMD values across varying levels of fluoride exposure using a restricted maximum likelihood random-effects model [29]. Additionally, we conducted a dose-response meta-analysis to assess bone fracture risk and BMD with increasing fluoride exposure, based on the one-stage approach [30], a methodology recently applied to pool epidemiologic data and characterize the dose-response relationship across the entire range of exposure [31–34]. Where mean or median values were unavailable for levels of exposure in open-ended categories, we estimated values 20% higher or lower than the nearest cut-point [35]. To allow for non-linear relationships, we used a restricted cubic spline model with three knots at fixed percentiles (10th, 50th, and 90th) of fluoride exposure. We assessed heterogeneity of included studies using the \hat{R}_I statistics evaluating the between-study heterogeneity relative to the variance of the pooled random-effects estimate [36] and through variation of study-specific curves evaluating

the variability across individual studies [29, 37]. We conducted funnel plot analyses and Egger's regression tests wherever sufficient data were available.

In the aggregate BMD analyses, when multiple measurements from different subregions of the hip were reported within a single study (e.g., femoral neck, Ward's triangle, trochanter), we selected only one to include in the meta-analysis to avoid multiple correlated estimates from the same anatomical region. To ensure consistency and comparability across studies, we applied a predefined hierarchy of hip subregions based on the relative frequency of reporting across studies, prioritizing them in the following order: hip or femur, femoral neck, Ward's triangle, trochanter, inter-trochanter. When more than one site was reported within a study, we included only the highest-priority site according to this hierarchy.

Whenever possible, we carried out stratified analyses separately for different levels of variables that might modify the effect measure, such as sex and age. We also carried out sensitivity analyses by excluding studies at high risk of bias. Additionally, we examined fragility fractures in females over 50, the average age of menopause onset [38], to assess how menopause and fluoride exposure jointly affect bone health. We used Stata software (v18.0, Stata Corp., College Station, TX, 2023) for all data analyses.

Results

Study selection and characteristics of the included studies

The detailed literature databases search and study selection process are in the PRISMA flowchart (Fig. 1). Regarding bone strength and density, we initially identified a total of 1257 articles. Following duplicate removal, 1049 articles remained, from which 1010 records were excluded after title and abstract assessment as they were considered not relevant or they were not written in English. After these exclusions, there were 39 articles remaining for full-text evaluation. We made additional exclusions after full-text review, excluding an additional total of 22 studies. Details on reasons for exclusion are provided in (Supplementary Table S3).

We applied the same selection process to assess fracture risk, initially identifying a total of 1097 articles before removing duplicates, and 982 articles afterward. Among these, 943 were excluded after screening titles and abstracts, as they were deemed unsuitable publication types, irrelevant to the outcomes, or non-English studies. Out of the 39 articles we assessed in full text, 13 were subsequently excluded. The articles excluded after full-text review, along with the reasons for their exclusion, are listed in (Supplementary Table S3). Furthermore, we retrieved one article regarding bone fractures and one article on whole-body BMD through citation chasing [39].

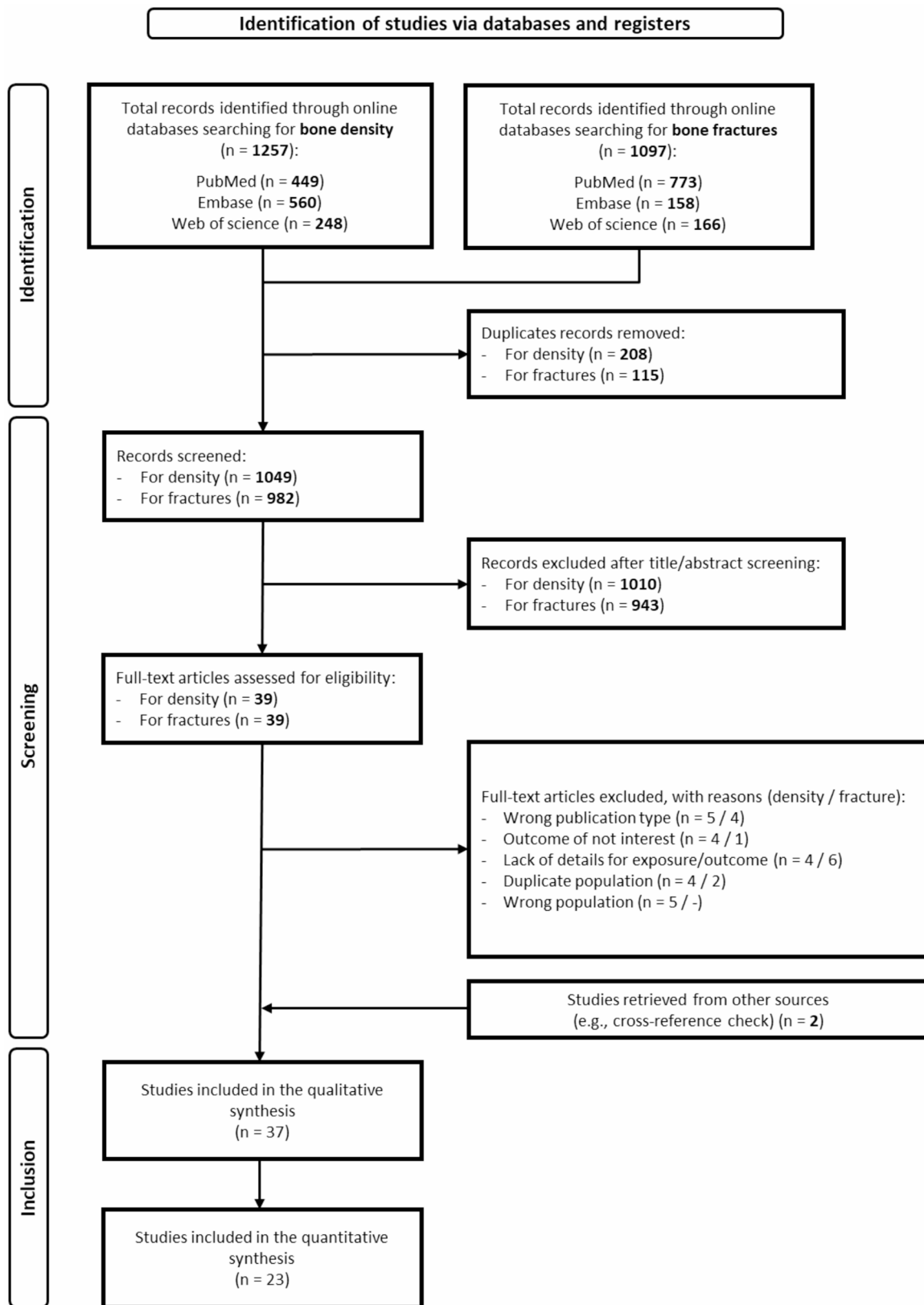


Fig. 1 PRISMA flowchart for study identification and inclusion. Studies included in the qualitative synthesis [16, 39–74]/studies included in the quantitative synthesis [39–41, 43, 45, 48–52, 54, 55, 57–59, 61, 63–65, 68, 69, 72, 73]

Ultimately, 37 studies were included in our meta-analysis and deemed suitable to assess the association between fluoride exposure and bone health: 10 pertaining to bone density only [40–48]; 19 on bone fractures only [39, 49–66]; and eight on both outcomes [16, 67–73].

Characteristics of the included studies

The details of the 37 studies included are summarized in Table 1. Regarding the year of publication: three studies were conducted before 1980 [39, 54, 58], three were carried out in the 1980s [40, 49, 64], the majority, 18, were published between 1990 and 1999 [41, 43, 45–48, 50–53, 56, 57, 59, 65, 67–69, 72], eight were published between 2000 and 2019 [42, 55, 61, 63, 66, 70, 71, 73], and five were published after 2020 [16, 44, 60, 62, 74].

The majority of studies focused on North American populations, with 16 being from the USA [39, 47, 48, 51, 53, 54, 56–58, 62, 67, 70–74] and two from Canada [41, 65]. The second most represented population was Northern Europe, with five studies from Finland [40, 49, 59, 64, 68] and three from Sweden [16, 46, 63]. Additionally, there were three studies from the UK [50, 55, 66], one from Poland [43], one from Italy [52], and one from Germany [75]. From Asia, two studies were included from China [42, 61], one from Taiwan [45], and one from South Korea [60]. Only one study originated from Africa, specifically from Ethiopia [44].

Sixteen studies had an ecological design [39, 43, 46, 49–52, 54, 56–58, 60, 61, 63–65], 12 a cohort design [16, 40, 41, 47, 48, 53, 59, 67, 70–72, 74], nine cross-sectional [42, 44, 45, 62, 66, 68, 69, 73, 74], with one being interventional [42], one a population-based case-control design [55]. Exposure was predominantly assessed by measuring fluoride drinking water content [39–50, 52, 54, 55, 57–69, 71–74] reported either in mg/L or ppm, which are numerically equivalent and directly comparable. Urinary fluoride content was expressed either as mg/L [42, 43, 74] or mg/g creatinine [16]. Dietary or daily fluoride intake was expressed as mg/day by two studies [16, 70]. One study assessed fluoride content in serum [73], one in plasma [74], one in hair [43], and one in toenails [53]. These alternative biomarkers were not integrated into pooled analyses, as exposure-response synthesis was only performed for studies using directly compatible exposure metrics.

Concerning outcomes, bone strength studies assessed BMD [16, 40–43, 45–48, 67–74], BMC [47, 70], bone compressive strength [40], bone width [47], and speed of sound [44]. Regarding bone density or strength, the investigated locations were lumbar spine or spine [16, 41, 43, 45, 48, 67–71, 73], hip and femur [16, 40, 43, 67–73], radius, tibia and forearm [44, 47, 48, 67, 71–73, 76], calcaneus [67, 71], tibia and phalanx [44], and whole-body [41, 46, 70, 74].

Risk of fractures was assessed with reference to arm, humerus, elbow and wrist [39, 52, 57, 58, 62, 67, 68, 71, 72], leg, knee and ankle [39, 57, 68, 72], hip and femur [16, 49–59, 61–67, 69, 71] vertebral [52, 67, 71], and nose [52]. Each study was categorized according to the most specific anatomical location it reported (i.e., if a study included both “arm fractures” and “humerus fractures”, we only considered the latter). Some studies used broader endpoints such as “all fractures” [39, 60, 61, 68, 70, 72], “all non-vertebral fractures” [71], and “osteoporotic” and “non-osteoporotic fractures” [73].

Risk of bias assessment

We provide details about study quality (Supplementary Table S4). Regarding bone density and strength, we deemed nine of the included studies to have overall “high” risk of bias [40, 43, 46, 47, 69–71, 76], five at “moderate” risk [41, 48, 67, 68, 72], and four at “low” risk [16, 44, 45, 73].

Considering bone fractures, we judged 18 of the included studies at “high” risk of bias for this outcome [39, 49, 50, 52, 54, 56–58, 60, 62, 64–66, 68–72], seven at “moderate” risk of bias [51, 53, 55, 59, 61, 63, 67], and two at “low” risk of bias [16, 73].

Regardless of the outcome, the main factors contributing to the high-risk rating included unaccounted sources of confounding ($n=11$) and bias in exposure measurement ($n=8$).

Dose-response meta-analysis on risk of fractures

Four studies [39, 61, 68, 72] assessed the overall risk ratio of fractures, regardless of the site. Figure 2 illustrates the dose-response curve and the threshold effect for all fractures risk in relation to fluoride exposure, in the overall study populations since no sex-specific analysis was feasible. At low levels of fluoride, specifically up to around 1.4 mg/L, there was no change in fracture risk (RR 1.00 at 1.2 mg/L; 95% CI 0.80–1.24). Above 1.4 mg/L, as fluoride concentrations increased, the risk of fracture gradually increased, with a RR of 1.06 (95% CI 0.80–1.41) at 2.0 mg/L, increasing to 1.19 (95% CI 0.87–1.64) at 3.0 mg/L, and to 1.35 (95% CI 0.94–1.95) at 4.0 mg/L. Study specific curves strongly support a consistent positive association between fluoride exposure and fracture risk across studies, with the only exception of one investigation of teen-age males aged 15–17 [39] (Supplementary Figure S1).

Dose-response meta-analysis on risk of fragility fractures

Dose-response analysis of fragility fractures also revealed a non-linear relation (Fig. 3), with a slight indication of a U-shaped dose-response pattern. The corresponding RRs were 0.93 (95% CI 0.84–1.02) for water fluoride concentrations up to 0.9 mg/L, 1.00 (95% CI 0.82–1.21)

Table 1 Characteristics of included studies

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Alhava et al. 1980 [40]	Cohort (1973–1978)	Finland	158 adults of both sexes aged > 45 years	14–18 years of exposure to Water [F] (ppm): 0.02–0.32; 0.95–0.99	Community water system testing for Water Fluoride content; Bone fluoride via ion selective electrode (ORION 94–09)	Mean bone strength (10^6N/m^2): - Female (sudden death): 8.29 ± 0.41 ; 9.06 ± 0.50 - Female (Chronic disease): 7.62 ± 0.29 ; 8.85 ± 0.57 - Male (sudden death): 10.40 ± 0.34 ; 9.69 ± 0.60 - Male (Chronic disease): 9.36 ± 0.52 ; 9.10 ± 0.26 BMD (kg/m^3): - Female (sudden death): 218 ± 27 ; 234 ± 17 - Female (Chronic disease): 191 ± 22 ; 211 ± 13 - Male (sudden death): 239 ± 6 ; 232 ± 9 - Male (Chronic disease): 205 ± 10 ; 212 ± 8	Strain transducer Nokso-Koivisto & Gamma ray attenuation method Cameron-Sorenson	Sex and cause of death
Arnala et al. 1986 [49]	Ecological (1972–1981)	Finland	NR number of adults of both sexes aged 50–80 years	NR years of exposure: Water [F] (ppm): <0.3; 1.0–1.2; > 1.5 Bone [F] (mg/g): 0.45; 1.59; 3.72	National Board of Health & Bone samples from the iliac crest tested using a fluoride selective electrode	Hip fractures 10-year incidence/10,000 (n of fractures): - 50–59 years: 1.2 (5); 1.9 (13); 0.7 (3) - 60–69 years: 7.8 (27); 7.7 (38); 8 (28) - 70–79 years: 16.4 (39); 16.3 (50); 20.5 (52) - ≥ 80 years: 93.2 (64); 93.6 (85); 74 (57)	Hospital Fracture Case Reports	Age
Arnold et al. 1997 [41]	Cohort (1994–1995)	Canada	57 females aged 18–25 years	95% of subject: lifetime; all subjects: >4y years of exposure to Water [F] (mg/L): <0.12–0.15; 0.90–1.25	Fluoridation Programme, Saskatoon Water Treatment Plant	Mean anterior-posterior lumbar spine BMD (g/cm^2): 0.986 ± 0.07 ; 1.028 ± 0.12 Mean volumetric lumbar spine BMD (g/cm^3): 0.218 ± 0.02 ; 0.225 ± 0.02 Mean total body BMD (g/cm^3): 1.051 ± 0.06 ; 1.065 ± 0.08 Mean proximal femur BMD (g/cm^2): 0.936 ± 0.09 ; 0.951 ± 0.14	DXA Hologic 2000	Sex (restricted to females) and age (18–25). Adjusted models including weight lacked sufficient data to estimate risk (no confidence intervals or standard deviations reported).
Caulley et al. 1995 [67]	Prospective cohort (ancillary to the Multicenter Study of Osteoporotic Fractures - SOF), (1988–1990, follow-up mean 5.9 years)	USA	2,076 females aged ≥ 65 years	0, 1–10, 11–20, > 20 years of exposure to Water [F] (-): Fluoridated; Nonfluoridated	Community water fluoridation and additional verification from local water companies & atomic absorption spectrophotometry	Mean BMD (g/cm^2): - Distal radius: 0.353, 0.352, 0.357, 0.363 - Proximal radius: 0.634, 0.622, 0.635, 0.637 - Calcaneus: 0.404, 0.395, 0.400, 0.405 - Femoral neck: 0.640, 0.638, 0.642, 0.658 - Ward's triangle: 0.426, 0.421, 0.428, 0.438 - Trochanter: 0.555, 0.548, 0.547, 0.568 - Intertrochanter: 0.883, 0.873, 0.878, 0.899 - Lumbar Spine: 0.842, 0.847, 0.844, 0.849 Wrist fracture (RR): ref: 1.17 (0.67; 2.05); 0.81 (0.32; 2.04); 0.95 (0.40; 2.25) Hip fracture (RR): ref: 0.89 (0.42; 1.92); 0.58 (0.14; 2.48); 0.44 (0.10; 1.86) Vertebral fracture (RR): ref: 1.02 (0.55; 1.88); 0.58 (0.21; 1.60); 1.63 (0.57; 4.67)	Single-photon Absorptiometry; Hologic QDR 1000	Age and sex

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Chen et al. 2013 [42]	Interventional	China	600 children of both sexes aged 6–12 years (50% girl and 50% boys)	Lifetime exposure to Water [F] (mg/L), before and after change in public water supply: 0.12; 2.17; 3.31; 3.99; 5.51 After the change of public water supply: 0.11 (6 years); 0.09 (14 years); 0.11 (15 years); 0.10 (17 years); 0.11 (control) Lifetime exposure to Urinary [F] (mg/L): After the change in water supply: 0.62; 0.51; 0.36; 0.27; 0.48	Ion electrode test based on the China's Drinking Water Standard Detection Method	Mean forearm (radius and ulna) BMD (SD)(g/cm ²): 0.29 (0.06); 0.26 (0.04); 0.28 (0.07); 0.29 (0.07); 0.27 (0.04)	Dual Energy X-Ray Bone Densitometer (DTX-200 US Osteometer MedITech)	Age

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Copper et al. 1990 [50]	Ecological (1990)	UK	20,393 adults of both sexes (4,121 males; 16,272 females) discharged from the hospital after hip fracture aged ≥ 45 years	NR years of exposure to Water [F] (mg/L): 0.005; 0.009; 0.03; 0.03; 0.04; 0.05; 0.05; 0.05; 0.07; 0.07; 0.08; 0.08; 0.08; 0.09; 0.1; 0.2; 0.23; 0.23; 0.24; 0.25; 0.25; 0.25; 0.25; 0.25; 0.25; 0.3; 0.32; 0.38; 0.44; 0.5; 0.51; 0.59; 0.66; 0.68; 0.7; 0.77; 0.9; 0.93; 0.99	NR (Water Research Centre)	Proximal femoral fractures (cases - participants): For male: 123-236,538; 73-115,873; 260-406,250; 144-194,595; 100-106,383; 26-43,333; 136-283,333; 126-159,494; 114-144,304; 69-104,545; 311-353,409; 34-44,737; 31-46,269; 48-72,727; 15-13,158; 31-88,571; 96-150,000; 102-98,077; 109-162,687; 100-142,857; 48-96,000; 200-289,855; 114-134,118; 47-75,806; 39-55,714; 17-16,998; 51-68,919; 41-82,000; 36-62,069; 146-211,594; 60-92,308; 83-136,066; 88-162,963; 42-84,000; 37-35,922; 37-52,857; 782-797,959; 133-170,513; 72-94,737 For female: 572-288,889; 439-159,058; 950-568,862; 488-236,893; 359-140,784; 87-53,704; 471-389,256; 516-346,309; 456-189,212; 331-132,400; 1347-493,407; 114-47,699; 116-54,717; 224-86,154; 39-16,738; 159-99,375; 309-193,125; 419-125,449; 485-212,719; 461-180,784; 129-108,403; 805-387,019; 526-163,863; 101-80,800; 119-66,111; 58-19,269; 171-74,348; 192-93,204; 180-72,581; 613-257,563; 249-99,203; 291-163,483; 387-205,851; 191-90,521; 133-42,765; 141-51,838; 2816-988,070; 492-207,595; 337-119,081 For both: 695-526,515; 512-284,444; 1210-1,008,333; 632-432,877; 459-250,820; 113-97,414; 607-689,773; 642-373,256; 570-339,286; 400-239,521; 1658-872,632; 148-89,157; 147-100,685; 272-158,139; 54-30,168; 189-181,731; 405-346,154; 521-226,522; 594-380,769; 561-326,163; 177-201,136; 1005-693,103; 640-297,674; 148-152,577; 158-120,611; 75-35,714; 222-138,750; 233-171,323; 216-133,333; 759-468,518; 309-185,030; 374-299,200; 475-371,094; 233-168,841; 170-78,341; 178-98,342; 3598-1,790,050; 426-256,626; 409-215,263	Hospital activity analysis data on discharge for fracture of proximal femur discharge during 1978 to 1982	NR

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Czarnowski et al. 1999 [43]	Ecological (1999)	Poland	300 adults of both sexes (235 females, 65 males) aged 24–77 (mean 50) years	> 10 years of exposure to Water [F] (mg/L): 0.32 ± 0.28; 1.69 ± 0.44; 2.74 ± 0.99 > 10 years of exposure, Urinary [F] (mg/L): 0.77 ± 0.49; 1.93 ± 0.82; 2.89 ± 1.39 > 10 years of exposure to Hair F (µg/g): 4.13 ± 2.24; 10.25 ± 6.63; 14.51 ± 6.29	Fluoride-specific ion electrode Fluoride-specific ion electrode	Mean left femur (g/cm ²): 0.92 ± 0.14; 1.03 ± 0.13; 1.05 ± 0.17 Mean lumbar spine BMD (g/cm ²): 1.09 ± 0.17; 1.13 ± 0.17; 1.17 ± 0.19	Lunar Expert Densitometer	NR
Danielson et al. 1992 [51]	Ecological cohort (1984–1990)	USA	6,049 adults of both sexes (males 41.1%) aged ≥ 65 years	NR years of exposure to Water [F] (ppm): < 0.30; 1.00	Washed with NaOH, then Fluoride-specific ion electrode Utah Department of Health, Dental Health Bureau, Family Health Services Division (Salt Lake City, Utah)	Femoral fractures (RR): Males: ref = 1.41 (1.00; 1.81) Females: ref = 1.27 (1.08; 1.46)	Utah Peer Review Organization (UPRO) (from 1984 to 1990)	Age and sex
Fabiani et al. 1999 [52]	Ecological (1982–1984)	Italy	198,945 subjects (NR age) of both sexes	NR years of exposure to Water [F] (mg/L): 0.04–0.58 (mean: 0.05); 0.15–3.40 (mean: 1.45)	Electro-chemical method with a selective electrode	Femoral, humerus, nose, wrist and vertebral fractures (RR): Males: Femoral neck: ref = 4.28 (4.16; 4.40), Humerus: ref = 0.95 (0.54; 1.36), Nose: ref = 1.31 (1.306; 13.15), Wrist: ref = 1.77 (1.54; 2.01), Vertebral: ref = 1.23 (0.92; 1.55) Females: Femoral neck: ref = 2.64 (2.54; 2.75), Femoral fracture not specified: ref = 3.35 (3.23; 3.46), Humerus: ref = 2.97 (2.82; 3.11), Nose: ref = 3.52 (3.37; 3.66), Wrist: ref = 2.08 (1.87; 2.28), Vertebral: ref = 0.54 (0.00; 1.18),	Hospital Admission Registers (1st admission only), from 1990 to 1991	Sex
Feskanich et al. 1998 [53]	Nested Cohort (Nurses Health Study) (1982–1984)	USA	62,641 females of 30–55 years (1982–1984)	NR years of exposure to Toenail [F] (ppm): < 2.00; 2.00–3.35; 3.36–5.50; > 5.50	Gamma emissions from the 20 F isotope induced by neutron capture, converted into weight of fluoride	Hip and forearm fractures (OR): - Hip: ref: 0.5 (0.2, 1.7); 0.4 (0.1, 1.8); 0.8 (0.2, 4) - Forearm: Ref: 1.5 (0.7, 2.9); 1.3 (0.7, 2.4); 1.6 (0.8, 3.1)	Self-report; a validation study within this cohort show that nurses can accurately report this information	Age, sex, menopausal status, and postmenopausal hormone use, caffeine consumption, and alcohol consumption

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Godebo et al. 2020 [44]	Cross-sectional (2018–2019)	Ethiopia	341 children and adults of both sexes (188 males, 153 females) aged 10–70 years	Residency at least as long as the age of sampled well, years of exposure to Water [F] (mg/L): <2; >2–6; >6–10; >10–15.5	Ion selective electrode and the hexamethyl-diisiloxane (HMDS)-facilitated diffusion method (further validated through urine F content)	Mean Difference tibia BMD (m/s): ref: 0.76 (–42.9; 44.5); –61.5 (–108; –16.3); –108 (–153; –63) Mean Difference radius, BMD (m/s): ref: –14.8 (–61.3; 31.7); –45.4 (–93.5; 2.63); –61.2 (–109.1; –13.4) Mean Difference phalanx BMD (m/s): ref: –4.4 (–6.24; –2.46); –43 (–110.2; –24.1); –102.6 (–171.9; –33.3)	Ultrasound scan (Sunlight Mini-Omni ultrasound device) to calculate SOS	Age, sex, BMI, toothpaste, smoking
Goggin et al. 1965 [54]	Ecological (1965)	USA	23,294 postmenopausal females aged ≥ 60 years	10 years of exposure to Water [F] (ppm): Before fluoridation (1948–1952): 0.01–0.02 After fluoridation (1953–1957): 1.00	NR (likely county fluoridation program)	Femoral fractures rate per 1000: From 1948 to 1952: –60–64 years: 1.4 –65–69 years: 2.9 –70–74 years: 6.2 –75–84 years: 10.5 –≥ 85 years: 19.7 From 1953 to 1957: –60–64 years: 1.4 –65–69 years: 2.6 –70–74 years: 3.4 –75–84 years: 12.4 –≥ 85 years: 25.8	Hospital Records	Age and sex
Helte et al. 2021 [16]	Cohort, Swedish Mammography Cohort - SMC (2004–2009)	Sweden	4,306 females aged < 85 years	Constant if 22–27 years of exposure; Urinary [F] (mg/g creatinine): 0.68 (0.14–0.88); 1.08 (0.88–1.30); 1.64 (1.30–116.51)	Urinary F: Ion-selective electrode (combined ISE F800 DIN)	Mean Difference BMD (g/cm ²): Urinary F: - Lumbar spine: ref: 0.007 (–0.006; 0.020); 0.013 (0.000; 0.027) - Femoral neck: ref: 0.007 (–0.001; 0.015); 0.009 (0.001; 0.016) Dietary F: - Lumbar spine: ref: 0.005 (–0.008; 0.019); 0.017 (0.004; 0.031) - Femoral neck: ref: 0.007 (–0.001; 0.015); 0.008 (0.000; 0.017) Hip Fractures (HR): Urinary F: - All fractures: ref: 0.98 (0.82; 1.16); 1.13 (0.95; 1.34) - Hip fractures: ref: 1.12 (0.75; 1.65); 1.50 (1.04; 2.17) Dietary F: - All fractures: ref: 1.02 (0.86; 1.21); 1.01 (0.85; 1.20) - Hip fractures: ref: 1.12 (0.76; 1.63); 1.59 (1.10; 2.30)	Dual Energy X-Ray Absorptiometry (DXA; Lunar)	BMD & Fractures: Age, sex, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen, and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L)

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Hillier et al. 2000 [55]	Population-based case-control (2000)	UK	1,041 adults of both sexes (males 20.6%) aged ≥ 50	Lifetime or 20 years of exposure to Water [F] (ppm): < 0.9; > 0.9	Information provided by water suppliers & Questionnaire	Hip fractures (OR): Lifetime: ref – 1.0 (0.7; 1.5) ≤ 20 years: ref – 0.90 (0.60; 1.40)	Cases from General Hospital ward admission books & controls from National Health Service (NHS)	Age, sex, BMI, physical-activity score, age at menopause, current alcohol consumption, ever smoked, current treatment with oral corticosteroids, dietary intake of calcium
Jacobson et al. 1992 [56]	National ecological cohort (1992)	USA	70 million adults of both sexes aged ≥ 65 years	NR years of exposure to Water [F] (-); Non-Fluoridated (less than 10% of the population received fluoridated water at any time through 1985); Fluoridated (proportion of the population served with fluoridated water increased from less than 10% to more than 66% within a 3-year-period);	County-level fluoridation of centralized water systems determined using a methodology developed by National Cancer Institute	Hip fractures (RR): For males: Ref – 1.17 (1–13; 1–22) For females: ref – 1.08 (1–06; 1–10)	Health Care Financing Administration (HCFA), Department of Veterans Affairs (VA) & Medicare Provider Analysis and Review Record (MEDPAR); from 1984 to 1987	Age and sex
Karas et al. 1996 [57]	Ecological (1986–1990)	USA	NR adults of both sexes aged 65–89 years	NR years of exposure to Water [F] (ppm): Non fluoridated (less than 10% of the population received fluoridated water, or natural F levels ≤ 0.3); Fluoridated (more than 66% of the population received natural or artificial fluoridated water of ≥ 0.7).	Fluoridation Census data	Hip (RR): Males: ref – 1.00 (0.92; 1.09) Females: ref – 1.01 (0.96; 1.06) Ankle (RR): Males: ref – 1.01 (0.87; 1.16) Females: ref – 1.00 (0.92; 1.08) Proximal humerus (RR): Males only: ref – 1.23 (1.06; 1.43) Distal forearm (RR): Males only: ref – 1.16 (1.02; 1.33)	Hospitalization, outpatient facility and physician claims	Sex

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Kong et al. 2024 [74]	Cross-sectional (National Health and Nutrition Examination Survey, 2015–2016)	USA	1413 individuals (males 51.5%) aged 8–19 years	NR years of exposure to fluoride: Water [F] (mg/L): ≤ 0.16 ; 0.17–0.42; 0.43–0.68; >0.68 Urine [F] (mg/L): ≤ 0.299 ; 0.300–0.496; 0.497–0.804; >0.804 Plasma [F] ($\mu\text{mol/L}$): ≤ 0.18 ; 0.18–0.29; 0.30–0.40; >0.40	Ion-specific electrode for all exposure Urine samples for fluoride concentration testing were obtained from spot urine collection	Total body less head BMD (g/cm^2): For water exposure: ref – -0.020 (-0.04 ; 0.00) – -0.040 (-0.10 ; 0.02) – -0.060 (-0.12 ; 0.00) For urinary exposure: ref – -0.000 (-0.03 ; 0.02) – -0.001 (-0.04 ; 0.03) – -0.001 (-0.04 ; 0.01) For plasma exposure: ref – -0.010 (-0.04 ; 0.03) – -0.030 (-0.06 ; 0.00) – -0.030 (-0.07 ; 0.00)	Dual Energy X-Ray Absorptiometry (DXA)	age, gender, race, Body Mass Index, poverty income ratio, physical activity, and milk product consumption
Korns et al. 1969 [58]	Ecological cohort (1966–1967)	USA	NR adults of both sexes aged ≥ 40 years	20 years of exposure to Water [F] (ppm): 0.05; 1–1.12	NR (community water system records)	Hip fractures (rate per 1,000): 55–65 years: Males: 2.9; 3.4 Females: 9.5; 8.3 All: 6.7; 6.2 >65 years: Males: 3.5; 6.1 Females: 13.9; 12.7 All: 9.8; 10.0 Wrist fractures (rate per 10,000): Males: 9.9; 4.0 Females: 37.2; 35.4	Wrist X-Rays & Hip Fractures Records	Age and sex; age
Kroger et al. 1994 [68]	Cross-sectional (1980–1989)	Finland	3,222 females aged 47–59 years	>10 years of exposure to Water [F] (mg/L): <0.30 ; 1.0–1.20	National Board of Health (Finland)	Lumbar spine BMD (g/cm^2): 1.121; 1.151 Femoral neck: 0.930; 0.940 Adjusted value without SD but with p-value; CI calculated via Cochrane Revman tool Occurrence of fractures during 1980–1989 (cases/participants): - Wrist: 70/2258; 43/977 - Ankle: 49/2227; 24/960 - All fractures: 302/2254; 148/691	Dual Energy X-Ray Absorptiometry (DXA; Lunar)	Age, sex, weight, menopausal status, calcium intake, physical activity class, number of deliveries, alcohol consumption, estrogen use Sex

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Kurtio et al. 1999 [59]	Retrospective cohort (1999)	Finland	144,627 adults of both sexes (46% males) aged 50–80 years	NR years of exposure to Water [F] (mg/L): ≤0.10; 0.11–0.30; 0.31–0.50; 0.51–1.00; 1.10–1.50; >1.50	Water Fluoride measurements by the Geological Survey of Finland	Hip fractures rate ratio: 50–80 years: - Males: ref; 1.05 (0.90; 1.22); 0.72 (0.81; 1.32); 1.03 (0.81; 1.32); 0.67 (0.46; 0.97); 0.98 (0.61; 1.60) - Females: ref; 0.93 (0.84; 1.02); 1.12 (0.93; 1.34); 1.12 (0.96; 1.31); 1.08 (0.88; 1.32) 1.08 (0.80; 1.46) 50–65 years: - Males: ref; 1.20 (0.91; 1.56); 0.81 (0.44; 1.49); 0.68 (0.41; 1.13); 0.60 (0.29; 1.25); 0.87 (0.35; 2.16) - Females: ref; 1.16 (0.93; 1.43); 1.31 (0.86; 1.99); 1.53 (1.08; 2.16); 1.24 (0.77; 2.01); 2.09 (1.16; 3.76)	Hospital Discharge Register	Age, sex, area
Lan et al. 1995 [45]	Cross-sectional (1990)	Taiwan	248 females aged ≥ 40 years	> 10 years of exposure (for 95% of subjects) to Water [F] (mg/L): All ages: <0.6; 0.8–0.8; 0.8–1.0; ≥ 1 Stratified by age: 0.085; 0.18; 0.98	Electrode Method quantification of drinking water sample	Mean BMD lumbar spine (g/cm ²), all ages: 1.144, 1.145, 1.163, 1.203 Mean BMD (g/cm ²) (SD), stratified by age: - 40–45 years: 1.323 (0.157); 1.335 (0.153); 1.322 (0.098) - 46–50 years: 1.199 (0.178); 1.159 (0.165); 1.288 (0.163) - 51–55 years: 1.117 (0.152); 1.196 (0.154); 1.210 (0.165) - 56–60 years: 1.068 (0.147); 1.099 (0.156); 1.147 (0.146) - 61–65 years: 1.081 (0.172); 1.031 (0.112); 1.125 (0.140) - > 65 years: 0.974 (0.152); 1.030 (0.093); 1.026 (0.070)	Dual-Photon Absorptiometry	Adjusted for all ages: Age, sex and BMI Unadjusted for BMI in 5-years stratification
Lee et al. 2024 [60]	Ecological cohort (2008–2012)	South Korea	52,872 (males 11,853 + 15,447) children aged 5–6	Lifetime exposure to Water [F] (mg/L): Non fluoridated (unspecified natural [F] levels); Fluoridated (0.8 ± 0.2)	Korea Health Promotion Agency	Bone fracture (HR): 0.892 (0.817; 0.973)	National Health Insurance Service (NHIS)	Sex; birthweight, prematurity, weight change from birth to 4–6 months of age, head circumference at 4–6 months of age, feeding type during the first 4–6 months of age, region of birth, economic status, birth years and perinatal conditions

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Lehmann et al. 1998 [69]	Cross-sectional (1987–1989)	Germany	656 adults of both sexes (females 415) aged 20–69 years	> 10 years of exposure to Water [F] (mg/L): 0.08–0.36; 0.77–1.20	NR, not specified who or how gave Cities Fluoride content measurements	Mean BMD (g/cm ²) (SD): Males: - Spine: 0.997 (0.129); 1.045 (0.171) - Femoral neck: 0.820 (0.101); 0.876 (0.120) - Ward's triangle: 0.655 (0.111); 0.725 (0.129) - Femoral trochanter: 0.724 (0.089); 0.771 (0.105) Females: - Spine: 1.055 (0.112); 1.046 (0.117) - Femoral neck: 0.814 (0.100); 0.809 (0.102) - Ward's triangle: 0.662 (0.110), 0.659 (0.109) - Femoral trochanter: 0.690 (0.088); 0.685 (0.800)	Dual Energy X-Ray Absorptiometry (DXA; Hologic QDR 1000)	Age and weight in females, age and BMI in males
Levy et al. 2014 [70]	Prospective cohort; Iowa Fluoride Population (IFS)/Iowa Bone Development Study (IBDS), (1992–2006)	USA	358 children of both sexes aged 15 years	Lifetime exposure to Daily F intake (mg/day): Males: 0.26–0.62; 0.63–0.85; 0.86–1.84 Females: 0.26–0.53; 0.54–0.75; 0.76–1.54	Detailed questionnaires	Hip fractures (OR): Males: - 60–64: ref – 2.14 (0.89; 5.2); - 65–69: ref – 0.55 (0.22; 1.39), - 70–74: ref – 0.78 (0.27; 1.39), - 75–79: ref – 1.05 (0.65; 1.69), - 80–84: ref – 1.02 (0.67; 1.55), - ≥ 85: ref – 1.92 (1.07; 3.45), Females: - 60–64: ref – 0.90 (0.51; 1.58), - 65–69: ref – 1.56 (1.00; 2.44), - 70–74: ref – 1.09 (0.76; 1.57), - 75–79: ref – 1.38 (1.06; 1.80), - 80–84: ref – 1.20 (0.95; 1.52), - ≥ 85: ref – 1.41 (1.10; 1.81)	Hospital Discharge Register and Operation Books (1987–1989)	Age and sex
Levy et al. 2014 [70]	Prospective cohort; Iowa Fluoride Population (IFS)/Iowa Bone Development Study (IBDS), (1992–2006)	USA	358 children of both sexes aged 15 years	Lifetime exposure to Daily F intake (mg/day): Males: 0.26–0.62; 0.63–0.85; 0.86–1.84 Females: 0.26–0.53; 0.54–0.75; 0.76–1.54	Detailed questionnaires	Spine BMC (g): 60.3; 59.3; 60.6 Whole-Body BMC (g): 2026.8; 2016.5; 2004.3 Hip BMD (g/cm ²): 1; 1; 0.99 Spine BMD (g/cm ²): 0.95; 0.93; 0.95 Hip BMC (g): 38.1; 37.8; 37.3 Females: - Spine BMC (g): 56.4; 58.3; 58.6 - Whole-Body BMC (g): 1682.2; 1722.4; 1701.6 - Hip BMD (g/cm ²): 0.95; 0.95; 0.94 - Spine BMD (g/cm ²): 1; 1.01; 1.01 - Hip BMC (g): 29.1; 29.8; 28.9	Dual Energy X-Ray Absorptiometry (DXA; Hologic QDR 4500 A)	Age, sex, height, weight, time since PHV, Tanner Stage, daily calcium intake, and ActiGraph MVPA
			All fractures n (%): 16 (8.7%); 28 (16.0%)		Questionnaire	NR		

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Li et al. 2001 [61]	Ecological cohort (six Chinese population) (2001)	China	8,266 adults of both sexes (males 45.6%) aged ≥ 50 years	Long-term (> 25 years) exposure to Water [F] (ppm): 0.25–0.34; 0.58–0.73; 1.00–1.06; 1.45–2.19; 2.62–3.56; 4.32–7.97.	Fluoride-specific electrode & Surveys for other environmental exposures (e.g., toothpaste use)	All fractures OR (p-value): ref; 1.17 (0.33); 1.50 (0.01); 1.25 (0.17); 1.18 (0.35); 1.47 (0.01) Hip fractures OR (p-value): ref; 2.13 (0.15); 0.99 (0.99); 1.12 (0.85); 1.73 (0.34); 3.26 (0.02)	Survey & Original records and x-ray for positive history	For all fractures: age and sex For hip fractures: age and BMI
Lindsay et al. 2023 [62]	Cross-sectional (2010–2020)	USA	106,423 children with fractures of both sexes aged 4–10 years	Lifetime exposure to Water [F] (mg/L): 0.56; 0.39; 0.60; 0.42; 0.65; 0.63; 0.55; 0.55; 0.66; 0.70; 0.67; 0.69; 0.53; 0.70; 0.43; 0.56; 0.44; 0.64; 0.69; 0.51; 0.55; 0.59; 0.60; 0.45; 0.67; 0.59; 0.70; 0.63; 0.60; 0.70; 0.60	Community Fluoridation data obtained from Centers for Disease Control and Prevention (CDC)	Supracondylar humerus fracture (rate per 100,000): 4.79; 4.43; 5.32; 4.47; 12.27; 7.70; 5.93; 17.34; 14.40; 11.38; 18.09; 17.48; 11.43; 23.29; 13.51; 18.03; 5.56; 23.35; 7.61; 6.92; 9.03; 12.73; 9.23; 4.86; 11.52; 4.58; 18.03; 20.65; 21.94; 10.80; 15.52 Forearm fracture (rate per 100,000): 12.86; 7.06; 11.01; 5.28; 18.24; 9.23; 16.92; 26.34; 25.91; 17.14; 29.32; 35.14; 17.47; 38.66; 23.96; 27.10; 9.56; 34.23; 14.65; 15.36; 19.02; 25.57; 17.30; 11.95; 19.25; 7.68; 34.91; 27.30; 21.51; 24.48; 20.82 Femoral Shaft fracture (rate per 100,000): 0.30; 0.00; 0.48; 0.33; 1.25; 0.57; 1.36; 1.86; 1.92; 1.10; 2.50; 2.05; 1.01; 2.30; 2.56; 2.37; 0.62; 3.61; 1.56; 0.97; 1.36; 1.32; 1.10; 0.00; 0.00; 0.00; 3.80; 2.62; 2.32; 1.63; 1.80	Fractures rates between 2010–2020 derived from National Insurance Database (PearlDiver)	NR
Lotborn et al. 1999 [46]	Ecological cohort (1993–1994)	Sweden	396 children aged 15 (184 males)	Lifetime exposure to Water [F] (mg/L): 1.1; <0.1	Personal communication from Chief Dental officer, Department of Preventive Dentistry	Total Body BMD (g/cm ³): - Males 1.12+0.08; 1.11+0.09 - Females: 1.13+0.07; 1.10+0.08	DXA Lunar DPX-L	Age, sex
McClure et al. 1944 [39]	Ecological cohort (1942–1943)	USA	3,987 males aged 15–25 years	Lifetime exposure to Water [F] (ppm): For 15–17 years old: 1.9; 1.7; 1.7–1.9; 1.2; 0.5; 0.1; 0.0; 0.0–0.1; 0.0 For 18–25 years old: 2.0–5.0; 0.3–1.0; 0.3–5.0; 0.5–1.0; 0.0–0.5; 0.2; 0.0; 0.0	Community water sample tested via unspecified methodology	15–17 years (incidence per 100): - Arm, wrist, elbow: 11.1; 14.4; 12.1; 12.9; 11.0; 12.1; 11.8; 12.0; 16.1 - Leg, knee, ankle: 2.9; 2.2; 2.7; 2.8; 4.1; 2.4; 3.4; 2.9; 2.4 - All fractures: 27.0; 31.0; 28.3; 25.3; 24.3; 21.3; 25.0; 23.2; 32.4 18–25 years (incidence per 100): - Arm, wrist, elbow: 15.8; 9.8; 13.3; 12.6; 11.6; 11.4; 10.8; 8.9 - Leg, knee, ankle: 2.1; 3.6; 2.7; 3.3; 4.3; 5.2; 4.7; 5.3 - All fractures: 30.5; 29.5; 30.3; 27.5; 25.8; 28.0; 24.9; 28.0	Personal interviews	NR

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Nasman et al. 2013 [63]	Ecological cohort, Swedish Registry of Population (1964–2006)	Sweden	473,277 adults of both sexes (males 53%), NR age	Lifetime exposure to Water [F] (mg/L): <0.30; 0.30–0.69; 0.70–1.49; ≥1.50	Swedish Water & Wastewater Association (SWWA)	Hip Fractures (HR): - All ages: ref: 0.97 (0.94; 0.99); 0.97 (0.94; 1.00); 0.98 (0.93; 1.04) - Age < 70 years: ref: 0.80 (0.74; 0.86); 0.81 (0.73; 0.89); 0.55 (0.41; 0.73) - Age 70–79 years: ref: 0.91 (0.87; 0.95); 0.93 (0.89; 0.98); 0.89 (0.81; 0.98) - Age ≥ 80 years: ref: 1.02 (0.99; 1.05); 1.01 (0.97; 1.06); 1.07 (1.00; 1.15)	Swedish National In-Patient Register (IPS) & Swedish Cause of Death Register (Cases from 1961 to 2006)	Age, sex, county of residence, calendar group
Phipps et al. 1990 [47]	Cohort (1990)	USA	151 females aged 39–87 years	Lifetime exposure to Water [F] (ppm): 0.7; 4.2	US Public Health Service	Radius BMC (g/cm): 0.78 ± 0.19; 0.75 ± 0.19 Radius Bone Width (cm): 2.39 ± 0.23; 2.37 ± 0.17 Radius Bone Mass (g/cm ²): 0.32 ± 0.07; 0.32 ± 0.07	Single-photon Absorptiometry	NR
Phipps et al. 1998 [48]	Cohort (1994–1995)	USA	741 adults of both sexes (317 males) aged > 60 years	> 20 years of exposure to Water [F] (mg/L): 0.03; 0.70; 2.50 > 20 years of exposure to F; F intake (mg/day): 0.10 ± 0.05; 1.40 ± 0.6; 4.30 ± 2.1	For water: Environmental Protection Agency (EPA) & Community water fluoridation; For overall intake per day: cups per day of city water consumed (regardless of the use, e.g. coffee, drinkable water...) and self-reported toothpaste use	Males BMD (g/cm ²): - Lumbar spine: 1.057; 1.070; 1.143 - Proximal femur: 0.913; 0.924; 0.925 - Forearm: 0.650; 0.635; 0.636 Females BMD (g/cm ²): - Lumbar spine: 0.894; 0.892; 0.938 - Proximal femur: 0.747; 0.747; 0.779 - Forearm: 0.494; 0.488; 0.481	Dual Energy X-Ray Absorptiometry (DEXA)	Age, weight, current estrogen use, history of osteoarthritis, family history of osteoporosis, estrogen deficiency, current smoker, caffeine intake per day, current thyroid hormone use, current thiazide diuretic use, age, weight, current alcohol use, current thiazide diuretic use, history of osteoarthritis, history of an ulcer, current smoker

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Phipps et al. 2000 [71]	Prospective cohort (1986–1988)	USA	7,129 females aged ≥ 65 years	44 years of exposure to Water [F] (-); No/Mixed/Continuous exposure	Questionnaire on residency history + Water System Maps & 1992 CDC Fluoridation Census	BMD (g/cm ³): - Lumbar spine: 0.849 (0.843–0.856); 0.853 (0.844–0.862); 0.871 (0.865–0.877) - Proximal femur (neck): 0.647 (0.643–0.651); 0.652 (0.646–0.657); 0.664 (0.661–0.668) - Distal radius: 0.371 (0.367–0.374); 0.362 (0.357–0.366); 0.364 (0.361–0.367) - Proximal radius: 0.645 (0.642–0.649); 0.637 (0.632–0.642); 0.636 (0.633–0.639) - Calcaneus: 0.408 (0.405–0.412); 0.402 (0.398–0.407); 0.413 (0.410–0.416) Vertebral fracture (RR): ref – 0.73 (0.50; 1.06) – 0.73 (0.55; 0.97) Non-vertebral fracture (RR): ref – 1.03 (0.87; 1.22) – 0.96 (0.83; 1.10) Hip fracture (RR): ref – 0.73 (0.49; 1.09) – 0.69 (0.50; 0.96) Humerus fracture (RR): ref – 1.03 (0.67; 1.57) – 0.85 (0.58; 1.23) Wrist fracture (RR): ref – 1.09 (0.78; 1.52) – 1.32 (1.00; 1.71)	Single-Photon Absorptiometry (Osteo-Analyzer) for distal and proximal radius, calcaneus; Dual Energy X-Ray Absorptiometry (Hologic QDR 1000) for lumbar spine and proximal femur Interview & Original records and x-ray for positive history; X-rays for vertebral fractures	Sex, age, weight, education, knee/grip strength, surgical menopause, calcium intake, drinks/week, current estrogen use, current thiazide use, non- \neq insulindependent diabetes, current thyroid hormone use, walking for exercise, and smoking status
Simonen et al. 1985 [64]	Ecological (1967–1978)	Finland	133,398 adults of both sexes (males 47%) aged ≥ 50 years	7–17 years of exposure to Water [F] (mg/L): 0.00–0.10; 1.00	NR	Femoral fractures (RR): - Males: 2.50 (1.60; 3.90); ref - Females: 1.50 (1.20; 1.80); ref 50–59 years (cases/participants) - Male: 13/2889; 3/3333 - Females: 14/4000; 16/4571 60–69 years (cases/participants) - Males: 14/2089; 8/2353 - Females: 23/3286; 31/3875 70–79 years (cases/participants) - Males: 25/772; 13/1000 - Females: 60/1527; 59/2201 ≥ 80 years (cases/participants) - Males: 8/139; 7/219 - Females: 49/377; 42/583	Hospital Discharge Data of Finland (cases from 1967 to 1978)	Age and sex

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Sowers et al. 1991 [72]	Cohort (1983–1984, 1988–1989)	USA	684 females aged 20–80 years	> 5 years of exposure to Water [F] (mg/L): 1.0; 4.0	Iowa University Hygienic Laboratory Method & FFQ	Radius bone mass (g/cm ²): - 20–35 years: 0.75 ± 0.008; 0.74 ± 0.006; 0.73 ± 0.008; 0.71 ± 0.006 - 55–80 years: 0.63 ± 0.008; 0.60 ± 0.007; 0.59 ± 0.008; 0.56 ± 0.007 Femoral (neck) bone mass (g/cm ²): 0.69 ± 0.011; 0.68 ± 0.009 Hand, arm, wrist, spine, pelvis, leg, hip and other fractures (RR): 20–35 years: - Any fractures: ref; 1.81 (0.45; 8.22) - Hip, wrist or spine: ref; 2.70 (0.16; 8.28) 55–80 years: - Any fractures: ref; 2.11 (1.01; 4.43) - Hip, wrist or spine: ref; 2.20 (1.07; 4.69) - Fractures at multiple sites: ref; 2.20 (1.04; 4.57)	Norland 278 Photon Absorptiometer & Norland 2600 Dual-Photon Densitometer	Age, sex and Quieteliet index
Sowers et al. 2005 [73]	Cross-sectional (2005)	USA	1,300 females aged 20–92 years	NR, years of exposure to F; Serum [F] (μmol/L): 1.60 ± 0.04; 2.11 ± 0.05	Ion-specific electrode (Orion Research 9409) and hexamethyldisiloxane-facilitated diffusion of Taves	BMD (g/cm ³) - Lumbar spine: 1.179; 1.195 - Femoral neck: 0.914; 0.912 - Distal radius: 0.651; 0.667	Dual Energy X-Ray Absorptiometry (DEXA; Lunar)	Sex, age, BMI, osteocalcin concentration, thiazide antihypertensive use, oral contraceptive use, hormone therapy use, menopausal status
Suarez-Almazor et al. 1993 [65]	Ecological (1981–1987)	Canada	NR adults of both sexes aged ≥ 45	NR, years of exposure to Water [F] (mg/L): 0.30; 1.00.	Iowa University Hygienic Laboratory & FFQ	Fracture frequency (fractures %): - Arm, Wrist, Hip, Femoral neck, Neck, Spine, Back, Ribs, Sternum: 1.4; 15.0 - Ankle, Clavicle, Foot, Hand, Leg, Pelvis, Scapula & Other: 3.2; 3.1	Self-report, subsequently validated by extracting medical records and copies of imagines Alberta Health Hospital Morbidity File	Age, sex, BMD, site
					NR (Federal Census)	Hip fractures (Rate Ratio with approximate CI 95%): All: 45–64 years: ref; 0.94 (0.82; 1.08) ≥ 65 years: ref; 1.00 (0.94; 1.06) Males: 45–64 years: ref; 1.07 (0.87; 1.32) ≥ 65 years: ref; 1.13 (1.00; 1.27) Females: 45–64 years: ref; 0.85 (0.70; 1.03) ≥ 65 years: ref; 0.96 (0.90; 1.03)		Age and sex

Table 1 (continued)

Reference	Study design, cohort name, year(s)	Country	Participants' characteristics	Fluoride exposure characteristics	Fluoride assessment method	Outcome	Outcome assessment method	Adjustments or stratification
Young et al. 2015 [66]	Cross-sectional (2007–2013)	UK	3,1619 adults of both sexes aged ≥ 65 years	NR years of exposure to Water [F ⁻]; Fluoridated; Nonfluoridated	Census data (LSOAs & Water Quality Zones) + GIS data	Hip fractures (Incidence Rate Ratio); ref: 0.7 (–1.0; 2.4)	Hospital Episode Statistics (Emergency Admission; 1st or 2nd diagnosis)	Age, sex, Index-Multiple-Deprivation, ethnicity

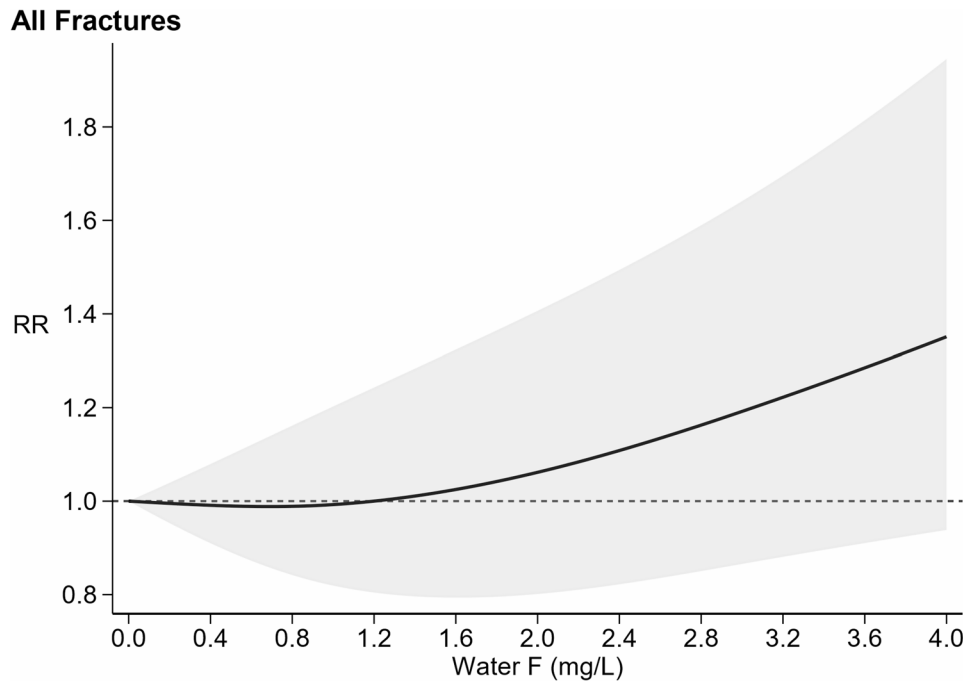


Fig. 2 Dose-response meta-analysis of fracture risk (all fractures) and exposure to fluoride (F) from water [39, 61, 68, 72] ($\hat{R}_I=15\%$). Fracture risk curve (black solid line) with 95% confidence interval (grey area). RR: risk ratio with reference at 1.0 (dash line)

at 1.48 mg/L, and 1.05 (95% CI 0.82–1.35) at 1.8 mg/L. In the sex-specific analysis, there was a clear evidence of a U-shaped curve only in females, with the lowest risk around 0.4 mg/L and a monotonic increase above 0.9 mg/L. Specifically, the RR was 0.84 (95% CI 0.67–1.07) at 0.34 mg/L, 1.00 (95% CI 0.79–1.27) at 0.9 mg/L, and rose to 1.13 (95% CI 0.93–1.37) at 1.1 mg/L. In contrast, the curve for males (seven studies) was generally indicative of a decreased risk with increasing fluoride exposure with Little indication of a U-shaped pattern, and RR ranging from 0.83 (95% CI 0.72–0.97) at 0.57 mg/L to 0.87 (95% CI 0.48–1.58) at 1.8 mg/L.

The study-specific curves for fragility fractures are depicted in (Supplementary Figure S2). In females, the individual curves tend to follow a similar pattern: a downward slope in RR at low fluoride levels (0.1–0.5 mg/L) followed by an upward turn as fluoride concentration increased, exceeding 1 beyond 1.0 mg/L. Above this level, most of the studies show an increase in risk, but two showed a flat dose-response curve, and only one displayed a consistent decline in risk. The same trend emerged in females, with most studies showing a U-shaped trend with minimum risk between 0.2 and 0.6 mg/L. On the other hand, Studies restricted to males showed very inconsistent patterns, i.e. an increase in risk above 0.6 mg/L, a flat dose-response curve, and a consistent decline in risk.

Dose-response meta-analysis on site-specific risk of fractures

Figure 4 shows the dose-responses curves for fractures typically associated with fragility, namely at the hip, femur, and wrist. For hip fractures, the curve indicated Little association and was nearly flat, with a comparatively narrow 95% confidence band. For femoral fractures, the curve was mildly U-shaped, with the RR showing decreasing risk of fracture as fluoride levels increased from zero to about 0.5 mg/L, with a RR of 0.86 (95% CI 0.71–1.05) at this point. Above 0.5 mg/L, however, the risk rose slightly with increasing fluoride exposure, reaching an RR of 1.06 (95% CI 0.67–1.69) at 1.8 mg/L. Throughout most of the range of fluoride exposure, the risk for femoral fracture was lower than the risk for those with no exposure to fluoride. For wrist fractures, risk declined monotonically and nearly linearly as fluoride exposure changed from zero to the highest levels. Specifically, the RR began at 1.00 (95% CI 0.99–1.01) at 0.01 mg/L and gradually declined to 0.84 (95% CI 0.43–1.65) at 1.5 mg/L. The study-specific curves for each exposure stratum are shown in (Supplementary Figure S3), indicating a high degree of variability between studies assessing risk of hip and femoral fractures across all levels of fluoride. Wrist fracture risk patterns showed a RR around 1.0 up to levels of water fluoride of 0.6 mg/L, where half of the studies started to exhibit an increase in risk, and the other half a decreased risk.

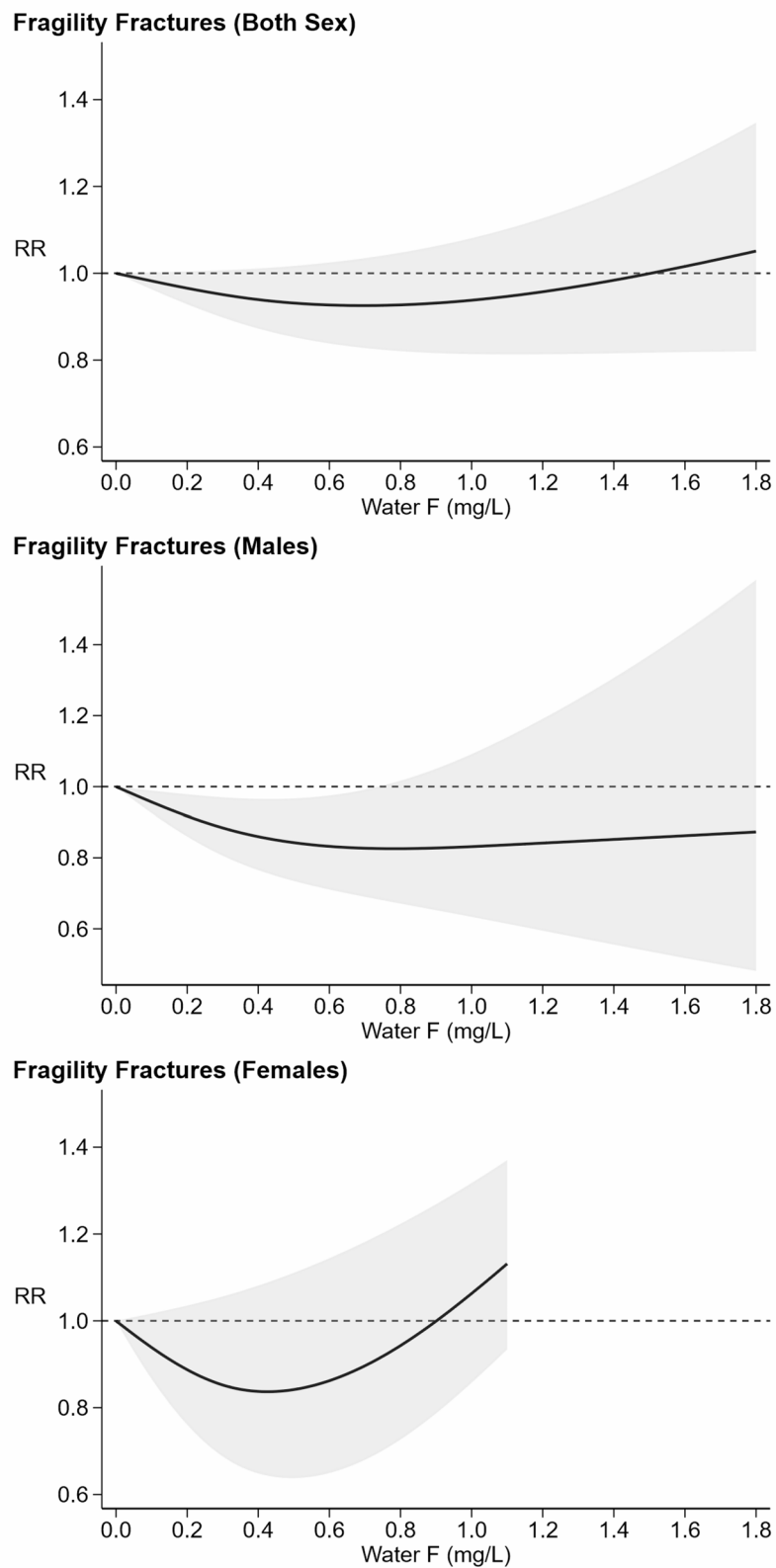


Fig. 3 Dose-response meta-analysis of fragility fracture (those that occur in districts such as hip, wrist, femur, and spine) risk and exposure to fluoride (F) from water, stratified by sex. Six studies [49, 50, 55, 61, 63, 65] analyzed the risk of fractures typically classified as fragility fractures in both sexes ($\hat{R}_I=35\%$). Eight studies [50–52, 58, 59, 64, 65, 69] considered fragility fractures in males ($\hat{R}_I=91\%$). Additionally, six studies [50, 54, 58, 68, 69, 73] evaluated this risk in females ($\hat{R}_I=17\%$). Fracture risk curve (black solid line) with 95% confidence interval (grey area). RR: risk ratio with reference at 1.0 (dash line)

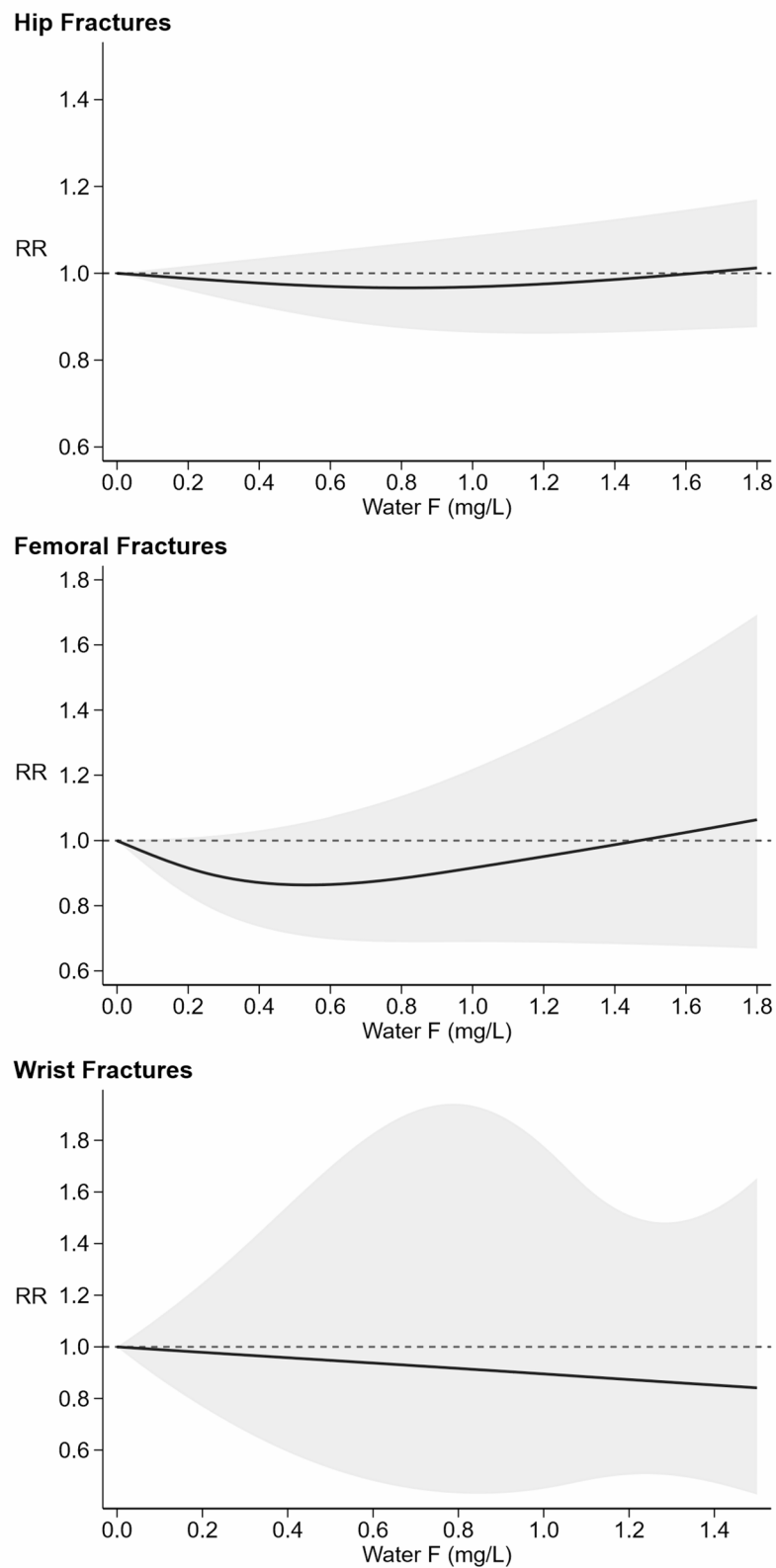


Fig. 4 Dose-response meta-analysis of fragility fracture risk and exposure to fluoride (F) from water, stratified by fracture site. Seven studies [49, 55, 58, 59, 61, 63, 65] assessed the risk of hip fractures ($\widehat{R}_I=9\%$). Six studies [50–52, 54, 64, 69] examined the risk for femoral fractures ($\widehat{R}_I=76\%$). Four studies [52, 58, 68, 72] focused specifically on wrist fractures ($\widehat{R}_I=90\%$). Fracture risk curve (black solid line) with 95% confidence interval (grey area). RR: risk ratio with reference at 1.0 (dash line)

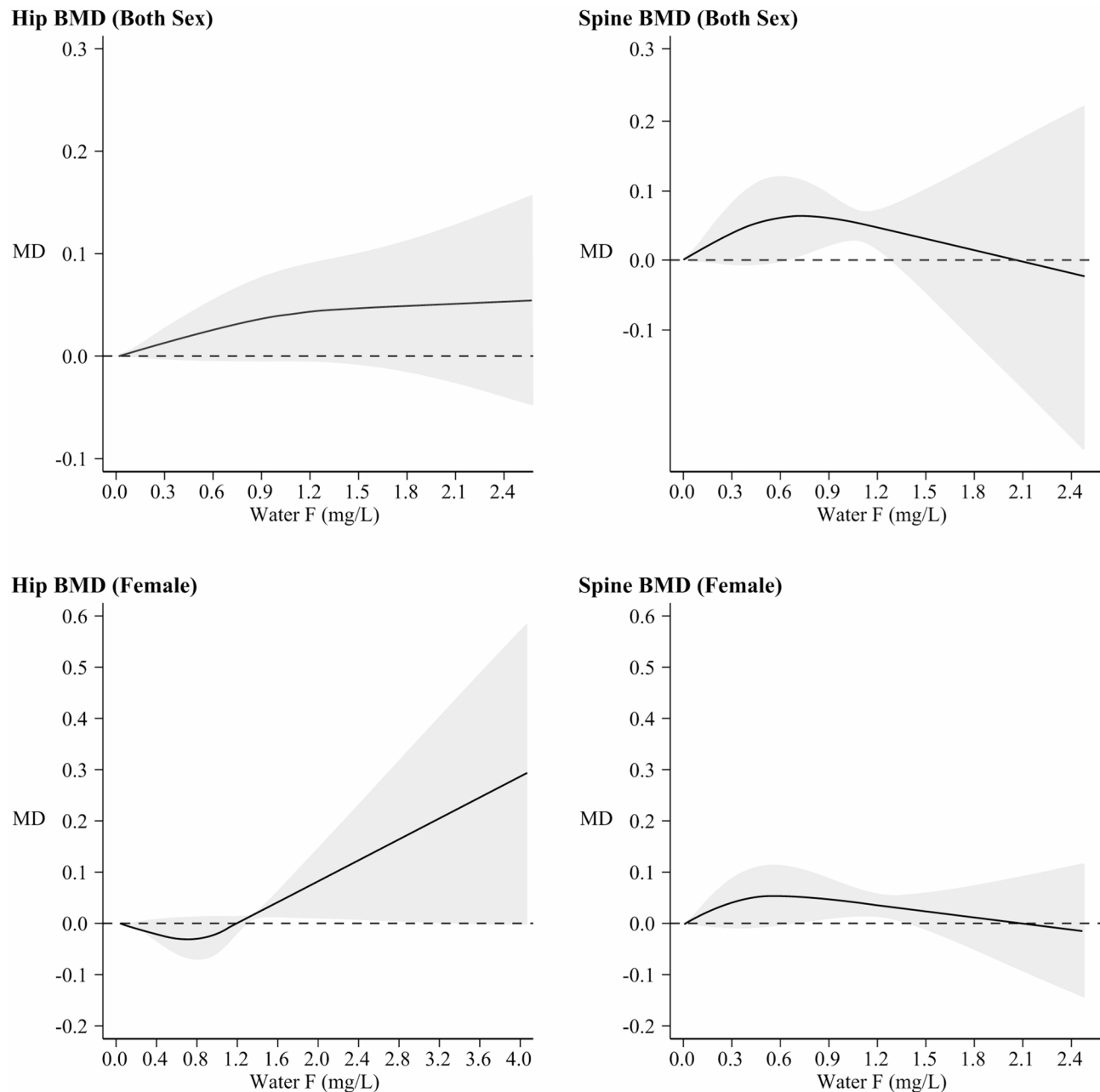


Fig. 5 Dose-response meta-analysis of bone mineral density (BMD) and exposure to fluoride (F) from water, stratified by site and sex (both sex and female). Seven studies [40, 41, 43, 48, 68, 69, 72] assessed hip BMD ($\widehat{R}_I=58\%$), and six studies [41, 43, 45, 48, 68, 69] for spine BMD ($\widehat{R}_I=96\%$), in both males and females. Additionally, six studies [40, 41, 48, 68, 69, 72] focused on hip BMD ($\widehat{R}_I=95\%$), and five studies [41, 45, 48, 68, 69] on spine BMD ($\widehat{R}_I=64\%$), in females only. Mean Difference BMD curve (black solid line) with 95% confidence interval (grey area). MD: mean difference with baseline at 0.0 (dashed line)

Dose-response meta-analysis on BMD

The relation between fluoride exposure from water and BMD, including data stratified by sex (both sexes and females) and site (hip or spine), is shown in Fig. 5. While hip BMD increase in both sexes, though linearly in males and non-linearly (starting above 1.2 mg/L) in females, for spine BMD there was an indication of an inverted U-shaped association both in males and in females, the

highest value being around 0.6 mg/L. In (Supplementary Figure S4), curves for hip and spine BMD MD are reported though females only due to insufficient data in males; these show a monotonic upward trend with increasing fluoride for hip BMD, starting above 1.2 mg/L of fluoride, whereas no change emerged for spine BMD, with a high heterogeneity as far as study specific curves in both sexes were concerned (Supplementary Figure S5).

Sensitivity analyses on risk of fractures and fragility fractures

Regarding fracture risk in females over 50 years of age (Supplementary Figure S6), the curve exhibited a steep upward trend, with the lowest risk around 0.25 mg/L and a sharp increase in fracture risk starting at around 0.5 mg/L. Specifically, the RR was 0.98 (95% CI 0.83–1.14) at 0.25 mg/L, 1.00 (95% CI 0.80–1.24) at 0.45 mg/L, and 1.26 (95% CI 1.10–1.46) at 1.0 mg/L. For this analysis, (Supplementary Figure S7) provides the funnel plot and Egger's test (slope: 1.72, 95% CI 0.19–3.62) indicating a largely symmetrical distribution and Little evidence of publication bias. Concerning BMD, a dose-response analysis in females over 50 was only possible for spine BMD, with an indication of an inverted U-shaped curve with a downward trend starting at a lower F concentrations than in the overall analysis (Supplementary Figure S8). There was some asymmetry in the published data, but not strong evidence of publication bias (Supplementary Figure S9).

Several studies [16, 48, 53, 55, 67, 68, 71, 73] adjusted the results depending on menopause onset and/or hormone replacement therapy use, another important factor in bone health status in females [77]. We had insufficient data, however, to report on this group of studies by themselves.

Concerning the effect of study quality on the pattern of associations, a subgroup analysis excluding the studies at higher risk of bias could be conducted only for a few endpoints, and not for the main analysis concerning risk of all fractures. Regarding overall RR of fragility fractures (Supplementary Figure S10), the RR decreased to 0.93 (95% CI 0.72–1.21) at fluoride exposure in the 0.8–1.5 mg/L range; it was 0.95 (95% CI 0.70–1.29) at 1.8 mg/L, with inconsistencies across the few studies available. In the analysis of hip fracture risk across all sexes after exclusion of studies at high risk of bias (Supplementary Figure S11), there was little change in the RR across the entire range of exposure, again with notable variation between studies: some studies clearly indicated a decrease in risk, while others showed a consistent increase as fluoride levels rise.

Sensitivity analyses on BMD

BMD outcomes for females, specifically for the hip and spine, restricted to studies with low-to-moderate risk of bias, are shown in (Supplementary Figure S12). Regarding hip BMD, the MD curve remained stable up to around 0.9 mg/L, after which a monotonic and almost Linear upward trend emerged. Specifically, MD increased to 0.04 g/cm² (95% CI –0.03–0.12) up to around 2.3 mg/L, reaching 0.09 g/cm² (95% CI –0.09; 0.27) at 4.0 mg/L. Study-specific curves consistently mirrored this pattern. For spine BMD, an initial rise leveled off at around

0.5 mg/L, with MD values of 0.02 g/cm² (95% CI –0.02; 0.07) at 0.20 mg/L and 0.06 g/cm² (95% CI –0.01; 0.12) from 0.7 to 2.35 mg/L, peaking at 0.07 g/cm² (95% CI 0.11; 0.24) above. Study-specific curves displayed variable shape, in one study peaking between 0.4 and 0.8 mg/L before declining at higher exposure, while others follow the general pattern of the pooled analysis.

(Supplementary Figure S13) illustrates BMD for both sexes, after excluding studies at high risk of bias. For hip BMD no relation with fluoride exposure emerged, with curves of the single studies generally aligning with this pattern. For spine BMD, there was little evidence of a relation with water fluoride concentrations: the curve initially rose to a MD of 0.06 g/cm² (95% CI –0.02; 0.13) around fluoride levels of 0.60 mg/L. However, as fluoride levels increased beyond 1.27 mg/L, the Line flattened at a 0.05 g/cm² (95% CI 0.01; 0.10) until 2.27 mg/L, followed by a slight decrease to 0.04 g/cm² (95% CI –0.21; 0.30) after this point. Results of individual studies were very inconsistent, showing discordant trends at increasing fluoride exposure.

Discussion

By pooling results from previously published studies across all the exposure levels investigated, we could model and characterize the dose-response pattern of fluoride exposure with bone thickness and fracture risk. We found evidence for a positive dose-response relation with fracture risk for doses exceeding a threshold that is close to the current WHO guideline value of 1.5 mg/L of drinking water fluoride. Previous reviews and meta-analyses did not consider the dose-response curve across the full range of fluoride exposure [78–82], concluding that while low and moderate fluoride exposures seem to have limited effects on fracture risk and can increase bone mass in some cases. The larger number of studies available for this review and the pooling of exposure-specific effect estimates allowed us to assess the relation between fluoride and bone quality quantitatively across the range of exposure characterizing the general population.

Our data indicated little relation between fluoride exposure and overall fracture risk below 1.5 mg/L of drinking water fluoride, with fracture risk starting to increase gradually above that threshold. The threshold level corresponds to around 3–3.5 mg/day of exposure from this source (assuming a water consumption of 2 L/day and little contribution of fluoride from other sources) [83, 84]. In several of our pooled analyses, some types of fractures showed a U-shaped pattern, with risk of fracture decreasing with increasing fluoride exposure from zero to moderate levels of exposure, but increasing as exposure increased from moderate to high levels of fluoride exposure. Such a pattern might be an artifact due to the more limited number of studies on which such

analyses were based, and a related higher uncertainty and statistical instability, especially in view of the small changes in RR involved. Nonetheless, the hypothesis that exposure to drinking water fluoride around 0.5–0.6 mg/L might have beneficial effects on fracture risk (compared with no exposure), at least on some specific fracture subsets, is consistent with our findings. We also note the inconsistencies between the findings for site-specific fractures (hip, wrist and femur), with different patterns of association, that mirror the inconsistencies found in the BMD analyses for hip and spine. Such inconsistencies may be due to the limited number of studies for these endpoints, or to real differences of the fluoride effects on specific bone districts. Bone composition might also play a role, as wrist is primarily composed of cortical bone while spine is predominantly trabecular bone, which is more metabolically active and responsive to agents that stimulate bone formation [85]. Interestingly, similar dose-response patterns and approximate thresholds have been observed in pooled analyses of fluoride exposure and two key health endpoints, IQ and thyroid function in children [10, 14].

Among females over 50 years, who are at notably higher fracture risk than younger subjects [86, 87], there was a stronger correlation between fluoride exposure and fragility fracture risk, starting at fluoride concentrations around 0.5 mg/L. Furthermore, the decline in spine BMD was slightly stronger in females aged 50 years or over, and the decline began at lower fluoride drinking water levels, compared with all females. Although these findings are based on a limited number of studies, the protective role of estrogen in bone health is well established [88, 89], and it is also widely recognized that postmenopausal females are particularly vulnerable to osteoporosis and fragility fractures [90]. Menopause accelerates bone loss by increasing bone resorption at a rate that surpasses bone formation, both directly [91], and indirectly [92]. The steep upward trend in fragility fracture risk in females > 50 years of age may reflect long-term continuous exposure to fluoride in drinking water or increased release of fluoride from bone stores. This possibility underscores the importance of cumulative exposure in a “potentially exposed or susceptible subpopulations,” according to EPA Toxic Substances Control Act [93]. Although our analysis stratified by age (i.e. females over 50) rather than confirmed menopause status, age likely serves as a reasonable proxy for menopausal status in this analysis. The possibility of a negative effect of fluoride exposure, assessed through water and plasma fluoride concentrations, on sex steroid hormones including estradiol is supported by the limited epidemiologic and toxicological evidence available, and post-menopausal fluoride release from bone post menopause could contribute to such adverse effects [10, 94–96].

Helte et al. reported an adverse effect of fluoride exposure on all fractures and hip fractures in a cohort study of postmenopausal Swedish females, which we could not include in our analysis because it was based on a urinary biomarker and on overall dietary exposure [16]. In that study, an excess risk for all fractures was apparent among those with urinary fluoride levels in the highest tertile even in an area with relatively low water fluoride concentration (≤ 1 mg/L) [16].

We could conduct this quantitative dose-response pooled analysis only for fluoride exposure in drinking water, and not from other sources, due to the limited number of studies investigating exposure biomarkers or directly assessing dietary intake. Unfortunately, most studies investigating risks associated with water fluoride content did not consider total fluoride exposure and particularly that from two major sources of dietary intake, tea and fluoridated salt, increasing the uncertainty inherent in the overall exposure assessment. Nonetheless, drinking water is generally the major source of fluoride intake even when its fluoride content is low (i.e. ≤ 1 mg/L) [2, 16, 97–99], therefore justifying an exposure assessment based on this indicator [10, 12–14]. Furthermore, there is evidence that exposure assessment based on biomarkers, although capturing additional sources of fluoride beyond drinking water, is limited by the short half-life of fluoride (around 6-hours), thus detracting from the utility of biomarkers compared with a long-term stable indicator of exposure such as drinking water fluoride content [100, 101]. Finally, the observational design of the studies relied upon here might be conducive to residual confounding, though the studies that were included generally attempted to control most relevant confounders.

The additional bone health indicator we assessed, BMD, refers to bone quality and is generally considered a key indicator of bone strength and a standard for clinical assessment, being used as the measure to predict fracture risk and assess responses to interventions [102]. The results for the association between fluoride and BMD were not consistent, and they also did not correspond to the pattern observed for fractures, raising the question about the usefulness of this endpoint. BMD only measures bone density, without providing information on bone morphology, architecture, tissue properties, or susceptibility to fracture [103–106]. Therefore, BMD does not provide a full picture of bone health and does not necessarily predict fracture risk, which is a direct outcome reflecting overall bone strength and health [107]. The hypothesis that a fluoride-induced increase in BMD could coexist with an increased fracture risk due to an inherently lower bone ‘quality’ should not be dismissed [108]. Heterogeneity across imaging methods and populations could also contribute to this discrepancy,

but again BMD only captures bone quantity (density), not bone quality (e.g., architecture, morphology, micro-damage, material properties). The latter aspects of bone health are crucial determinants of fracture risk. The association between fluoride exposure and hip BMD were similar in our dose-response meta-analysis and the above mentioned Swedish study [16], whereas spine BMD was not investigated in the latter.

Conclusions

Overall, our findings about the effects of fluoride exposure on fracture risk, assessed through drinking water concentrations, indicate a non-linear, positive dose-dependent relation, with an indication of a U-shaped association with fragility fractures. The association with BMD was less consistent. We also found evidence for an enhanced susceptibility of postmenopausal females to the adverse effects of fluoride on fracture risk. The observed effects that begin near regulatory thresholds and extend into high levels of fluoride exposure may be important to consider in shaping any public health policy that attempts to balance risks against benefits of fluoride exposure.

Abbreviations

BMC	Bone mineral content
BMD	Bone mineral density
CI	Confidence interval
HR	Hazard ratio
IQR	Interquartile range
MD	Mean difference
OR	Odds ratio
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
ROBINS-E	Risk of bias for non-randomized studies of exposures
RR	Relative risk
SD	Standard deviation
SE	Standard error

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12940-025-01226-y>.

Supplementary Material 1.

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Authors' contributions

RM, TF, and MV drafted the manuscript. TF, FV, LSB, KJR, and MV contributed to the study design and methodology. RM, IL, and LDP conducted the primary literature search, data extraction, and synthesis of results. TF, LSB, and MV assisted in the literature search and data extraction. TF and MV resolved conflicts regarding study inclusion and data extraction. RM and TF conducted the statistical analysis. All authors contributed to critical revision of the manuscript for important intellectual content and gave final approval for the decision to submit for publication.

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Data availability

Data in this systematic review and meta-analysis are extracted from published studies available elsewhere. All processed data are presented in this article and the supplementary material.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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