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ORIGINAL ARTICLE

Association between loop diuretic use and fracture risk

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Abstract
Summary Loop diuretic use has been shown to be associated with an increased fracture risk, but the findings have been inconsistent. The present meta-analysis suggests that loop diuretics show a significant positive association with the overall risk of total fractures and, specifically, hip fractures.
Introduction Despite being widely used, there is limited, prospective randomized trial evidence regarding the skeletal effects of loop diuretics. Previous observational studies have reported conflicting findings regarding the association between loop diuretic use and the risk of fractures.
Methods This meta-analysis of observational studies assessed the association between loop diuretic use and the risk of fractures. The PubMed, EMBASE, and OVID databases were searched for prospective cohort and case–control studies. Relative risks (RR) with 95 % confidence intervals (CI) were derived using random-effects models throughout the analysis.
Results Thirteen studies (4 cohort studies and 9 case–control studies) were included, involving 842,644 participants and 108,247 fracture cases. Compared with non-users, people who had taken loop diuretics had an approximately 15 % higher risk of total fractures (95 % CI, 1.04–1.26; $p<0.01$), with high heterogeneity between studies ($I^2=80.5$ %; $p<0.01$). The RR was 1.14 (95 % CI, 1.08–1.19) for hip fractures and 0.99 (95 % CI, 0.93–1.05) for lower arm or wrist fractures. The RR was 1.05 (95 % CI, 1.00–1.11) in prospective cohort studies and 1.22 (95 % CI, 1.00–1.44) in case–control studies. There was no evidence of publication bias.
Conclusion The results suggest that loop diuretics show a significant positive association with the overall risk of total fractures and hip fractures.

Keywords Case–control study · Fracture · Loop diuretic · Meta-analysis · Prospective cohort study

Abbreviations
RR Relative risk
CI Confidence interval
HF Heart failure

Introduction

Fractures are major causes of morbidity, including pain and loss of function, and also cause considerable mortality. The medical costs associated with fractures also cause a tremendous financial burden on the family, and the overall society [1–3]. Therefore, identifying and confirming the risk factors for preventing fractures has significance for public health and

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clinical medicine [4–6]. Known factors associated with the incidence of fractures include physical activity [7], age [8], smoking [9], alcohol consumption [8], and body mass index (BMI) [10]. However, the relationship between drug use and the risk of fractures requires more attention [11].

Loop diuretics are typically prescribed to manage hypertension, especially when associated with renal insufficiency (glomerular filtration rate, <30 mL/min) or resistant hypertension [12, 13]. In the USA, loop diuretics are the third and sixth most commonly prescribed medications among community-dwelling men and women, ≥65-years-old, respectively; 12 % of men and 9 % of women in this demographic are estimated to use these medications [14]. Moreover, loop diuretic use is associated with significantly increased urinary calcium excretion [15, 16]. Previous studies have shown that loop diuretics affect bone turnover and increase the rate of bone loss and the risk of falls [12, 17, 18]. However, whether treatment with loop diuretics increases the fracture risk is controversial. Several epidemiological studies have reported that loop diuretics appear to increase the risk of fractures [19, 20], but the findings have been inconsistent [21, 22]. Therefore, the objectives of the present meta-analysis were to quantitatively assess the available observational studies that have examined the association between loop diuretics and fracture risks and to evaluate the association between their use and fracture subtypes.

Methods

We conducted this study according to the Meta-analysis Of Observational Studies in Epidemiology group guidelines and used the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement to guide our methods [23–25].

Search strategy

We conducted a systematic search of the MEDLINE, EMBASE, and OVID databases, from their dates of inception to March 1, 2014, and identified all potentially relevant articles. Although the search was limited to humans, language restrictions were not employed. The searches were performed using either Medical Subject Headings or free-text words. We combined search terms for the outcome (fracture) and the influencing factor (loop diuretics, diuretics, furosemide, bumetanide, ethacrynic, torasemide, piretanide, azosemide, indacrinone, etozolin, ozolinone, cicletanine, tienilic, and tizolemide). We also searched the reference lists of the full-text papers and reviewed studies from all of the relevant publications to identify any omitted studies. Moreover, we searched the conference abstracts in the ISI Proceedings database, the American Society for Bone and Mineral Research, and the proceedings of the International Osteoporosis Foundation World Conference on Osteoporosis from 2000 to 2014. However, none of the meeting abstracts were included in this meta-analysis.

Selection criteria

Two reviewers independently assessed the content of the studies to identify potentially eligible articles. Any discrepancies between the two reviewers regarding study inclusion and data interpretation were resolved by arbitration with a third reviewer; consensus was reached after discussion. Studies were eligible for inclusion in this meta-analysis if they (1) were observational studies (case–control or cohort), (2) involved an adult population, (3) investigated the association between loop diuretic use and the risk of fractures, and (4) provided risk estimates, such as relative risks (RRs), odds ratios, hazard ratios, or other measures that could be transformed into RRs, with 95 % confidence intervals (CIs). If different papers came from the same cohort, the paper with the most comprehensive design, based on a quality assessment, was included in the analysis.

Data extraction and quality assessment

Two reviewers independently extracted data for analysis using a standardized data collection form. Discrepancies were resolved by consensus, involving another two reviewers, after consulting the original article(s). The following data were collected from each study: the first author's last name, publication year, country where the study was performed, study design, duration of follow-up, recruitment time, sample size, participant sex and age, methods of fracture determination, adjustment variables, types of fracture (e.g., hip, wrist, or all fractures), and the risk estimates with their corresponding CIs. The study quality was assessed by two reviewers, based on a previously published 10-point scale corresponding to the five methodological characteristics of either cohort or case–control studies [26]. A third reviewer was enlisted to resolve discrepancies regarding the abstracted data.

Data synthesis and statistical analysis

RRs were used as the common measure of association between the loop diuretic use and fracture risk [27]; odds ratios were transformed into RRs [27, 28]. We only extracted the RRs and 95 % CIs that reflected the greatest degree of control for potential confounders for loop diuretic use in our main analyses.

For the meta-analysis, we used a random-effects model to calculate pooled RRs and 95 % CIs, as this model best accounts for heterogeneity between studies [29]. Heterogeneity between studies was assessed using I^2 statistics; values of 25, 50, and 75 % were defined as low, moderate, and high, respectively [30]. We used subgroup analyses to identify associations between the risk of fractures and the study characteristics (design of study, sex, number of participants, and adjustment for other drugs, prior fracture, and falls) that may have served as possible sources of heterogeneity.

Publication bias was detected by inspecting funnel plot asymmetry, and the Egger's and Begg's regression tests were applied to measure funnel plot asymmetry [31, 32]. We also performed a "trim and fill" procedure to further assess the possible effect of publication bias on our meta-analysis [33]. This method considers that hypothetical, "missing" studies exist, imputes their RRs, and recalculates a pooled RR that incorporates the hypothetical missing studies as though they had actually been performed. All of the analyses were conducted using Stata 12 (StataCorp, College Station, TX, USA); p values <0.05 were considered to be statistically significant.

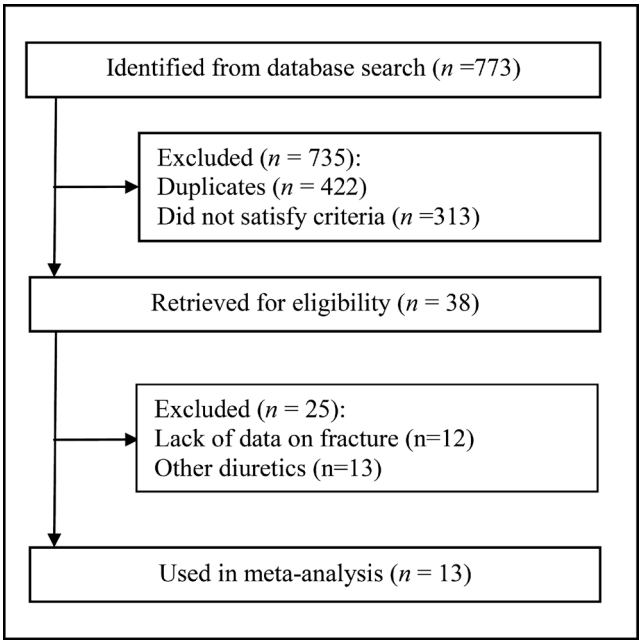

Fig. 1 Flowchart describing study selection

Results

The strategy used to identify the relevant studies is presented in Fig. 1. There were 773 potentially relevant citations that were obtained from the database search. After an evaluation of the titles and abstracts, we excluded 735 citations that were duplicated or that included patients, interventions, or outcomes that did not satisfy the inclusion criteria. As a result, 38 articles were included in the detailed evaluation. Of these, 25 studies were excluded because of insufficient data or the absence of data on loop diuretics, as opposed to the use of other diuretics. After the evaluation, we included four cohort studies [34–37] and nine case–control studies [19–22, 38–42] in the meta-analysis. The observers demonstrated good agreement on the selection of studies appropriate for inclusion (Cohen's unweighted κ=0.92).

Included study characteristics

The included studies were published between 1986 and 2013 (Table 1), describing 842,644 participants from 13 studies, and involving 108,247 fractures. The studies were from different countries (five from the USA [35–38, 42], seven from Europe [19–21, 39–41], and one from Australia [22]). Nine studies recruited mixed-sex groups [19–21, 34, 37–39, 41, 42], and the other four recruited only women [34–36, 40]. The follow-up durations for the cohort studies ranged from 1 to 9.6 years. Fractures were ascertained using self-reporting, radiographic reports, medical records, questionnaires, or administrative data. The most frequent confounders, primarily age, sex, and body mass index, were adjusted in the studies.

Loop diuretic use and fracture risk

The multivariate-adjusted RRs for each study are presented in Fig. 2. Compared with participants who had not used loop diuretics, those who had taken loop diuretics had an approximately 15 % higher risk of total fractures (95 % CI, 1.04–1.26; p<0.01), with high heterogeneity across studies (p<0.01; I^2=80.5 %). The analysis of fracture subtypes showed an increased risk of hip fractures (RR, 1.14; 95 % CI, 1.08–1.19; p<0.01). However, the association between loop diuretic use and the risk of lower arm or wrist fractures was not statistically significant (RR, 0.99; 95 % CI, 0.93–1.05; p<0.01) (Table 2).

Subgroup and sensitivity analyses

In the subgroup analyses, we examined study design, participant numbers, participant sex, adjustments for other drugs, prior fracture, and falls as possible sources of heterogeneity (Table 2). The analyses indicated that the study design did not influence the associations between loop diuretic use and fracture risk. The RR was 1.05 (95 % CI, 1.00–1.11; p<0.01) for prospective cohort studies and 1.22 (95 % CI, 1.00–1.44; p<0.01) for case–control studies; no significant interactions were observed between subgroups (p=0.57), and no heterogeneity was found (p=0.49; I^2=0 %) for the analysis of case–

Table 1 Characteristics of the studies included in the meta-analysis of published studies on loop diuretics use and fracture risk

Study (year)	Country	Design	Age	Sex	Recruitment time (follow-up time)	No. of participants (fractures)	Fracture ascertainment	Fracture sight	Adjustments	Quality score
Rashiq, 1986	UK	Case–control	≥60	Both	1984–1984	306 (102)	Operating theater records	Femoral neck	NA	4
Heidrich, 1991	USA	Case–control	≥50	Both	1977–1983	924 (462)	Medical and pharmacy records	Hip	Age, sex, alcohol, OBS, leg paralysis, stroke, hospitalization, nursing home residence, BMI, use of phenobarbital, corticosteroids, thiazides.	7
Jensen, 1991	Denmark	Case–control	≥59	Both	1988–1988	400 (200)	Medical records	Femoral neck	NA	5
Cummings, 1993	Australia	Case–control	≥65	Both	1990–1991	416 (209)	Medical records, office books	Hip	Age, sex, and type of residence	7
Tromp, 2000	Netherlands	Cohort	≥70	Female	NA (5 y)	348 (33)	Questionnaire	All fractures	Age, sex, weight, BMD, age and history of postmenopausal fracture	4
Partanen, 2002	Finland	Case–control	63–84	Female	1998	114 (74)	Medical records	Hip	Age	5
Rejnmark, 2006	Denmark	Case–control	≥40	Both	2000–2000	258,810 (64,699)	Medical records	All fractures	Age, sex, prior fracture, Charlson index, use of corticosteroids, antiepileptic drugs, oral anticoagulants, potassium sparing diuretics, thiazide diuretics, other types of diuretics, antihypertensive (except diuretics), anxiolytics, neuroleptics, antidepressants, hospitalization, number of contacts to GP/specialist in 1999, employment status, income, living alone or not	8
Lim, 2009	USA	Cohort	≥65	Female	1992–2004 (9.6 for hip, 8.0 for non-spine)	7292 (2521)	Radiograph reports	Non-spine	Age, weight, functional status, calcium intake, physical activity, health status, CHF, COPD, type 2 diabetes, smoking, falls	8
Carbone, 2009	USA	Cohort	59–79	Female	1993–1998	13,3855 (3411)	Radiologic reports, medical records, or self-report	All fractures	Age, race, BMI, smoking, alcohol, calcium and vitamin D intake, prevalent fractures, falls, comorbidity, history of CHD, prevalent CHF, time-dependent incident CHF, physical function construct, use of β-blockers, thiazides, bisphosphonates, use of hormone therapy or estrogen, ACE inhibitors, statins, corticosteroids, anticonvulsants, SERMs, calcitonin, heparin or warfarin sodium, age of menopause, physical activity levels,	8

Table 1 (continued)

Study (year)	Country	Design	Age	Sex	Recruitment time (follow-up time)	No. of participants (fractures)	Fracture ascertainment	Fracture sight	Adjustments	Quality score
									parental history of hip fractures, study site region, and self-reported health	
Bilik, 2010	USA	Case–control	≥18	Both	2000–2001	3443 (786)	Administrative data	All fractures	NA	8
Solomon, 2011	USA	Cohort	≥65	Both	NA (1 year)	370,061 (2543, hip fractures; 1492, wrist fractures; 1026, humerus fractures; 1996, pelvis fractures)	Medical records	Hip, distal forearm, humerus, pelvis	Age, sex, race, prior fracture, BMI, osteoporosis, use of steroids, anticonvulsants, benzodiazepines, antidepressants, proton pump inhibitors, Parkinson's, Alzheimer's disease, falls, number of physician visits, hospitalization, number of medications, comorbidity scoring	5
Arampatzis, 2013	Netherlands	Case–control	≥50	Both	2009–2010	10,249 (480)	Administrative records	All fractures	Age, sex, hyponatremia, hyperkalemia, hypomagnesemia, hypocalcemia, creatinine, amiloride	7
Berry, 2013	UK	Nested case–control study	≥50	Both	1986–2010	56,426 (28,213)	Administrative data	Hip	BMI, smoking status, prior history of fracture, and use of osteoporosis medications	6

OBS organic brain syndrome, *BMI* body mass index, *BMD* bone mineral density, *GP* general practitioner, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disorder, *CHD* coronary heart disease, *SERMs* selective estrogen receptor modulators

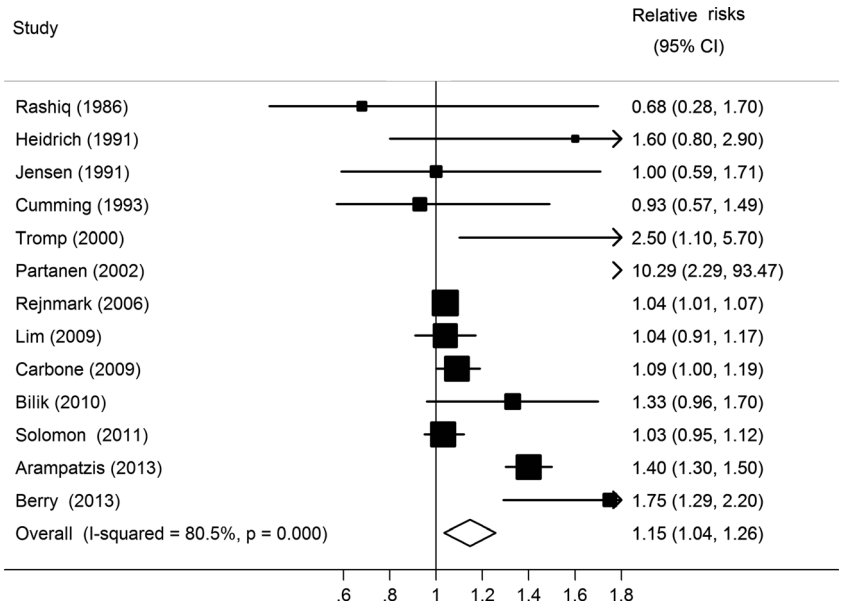

Fig. 2 Adjusted relative risk (*RR*) of loop diuretic use (95 % confidence intervals) and factures using a random-effects model

Table 2 Stratified and subgroup analyses of relative risk of fracture according to loop diuretics

	No of studies	RR (95 % CI)	I^2 (%)	*P* value for heterogeneity	*P* value between groups
Overall studies					
Fracture subtypes					
Hip fracture	11	1.14 (1.08, 1.19)	32.9	0.14	
Lower arm or wrist fracture	3	0.99 (0.93, 1.05)	0	0.78	
Subgroup analyses for total fracture					
Design of study					
Prospective cohort	4	1.05 (1.00, 1.11)	86.4	<0.01	0.57
Case–control	9	1.22 (1.00, 1.44)	0	0.49	
No. of participants					
<3000	6	0.99 (0.69, 1.29)	0	0.56	0.60
≥3000	7	1.17 (1.05, 1.29)	89.5	<0.01	
Gender					
Both	7	1.07 (1.05, 1.09)	89.4	<0.01	
Men	2	1.10 (0.53, 1.66)	0	0.77	0.89
Women	6	1.09 (1.01, 1.16)	7.1	0.37	
Quality score					
<7	6	1.18 (0.81, 1.55)	58.6	0.03	0.63
≥7	7	1.15 (1.01, 1.29)	87.8	<0.01	
Adjustment for confounders					
Other drugs					
Yes	6	1.21 (1.03, 1.38)	88.5	<0.01	<0.01
No	7	1.04 (1.01, 1.71)	0	0.51	
Prior fracture					
Yes	5	1.08 (1.00, 1.16)	66.2	<0.01	<0.01
No	8	1.15 (0.94, 1.38)	71.5	0.02	
Falls					
Yes	3	1.05 (1.00, 1.11)	0	0.64	0.54
No	10	1.23 (1.01, 1.45)	85.1	<0.01	

control studies. With respect to sex, the RRs were 1.10 (95 % CI, 0.53–1.66; $p<0.01$) for men, 1.09 (95 % CI, 1.01–1.16; $p<0.01$) for women, and 1.07 (95 % CI, 1.05–1.09; $p<0.01$) for mixed-sex studies. Significant interactions were not observed between subgroups ($p=0.89$), and heterogeneity was not found for the men ($p=0.77$, $I^2=0$ %) or women ($p=0.37$, $I^2=7.1$ %), but was found for the mixed-sex studies ($p<0.01$, $I^2=89.4$ %). We also examined the number of participants as a possible source of heterogeneity. The RRs were 0.99 (95 % CI, 0.69–0.1.29; $p<0.01$) for studies involving fewer than 3000 participants and 1.17 (95 % CI, 1.05–1.29; $p<0.01$) for those including ≥3000 participants; no significant interactions were observed between subgroups ($p=0.60$).

To examine the effects of adjustments for potentially confounding factors, we considered four studies that had provided both unadjusted and multiple-adjusted coefficients. The unadjusted RR for the association between loop diuretic use and fracture risk was 1.37 (95 % CI, 1.21–1.53; $p<0.01$) with high heterogeneity across studies ($p<0.01$; $I^2=91.4$ %). There was no evidence of attenuation of unadjusted and multiple-adjusted coefficients of the RR for loop diuretic use associated with fractures. However, further subgroup analyses showed that adjustment for other drug use and prior fractures were possible sources of heterogeneity. A sensitivity analysis showed that the exclusion of any one study from the pooled analysis did not substantially vary the results (RRs ranged from a low of 1.22 [95 % CI, 1.09–1.35] to a high of 1.38 [95 % CI, 1.16–1.60]) (Fig. 3).

Publication bias

The funnel plot did not show asymmetry, suggesting the absence of a publication bias among the included studies. Egger's test ($p=0.329$) and Begg's test ($p=0.154$) further confirmed the absence of statistical evidence of publication bias, and the "trim and fill" method showed that there were no missing studies (Supplemental Fig. S1).

Discussion

Main findings

This meta-analysis included data from 13 observational studies, revealing that the use of loop diuretics was associated with an increased risk of fractures (approximately 15 %). An analysis, stratified by fracture subtype, suggested that the use of loop diuretics was associated with a 14 % greater risk of hip fracture. However, we did not observe an increased risk of lower arm or wrist fractures associated with the use of loop diuretics.

Implications

The present study highlights important aspects of the relationship between the use of loop diuretics and the risk of fractures, with several plausible mechanisms for this relationship possible. An obvious explanation for the increased fracture risk is the increased urinary loss of calcium. Persistent calcium loss, induced by loop diuretics, might result in higher rates of bone loss and increased bone porosity [43, 44]. A randomized-controlled trial that included 87 postmenopausal women revealed that 1-year treatment with a loop diuretic (bumetanide) decreased bone mineral density and increased bone turnover marker levels compared with placebo [17]. Recently, a cohort study involving 2980 older women showed that loop diuretic use was associated with a small, but significantly higher, rate of hip bone loss than was observed among non-users [36]; the findings were also replicated in older men [12]. Since substantial evidence indicates that loop diuretics are associated with an increased risk of bone loss, and lower bone mineral density is an important risk factor for fractures [9], loop diuretics may increase the risk of fractures by increasing the risk of bone loss. A recent study investigating the relationship between diuretic-induced hyponatremia and osteoporotic fractures indicated a clinical association between hyponatremia during loop diuretic use and an increased risk of osteoporosis-associated fractures. The authors suggested that loop diuretic therapy exerts negative long-term effects on calcium homeostasis and increases the risk of fall-related fractures [19].

An additional explanation for the relationship between loop diuretic use and the increased risk of fractures is an increased incidence of falls. Loop diuretics may potentially cause orthostatic hypotension [45], which might be positively associated with an increased risk of falls and, subsequently, an increased risk of fractures [37]. However, a large meta-analysis failed to confirm an independent relationship between orthostatic hypotension and falls [46]. Additionally, urinary urgency and frequency is commonly associated with the initiation of loop diuretics, and could result in an increased number of falls when patients are hurrying to the toilet [20]. Berry et al. demonstrated that following a new prescription or increased dose of a loop diuretic drug, patients in nursing home residents had an increased risk of day time falls [47]. However, a prospective cohort study, including 6244 participants, failed to show an association between loop diuretic use among older women and a greater risk of falls [36]. Furthermore, a meta-analysis showed there was no relationship between loop diuretic use and the risk of falls (odds ratio, 0.90; 95 % CI, 0.73–1.12) [18]. Thus, further investigations are needed to better understand whether loop diuretics increase the risk of falls.

The analysis of fracture subtypes showed an increased risk of hip fractures, but not of lower arm or wrist fractures. A possible explanation for the lack of such an association in this study is the limited amount of relevant data pertaining to lower

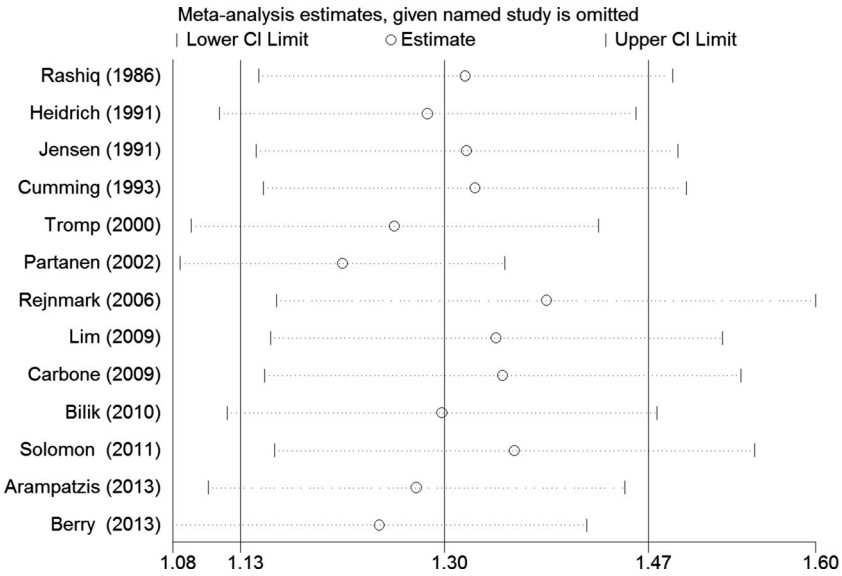

Fig. 3 Sensitivity analysis of loop diuretic use (95 % confidence interval) and factures

arm or wrist fractures; the absence of an association might be ascribed to chance effects or it may result from systematic errors (e.g., residual confounding or selection bias). Therefore, the results should be interpreted with caution, and further well-designed and stratified cohort studies should be conducted to examine the association between fractures and loop diuretic use.

Strengths and limitations

There are several strengths associated with the present study. First, we conducted the most comprehensive literature search, to date, using the MEDLINE, EMBASE, OVID databases, as well as related conference abstracts and reference lists describing the effect of loop diuretics on the risk of fractures. The size of the study and the absence of a language restriction also minimized the possibility of selection bias. Second, we included a substantial number of participants (842,644) and cases involving fractures (108,247). Compared with separate case–control or cohort studies, our analysis significantly enhanced the study's statistical power. Third, literature retrieval, data extraction and analysis, and methodological quality assessments were conducted by two independent investigators, and an experienced arbitrator verified the consistency of these two sets of reports, ensuring the accuracy of the data used in our meta-analysis.

Despite these strengths, several limitations must be considered. First, the quality of individual studies varied; several included studies had limited adjustment for potential statistical confounding, including three studies without clear adjustment [21, 39, 42]. The present study was also subject to confounding factors within the selected studies, which is an innate limitation of all observational studies and meta-analyses. Although most of the included studies were adjusted for age and sex, confounding by other risk factors remains a potential explanation for the observed findings. We examined the effect of adjustment in studies that provided unadjusted coefficients, but there was no evidence of attenuation of the RR of fractures associated with loop diuretics use after adjustment for multiple factors. Second, not all articles involved prospective cohort studies, which reduced the reliability of the conclusions to a certain extent. However, our sensitivity analyses and subgroup analyses show that different types of study designs were not the main sources of heterogeneity. Third, there was a high degree of heterogeneity among the included studies, which might have reduced the strength of our conclusions. We should interpret the results discreetly. The Egger's and Begg's tests confirmed the absence of statistical evidence of a publication bias, and the "trim and fill" method showed that there were no missing studies.

Suggestions for future studies

Based on our meta-analysis, several key points should be considered in future studies. First, because our study did not perform a dose–response analysis, the existence of a dose–response relationship between loop diuretics and fracture risk remains unknown. Second, we could not stratify the population based on current or past use of these drugs, nor on the duration of use. Therefore, several well-designed and stratified cohort studies are needed to clarify the relationship between dose and fracture risk, duration of treatment and fracture risk, and the use of loop diuretics and the fracture site (hip, pelvis, humerus, vertebrae, and other sites). Meanwhile, future studies should also adjust for other factors that may potentially increase the risk of fracture risk, including patient age, bone mineral density, body mass index, diabetes, cardiovascular disease, supplementary vitamins, alcohol consumption, and

amount of exercise. Notwithstanding, this study found a small, statistically significant increase in the risk of hip fracture among users of loop diuretics. However, the results should be interpreted discreetly, and evaluated with respect to the cost-effectiveness of loop diuretics and their clinical significance.

Conclusion

In conclusion, loop diuretics show a significant positive association with the overall risk of total fractures and hip fractures. Additional well-designed and stratified cohort studies, with broad coverage of confounding factors, are needed to facilitate a more comprehensive understanding of the underlying biology of the association between loop diuretic use and the risk of fractures.

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Conflicts of interest None.

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