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Recommendations and metaanalyses

Associations of hyperuricemia, gout, and UA-lowering therapy with the risk of fractures: A meta-analysis of observational studies

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ABSTRACT

Objective: A systematic review and meta-analysis were conducted to investigate the associations of hyperuricemia, gout, and uric acid (UA)-lowering therapy with the risk of fractures.
Methods: Electronic searches on PubMed, the Cochrane Library, and Embase were conducted from inception to January 2, 2019. Observational studies assessing the effects of hyperuricemia, gout, and UA-lowering therapy on fractures were included in the meta-analysis. Summary risk estimates with 95% confidence intervals (CI) were calculated by a random-effects model.
Results: A total of 14 eligible studies with 909 803 participants and 64 047 incident fractures were included. The results suggested that hyperuricemia and gout are not associated with any type of fracture (relative risk [RR], 0.98, 95% CI 0.85–1.11; $P = 0.71$) or osteoporotic fractures (RR, 1.02, 95% CI 0.90–1.14; $P = 0.79$). Further analysis indicated that hyperuricemia is associated with a lower risk of fractures (RR, 0.80, 95% CI 0.66–0.96; $P = 0.02$) but not with osteoporotic fractures (RR, 0.84, 95% CI 0.68–1.03; $P = 0.10$). However, gout is associated with an increased risk of fractures (RR, 1.17, 95% CI 1.04–1.31; $P = 0.007$) as well as osteoporotic fractures (RR, 1.13, 95% CI 1.00–1.26; $P = 0.045$). Furthermore, no significant association of UA-lowering therapy with the risk of fractures was found compared with the placebo (RR, 0.88, 95% CI 0.76–1.03; $P = 0.11$). Evidence supporting a non-linear association between serum UA levels and fractures was found ($P < 0.001$ for non-linearity), which revealed a U-shaped curve.
Conclusion: Our meta-analysis revealed that hyperuricemia was associated with lower risk for any type fracture but not associated with osteoporotic fractures; however, gout was associated with an increased risk of any type fracture as well as osteoporotic fractures. Notably, a U-shaped relationship may exist between the serum UA level and fractures. The associations observed in our study may be due to reasons other than causality.

1. Introduction

Uric acid (UA) is produced by the degradation of purine compounds [1]. Hyperuricemia can be caused by either overproduction or underexcretion of UA. Gout is a type of inflammatory arthritis that may be caused by an increased serum level of UA [2]. Hyperuricemia in humans is common, increases with age, and is reported to be an independent risk factor for death, cardiovascular diseases (CVD) and diabetes [3–6]. However, prior studies have also suggested that UA, as a strong endogenous antioxidant, protects cells from oxidative damage, which raises a contrasting theory regarding the role of UA in health [7,8]. In recent decades, concern has mounted regarding hyperuricemia and its effect on bone [9–14]. Bone metabolism has long been found to be detrimentally affected by oxidative stress or low circulating levels of antioxidants [15–18]. UA may be linked to bone health through its antioxidant or pro-oxidant effects, thereby affecting bone resorption and formation [11]. Approximately 40% of 50-year-old women will reportedly sustain major osteoporotic fractures during the remainder of their lifetimes [19], and these fractures are closely related to the quality of life of the elderly [20]. The increased social and economic burdens associated with osteoporosis-related fractures worldwide render their prevention a major public health goal [21]. The literature suggests that UA may actually play a positive role in bone homeostasis [22–24]. However, no consensus is available on this association, as both protective and detrimental effects have been observed in previous studies [9,11,13]. Therefore, whether hyperuricemia is protective or detrimental for bone health, whether any difference exists in the effects of hyperuricemia and gout on fractures, and whether UA-lowering therapy has any effect on frac-

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tures have not been clearly established. To clarify the associations of hyperuricemia, gout, and UA-lowering therapy with the risk of fractures, we conducted a systematic review and meta-analysis based on published observational studies.

2. Methods

A systematic review, meta-analysis, and meta-regression of observational studies assessing the associations of hyperuricemia, gout, and UA-lowering therapy with the risk of fractures was performed according to the MOOSE Reporting Guidelines [25].

2.1. Search strategy

We conducted a literature search on PubMed, Embase and the Cochrane library from inception to June 15, 2018. Then, a manual search was conducted according to the references of the retrieved relevant articles. The search was later updated through January 2, 2019. One newly identified study was included in the analyses. Details of the search strategy and data extraction are shown in Appendix A [Document S1; See the supplementary material associated with this article online].

2.2. Study selection

The objective of the meta-analysis was to assess the associations of hyperuricemia, gout, and UA-lowering therapy with the risk of fractures. The primary outcomes were risks for any fracture. Any fractures were defined as those occurring at all sites or when the studies did not describe the sites of fractures in detail [21]. If a study reported only the number of participants with fractures at a single site, such as hip fracture, we also considered this to be any fracture. The secondary outcomes were risks for osteoporotic fractures (vertebra, hip, or wrist fractures) [26]. The following inclusion criteria were required for a study to be eligible for the meta-analysis:

- an observational study, including cohort, case-control or cross-sectional studies, conducted in a population aged 18 years or older;
- a study including at least one group of participants with hyperuricemia or gout with or without treatment; and;
- a study including reported relative risk (RR) estimates of fractures, such as risk ratios, incidence rate ratios, hazard ratios, or odds ratios with 95% confidence intervals (CIs).

We excluded reviews, editorials, or studies on animals, letters without sufficient data, and duplicated studies. In multiple same-population studies, we selected and included the study with the longest follow-up time.

2.3. Data extraction

Studies were selected and appraised by two trained clinician reviewers (QZ and YH). Data were extracted from the included studies using a specially developed data extraction form by two independent reviewers (QZ and QZ). Any disagreement was resolved by discussion with a third review author to reach a consensus (XZ). For each eligible study, we extracted data on the name of the first author, year of publication, study name, study location, design, years of follow-up, sample size, participant characteristics (age and sex), available outcomes (number of events), outcome ascertainment, covariates adjusted in multivariable analyses, and RRs (95% CIs) for the main study outcomes, and we adjusted for potential confounding factors (Table 1).

We contacted the authors if the data of interest were not directly provided in the publications.

2.4. Statistical methods

We performed this meta-analysis to calculate fully adjusted RR estimates for the associations of hyperuricemia, gout, or UA-lowering therapy with fractures reported in the publications using a random-effects model. RRs that were often differently reported by each study (such as per 1-SD change or comparing quintiles, quartiles, thirds, and other groupings) were transformed using methods first reported by Danesh et al. [27]. Any results stratified by sex or fracture type were treated as separate reports. The lowest category in studies with three or more categories of serum UA levels was used as the reference. When a fully adjusted RR with a 95% CI was unavailable, we calculated the crude RR with the 95% CI according to the participants and events provided in the publication. The method described by Greenland and Longnecker [28] and Orsini and colleagues [29] was used to calculate the trend from the correlated estimates for the log RR across categories of UA levels.

In the dose-response analysis, publications that provided adjusted RRs and 95% CIs for three or more categories of UA levels were eligible. The midpoint of the upper and lower boundaries was considered the dose of each category if the median or mean UA level was unavailable. If the highest or lowest category was open-ended, then the midpoint of the category was calculated as 1.5-times the lower or higher boundary [30]. The potential curve linear association was evaluated by the restricted cubic spline model with three knots selected at the 10th, 50th, and 90th percentiles of the distribution [31]. The P-value for curve linearity or nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero.

The quality of cohort and case-control studies was assessed according to the Newcastle-Ottawa Quality Assessment (NOS) scale [32]. This scale awards nine scores to each study as follows: four for the selection of participants and measurement of exposure, two for the comparability of cohorts on the basis of the design or analysis, and three for the assessment of outcomes and the adequacy of the follow-up. A study was considered high quality if it had a score of 7.0 or higher. For quality assessment of the cross-sectional studies, we used the relevant criteria of the NOS checklist proposed by Meeus et al. [33]. This checklist contains only the three following items: representativeness of the participants, exposure, and outcome ascertainment. We assigned scores of 1/3, 2/3, and 3/3 for low-, moderate-, and high-quality studies, respectively.

Furthermore, the potential publication bias was assessed by Egger's regression test, and a two-sided P-value < 0.05 was considered statistically significant [30,34]. To correct for a suspected publication bias, we followed the Duval and Tweedie trim and fill procedure as a method of adjustment [35]. Sensitivity analyses were conducted by omitting one report at a time from the analysis and assessing the effect on the overall findings. Statistical heterogeneity among the summary data was evaluated using the I^2 statistic [36,37]. To further explore the possible sources of heterogeneity, subgroup and meta-regression analyses were conducted. In the meta-regression, variables in the univariate analyses with P-values < 0.1 were considered statistically significant and were included in multivariable models, and an overall P-value < 0.05 was considered statistically significant in the multivariable models [38]. If fewer than 10 studies reported the explanatory variable(s) of interest, meta-regression analyses were not performed [39].

The statistical analyses were conducted using Stata statistical software version 13.0. A 2-sided P-value less than 0.05 was considered statistically significant.

Table 1
Descriptive characteristics of included studies.

Author	Publication year	Study name	Country	Participants	Number of Participants and sex	Age at baseline (years)	Design, mean length of follow-up (years)	Available outcomes (number of events)
Nabipour [24]	2011	CHAMP study	Australia	Community residents	1673 (Male)	76.9± 5.5	Cross-Sectional Study	Vertebral (321) and nonvertebral fractures (85)
Makovey [23]	2012	Northern Sydney Twin Study	Australia	Female twin participants of NHMRC Twin Registry	356 (Female)	Mean age 60.5 years	A longitudinal study, 9.7±1.8 years	Fractures (39)
Lane [22]	2014	The MrOS Study	USA	Community-dwelling me	5994 (Male)	≥ 65	Cohort, 5.3 years	Nonspine fractures (387), hip fractures (73)
Mehta [40]	2014	CHS	USA	Participants was recruited from Medicare-eligible individuals	4692 (Male and female)	≥ 65	Cohort, 10 years	Hip fractures(519)
Kim BJ [39]	2014	/	Korea	Participants from Asian Medical Center	16,078 (Male)	≥ 50	A longitudinal study, 3 years	Osteoporotic fractures (158)
Veronese [41]	2015	Progetto Veneto Anziani	Italian	Age- and sex-stratified Caucasian participants	1586 (Male and female)	≥ 65	Cohort, 4.4 years	Fractures (185)
Muka [14]	2016	The Rotterdam Study	Netherlands	Participants were continuously followed for vital status and medical outcome.	5074 (Male and female)	≥ 55	Cohort, 10.9 years	All fractures (1297), non-vertebral fractures (1156) and vertebral fractures (254)
Tzeng [13]	2016	/	Taiwan, China	Data were randomly selected and followed from a cohort of 1 million people covered by the national insurance program	130,941 (Male and female)	50.9± 16.0	Cohort, 11 years	Fractures (18 404)
Author	Publication year	Study name	Country	Participants	Number of Participants and sex	Age at baseline (years)	Design, mean length of follow-up (years)	Available outcomes (number of events)
Paik [22]	2016	The Nurses' Health Study	USA	Female registered nurses	103,799 (Female)	30–55	Cohort; 14 years (wrist fracture), 22 years (hip fracture)	Wrist fracture (3 769), hip fractures (2 147)
Kim SC [12]	2017	/	USA	Community residents (non-gout group and hypertension group)	292,808 (Male and female)	60	Cohort, 11 years	Non-gout group: non-vertebral fracture (423), hip fracture (125). Gout group: non-vertebral fracture (1150), hip fracture (392).
Wang [9]	2018	/	China	Community residents in Shanghai	2674 (Male and female)	55–85	Cross-sectional study	Osteoporotic fractures (388)
Dennison [43]	2015	/	UK	Individuals who had at least one allopurinol prescription	172,078 (Male and female)	63	Cohort, 15 years	Any fracture (25,241)
Basu [42]	2016	/	UK	Participants were from social services	17,308 (Male and female)	≥ 65	Cohort, 12 years	Hip fracture (618)
Sultan [44]	2018	/	UK	Participants were from the Clinical Practice Research Datalink, and the large database is representative of the general UK population	154,742 (Male and female)	63.2 ± 12.3	Cohort, 10.8years	Fragility fracture (8934)

CHAMP: concord health and ageing in men project; MrO: osteoporotic fractures in men; CHS: cardiovascular health study.

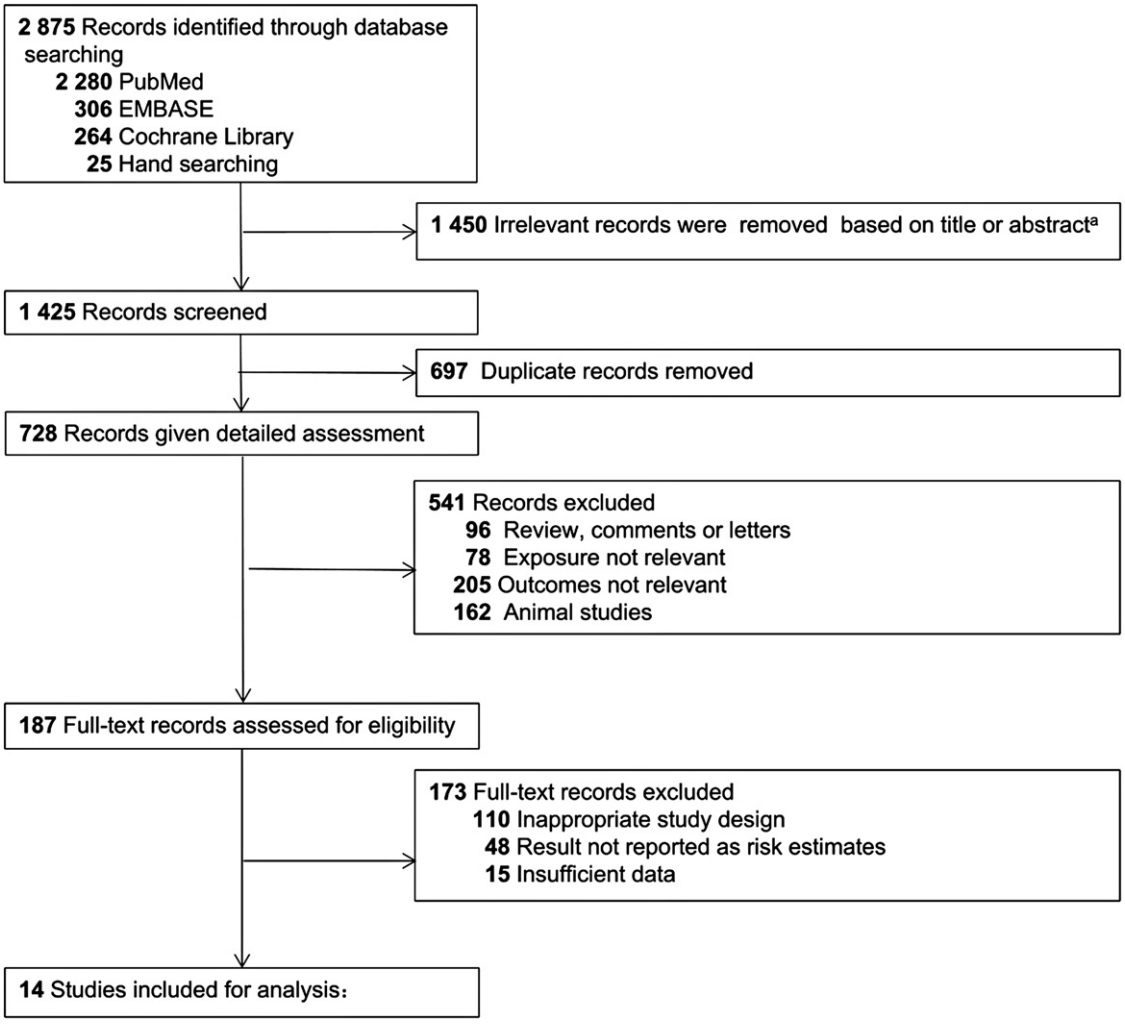

Fig. 1. Flow diagram of the study selection process. a: Exact reasons for exclusions were not documented.

3. Results

3.1. Study selection and characteristics

3.1.1. Study selection

From the searches for systematic reviews or meta-analyses, 2875 potentially eligible records were identified. Of these studies, 2688 were excluded based on title/abstract contents, duplicate records, or an inappropriate study type. The full texts of 187 records were read, and 14 studies ultimately met the inclusion criteria (details in Fig. 1) [9,11–14,22–24,40–44]. Among these studies, seven studies reported the statistical effects of hyperuricemia [14,22–24,40–42], four studies reported data on gout [9,11–13], and four studies reported the effects of UA-lowering therapy [13,43,44].

3.1.2. Study characteristics

After the ineligible studies were excluded, a total of 14 studies involving 909 803 participants and 64,047 incident fractures were included in our meta-analysis, including 12 cohort [11–14,22,23,40–45] and two cross-sectional [9,24] studies (descriptive characteristics of the studies and outcomes are shown in Table 1) [9,11–14,22–24,40–44]. The participants were aged 30 to 82 years, and more than half of these participants were older than 60 years. Four of the studies were conducted in North America [11,12,22,41], five in Europe [14,42–45], three in Asia [9,13,40], and two in Oceania [23,24]. The duration of the cohort studies ranged from three to 22 years. Two studies [14,40] reported RRs and 95% CIs for the per SD increase, and the remaining studies reported dichotomous variables (Appendix A, Tables S1a,b). All studies were assessed as high-quality according to the NOS scale (Appendix A, Table S1c).

3.2. Hyperuricemia, gout, and uric acid-lowering therapy and fractures

3.2.1. Primary outcome

Eleven studies (nine cohort [11–14,22,23,40–42] and two cross-sectional [9,24] studies) with 15 reports were included to analyze the associations of hyperuricemia and gout with the risk for any fracture. In total, the studies included 29,272 incident fractures among 565,675 participants. Pooled estimates showed that hyperuricemia and gout were not significantly associated with the risk for fractures (RR, 0.98, 95% CI 0.85–1.12; $P = 0.71$; Fig. 2). Heterogeneity among these studies was detected ($I^2 = 78.9\%$; $P < 0.001$).

Four of these studies investigated the association between gout and the risk for fractures [9,11–13], and five of them assessed the association between hyperuricemia and the risk for fracture. Further analysis indicated that hyperuricemia was associated with a lower risk of fracture (RR, 0.80, 95% CI 0.66–0.96; $P = 0.018$; Fig. 2), with heterogeneity identified among the studies ($I^2 = 52.5\%$; $P = 0.032$ for heterogeneity; Fig. 2).

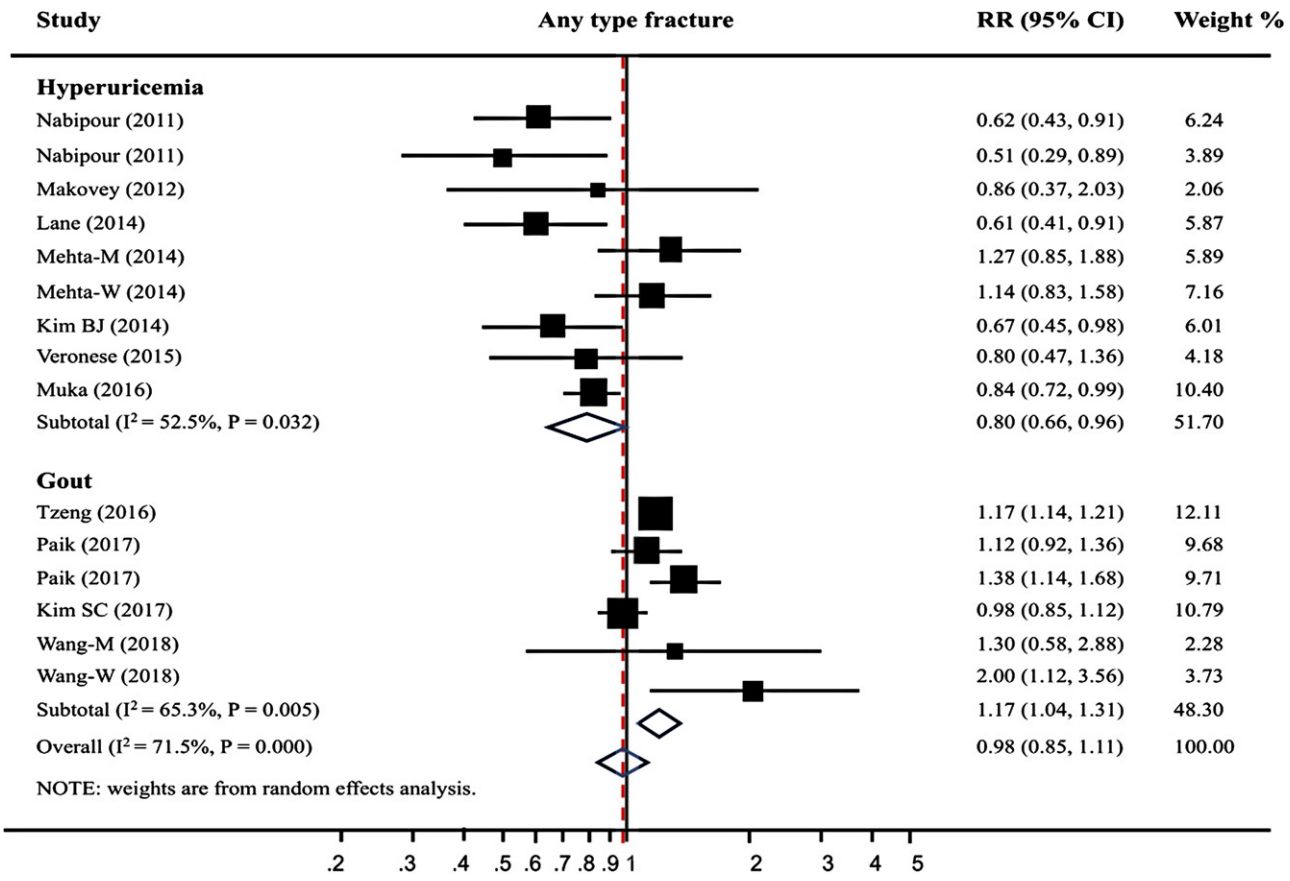

Fig. 2. Summary RRs for the associations of hyperuricemia and gout with the risk for any fracture. RRs and 95% CIs were calculated using the random-effects model used to pool the data. Abbreviations: RR: relative risk; CI: confidence interval; W: women; M: men.

The summary RR for gout and the risk for fractures was 1.17 (95% CI 1.04–1.31; $P = 0.007$; Fig. 2) using a random-effects model ($I^2 = 60.4\%$; $P = 0.027$ for heterogeneity; Fig. 2).

3.2.2. Secondary outcomes

Ten studies [9,11–14,24,40–42] with 15 reports assessed the associations between hyperuricemia/gout and the risk for osteoporotic fractures. The summary RR was 1.02 (95% CI 0.90–1.14; $P = 0.79$; Fig. 3), which is consistent with the primary outcome. Further analysis suggested that hyperuricemia was not associated with osteoporotic fractures (RR, 0.84, 95% CI 0.68–1.03; $P = 0.10$; Fig. 3); however, gout was associated with an increased risk for osteoporotic fractures (RR, 1.13, 95% CI 1.00–1.26; $P = 0.045$; Fig. 3).

3.2.3. Uric acid-lowering therapy and fractures

Four studies [13,43–45] with five reports including 44 804 incident fractures among 357,169 participants assessed the effect of UA-lowering therapy on fractures. No significant association of UA-lowering therapy with the risk of fractures was found compared with placebo or no treatment (RR, 0.88, 95% CI 0.76–1.03; $P = 0.11$; Fig. 4). Heterogeneity among these studies was detected ($I^2 = 98.5\%$; $P < 0.001$).

3.3. Dose-response meta-analysis

Four studies [22,23,41,42] with six reports were eligible for the dose-response analysis of the RR of any type of fracture with hyperuricemia. Evidence supporting a nonlinear association between the serum UA level and fractures was found ($P < 0.001$ for nonlinearity), which revealed a U-shaped curve (Fig. 5). No significant associations were found when the serum UA level was lower than 291 umol/L. The pooled estimated RR for fractures was 0.93 (95% CI 0.87–0.99) when the serum UA level was at 291 umol/L and continued to decrease as the UA level increased compared to the reference category (162 umol/L). No significant association was found between hyperuricemia and fractures when the serum UA level was greater than 534 umol/L. The pooled estimated RR for fractures was 0.89 (95% CI 0.73–1.09) when the serum UA level was 534 umol/L and continued to increase as the UA level increased, but it did not reach statistical significance. These results suggest the possibility of a significant association of hyperuricemia with an increased fracture incidence when the serum UA level is greater than 534 umol/L, but the current analyses may have lacked statistical power to show this association. No publication bias was detected with the Egger test ($P = 0.05$).

3.4. Basic population characteristics

We summarized the weighted mean differences (WMDs) of the highest-category vs. lowest-category UA levels for basic population characteristics to investigate potential confounding factors. Our results suggested that a high UA level is usually associated with a higher body mass index (BMI) (WMD 2.38, 95% CI 1.57–3.19; Appendix A, Table S1d), higher bone mineral density (BMD) (WMD 0.04, 95% CI 0.03–0.06; Appendix A, Table S1d), higher parathyroid hormone (PTH) levels (WMD 9.67, 95% CI 7.63–11.71; Appendix A, Table S1d), and a lower glomerular filtration rate (GFR) (WMD −13.33, 95% CI −12.22– −12.44; Appendix A, Table S1d).

3.5. Meta-regression

Substantial heterogeneity ($I^2 > 50\%$) was present for any type of fracture. When sufficient data were available, a meta-regression

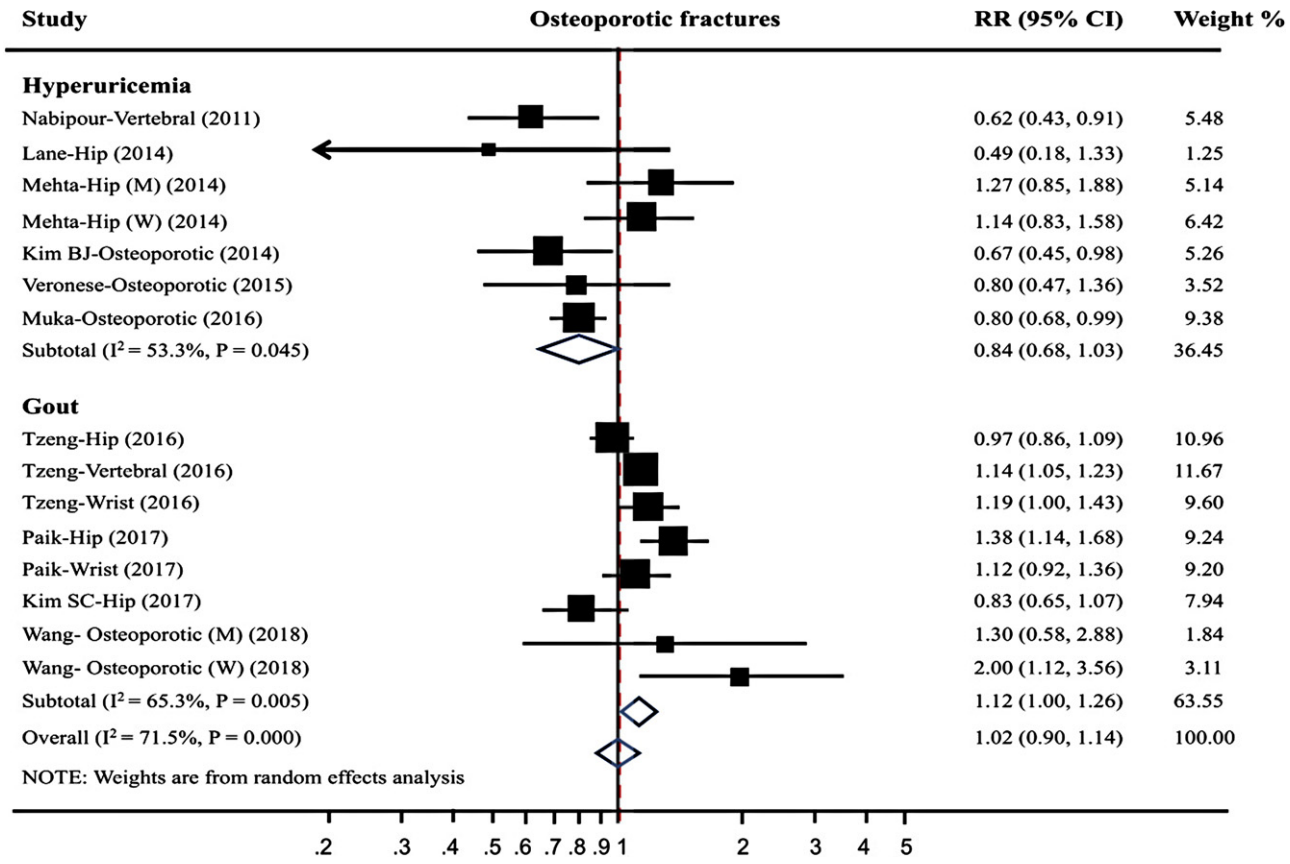

Fig. 3. Summary RRs for the associations of hyperuricemia and gout with the risk for osteoporotic fractures. RRs and 95% CIs were calculated using the random-effects model used to pool the data. Abbreviations: RR: relative risk; CI: confidence interval; W: women; M: men.

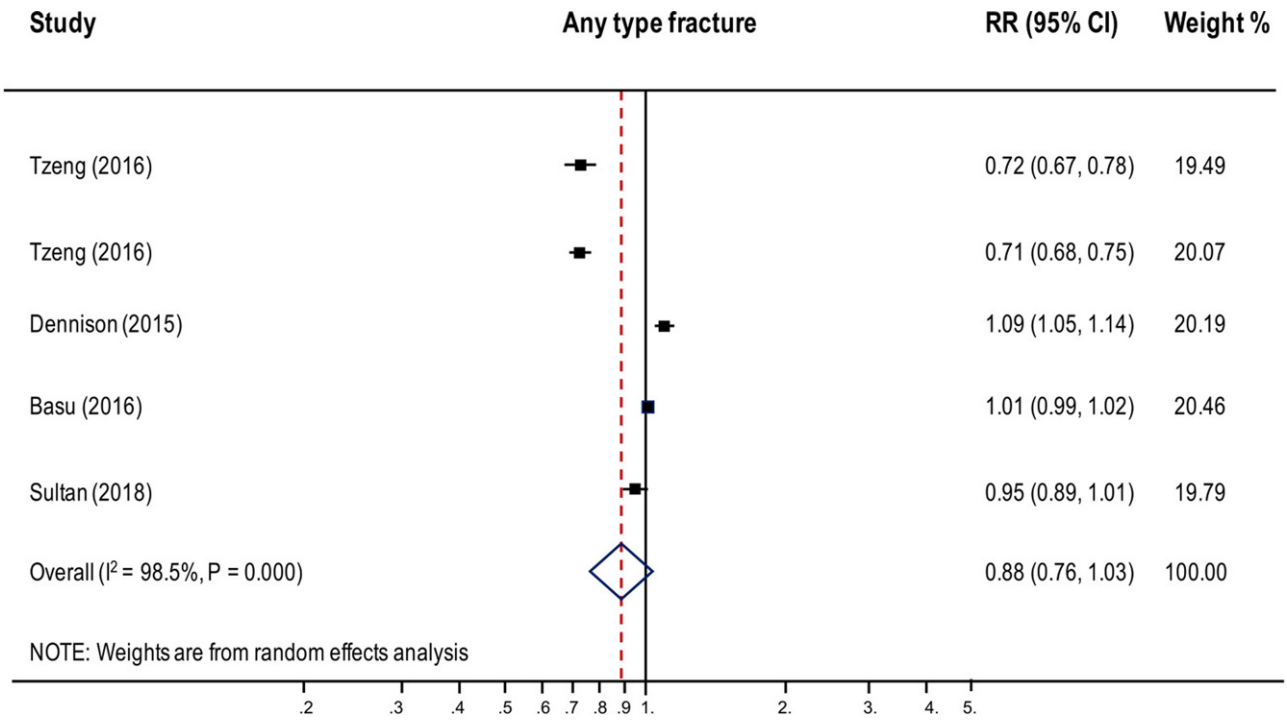

Fig. 4. Summary RRs for the association of UA-lowering therapy with the risk for any fracture. RRs and 95% CIs were calculated using the random-effects model used to pool the data. Abbreviations: RR, relative risk; CI, confidence interval.

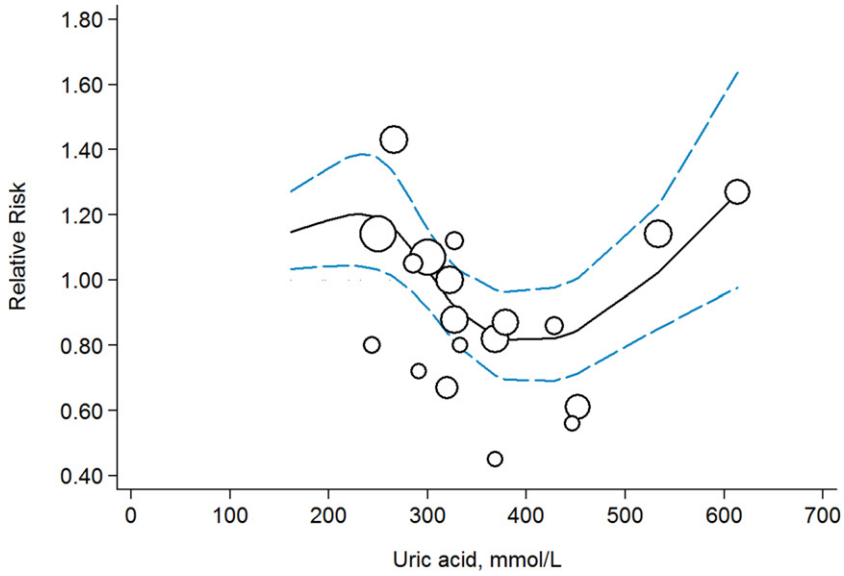

Fig. 5. Summary RRs for the dose-response analysis of the relative risk of any type of fracture with hyperuricemia. RRs and 95% CIs were calculated using the random-effects model used to pool the data. Abbreviations: RR: relative risk; CI: confidence interval.

analysis was performed to investigate possible sources of heterogeneity, including the following: study type, age, sex, study location, sample size, incidence, duration, fracture type, study quality, follow-up rate, population setting and whether the study excluded UA-lowering treatment or osteoporosis medications. The results suggested that duration ($P = 0.09$ in the univariate models), study quality ($P = 0.09$ in the univariate models), exclusion of UA-lowering therapy ($P = 0.04$ in the univariate models) or osteoporosis treatment medications ($P = 0.04$ in the univariate models), and whether the study assessed the association of hyperuricemia or gout with fractures ($P = 0.01$ in the univariate models) may contribute to the heterogeneity in the studies for analyses of all-cause mortality (the overall $P < 0.01$ in the multivariable models, Appendix A, Table S1e). The analysis was not performed among studies of UA-lowering therapy due to an insufficient number of studies.

3.6. Sensitivity and subgroup analyses

Sensitivity analyses excluding one report at a time did not alter the results [Appendix A, Figure S1-S3]. To evaluate whether the association between UA and fractures was modified by clinical characteristics, we performed subgroup analyses stratified by study type, sex, age, BMI, study location, sample size, incidence, duration, study quality, follow-up rate, population setting, and whether the study excluded UA-lowering treatment or osteoporosis medications (Appendix A, Table S1f). The subgroup analyses showed that these results were generally consistent, except for studies in Oceania and Europe, which suggested that hyperuricemia may protect against fractures in these populations ($P < 0.05$; Appendix A, Table S1f).

3.7. Publication bias

No evidence of a publication bias was observed according to the Egger test in the analysis of the associations between hyperuricemia/gout ($P = 0.05$) and the risk for fractures or for the association between UA-lowering therapy and the risk for fractures ($P = 0.45$).

4. Discussion

In this meta-analysis of 14 observational studies involving more than 900,000 participants, no associations between hyperuricemia/gout and the risk for any fracture as well as osteoporotic fractures were detected. Further analysis suggested that hyperuricemia may play a protective role in bone homeostasis; however, gout was associated with an increased risk of fractures. These findings are further supported by a nonlinear association between the serum UA level and fractures, which shows a U-shaped curve. Sensitivity analyses excluding one report at a time did not alter these results. Furthermore, these results were generally consistent regardless of study type, sex, age, BMI, sample size, incidence, duration, study quality, follow-up rate, population setting, and whether the study excluded UA-lowering treatment.

Hyperuricemia was reported to be an independent risk factor for death, CVD, and diabetes [3–6]. An important purpose of lowering serum urate levels is to prevent acute flares and the development of tophi [11]. Furthermore, increasing evidence has suggested that UA is a strong endogenous antioxidant, protecting cells from oxidative damage [11,15–18]. Previous meta-analyses have demonstrated that hyperuricemia may actually play a positive role in bone homeostasis [46,47]. In the current analyses, the point estimate regarding the associations of hyperuricemia and gout with fractures was decreased, but this finding did not reach statistical significance. Our findings are further supported by the null associations between hyperuricemia/gout and osteoporotic fractures. The disparity between our result and those of previous studies may be due to the more recently published trials reporting neutral or harmful associations between hyperuricemia and the fracture incidence [9,11–13]. Another possible reason for the differences in conclusions is that we combined hyperuricemia and gout in the analysis. Therefore, we further analyzed the effects of hyperuricemia and gout on fractures separately. The results suggested that hyperuricemia is associated with a lower risk for fractures as supported by the association between higher BMD and high UA levels reported in three studies [14,23,24]. However, hyperuricemia is not associated with osteoporotic fractures. One possible explanation for the disparity association is that the average age of patients in studies which showed a positive association is lower than patients in

studies showed null association. The protective role of UA in bone homeostasis cannot reverse the bone loss with age.

There is no clear biological mechanism accounting for the association between hyperuricemia and the fractures. Supporting evidence derives from epidemiological studies reporting that serum UA played a protective role against bone loss and promoted fracture healing [10,48]. UA has a strong antioxidant effect at physiologic concentrations [49], and oxidative stress has been identified recently as a potential mechanism that attenuates osteoblast genesis and bone formation [50,51], which may explain the first half of the downward trend of the U-shaped curve at a UA level lower than 534 umol/L, although this result did not reach statistical significance. However, higher serum UA levels were previously reported to be associated with an increased risk of incident and recurrent gout [52]. Dennison et al. [44] also reported that a very high urate level was associated with acute, intense inflammatory arthritis, which was not beneficial to bone health.

However, gout was associated with an increased risk of any type fracture as well as osteoporotic fractures. It was supported by a population-based longitudinal study involving 108,060 individuals which suggested gout have a modest increase in the risk of developing osteoporosis in future [53]. The different pathophysiological states may account for the disparity between hyperuricemia and gout. Gout is characterized by UA crystals and inflammation, which distinguish this disease from asymptomatic hyperuricemia [11]. Urate crystals reportedly may promote osteoclast development within tophi and their vicinity [51] and may reduce osteoblast activity in vitro [54]. Consistent with these reports, fractures have been noted at the site of tophi in patients with tophaceous gout [55]. This inflammatory environment in gout patient can also disrupt osteoblast function [56] and promote osteoclastogenesis [57,58]. Further analysis of UA-lowering therapy suggested that treatment for hyperuricemia did not improve the risk of fractures compared with placebo or no treatment. These findings suggest that hyperuricemia may play a positive role in bone homeostasis; however, a very high urate level and gout were associated with an increased risk of fractures.

Many potential confounding factors were identified for the associations of hyperuricemia and gout with the risk of fractures because of the complex relationship between serum UA levels and other diseases, such as metabolic diseases, CVD, and kidney diseases. Therefore, we further analyzed the WMDs of potential confounding factors. Previous studies have suggested that patients with elevated serum UA levels frequently have reduced renal function [22,41]. Reduced renal function alters the conversion of 25 vitamin D to 1.25 vitamin D as the 1 hydroxylase enzyme levels are reduced, which can lead to an increase in serum PTH levels, consistent with our results that a high UA level is usually associated with higher PTH levels and a lower GFR. Obesity may have been another important confounder in our study. A high BMI is associated not only with higher UA levels as shown by our results [59] but also with a higher morbidity of postmenopausal osteoporosis [60]. Although variations in BMI had been adjusted in the analyses of most studies, residual confounding is difficult to exclude.

To our knowledge, this is the first meta-analysis to comprehensively summarize results regarding the associations of hyperuricemia, gout, and UA-lowering therapy with the risk of fractures. More than 900,000 participants in 14 observational studies were included in our meta-analysis. The large sample size provided sufficient statistical power to detect significant associations. Second, detailed dose-response analyses, meta-regression, a risk of bias appraisal, and stratified and sensitivity analyses were undertaken to support our conclusion.

Several limitations also exist. First, the findings from this review are based on observational data, and no causal links can be concluded. They may be applicable at the population level, but recommendations need to be individualized when applied clinically. Second, few studies were included in the respective analysis of the associations of hyperuricemia and gout with the risk of fractures; therefore, meta-regression and publication bias assessment were not performed due to insufficient studies. Third, study heterogeneity may have affected the reliability of the results, although the meta-regression identified potential sources of this heterogeneity. Finally, although detailed subgroup analyses were conducted and many covariates were adjusted for in most of the included studies, such as BMI, BMD, the GFR, and pre-existing disease, the results of this study may be subject to residual confounding. Thus, we cannot exclude the possibility that these variations may at least partly explain the association between serum UA levels and bone health beyond a direct causative link.

Author contributions

Tao Wang designed the study, and he is the guarantor of this work. He had full access to all the data in the study and assumes responsibility for the integrity of the data and the accuracy of the data analysis. Qunchuan Zong initiated the study, acquired the data, analyzed the statistics, drafted the manuscript, critically revised the manuscript, contributed to the interpretation of the results and approved the final version. Yibo Hu and Qifu Zhang analyzed the statistics, interpreted the data, and critically revised the manuscript. Xiuxiu Zhang and Jingwen Huang analyzed the statistics. All authors read and approved the final manuscript.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2019.03.003.

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