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ORIGINAL ARTICLE

Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis

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Abstract

Summary This study is the first meta-analysis investigating the pooled incidence rates of fractures among patients with RA. Our results demonstrated that this population is at high risk of overall and fragility fractures. Consideration of vertebral imaging and RA-specific risk factor assessment may aid in fracture prevention for this vulnerable group.

Introduction This systematic review and meta-analysis aims to estimate the incidence of fractures (overall and fragility) in patients with rheumatoid arthritis (RA).

Methods MEDLINE, EMBASE, and CENTRAL were searched for cohort studies reporting incidence of fractures among patients with RA. Two reviewers independently assessed all studies for inclusion and extracted data. Pooled analyses of incidence rates and relative risk of fractures were conducted using a random-effects model. Subgroup analyses investigated potential sources of heterogeneity, and predictors of fractures were summarized.

Results Twenty-five studies were included in total. The pooled incidence rates of overall and fragility fractures were 33.00 (95% CI 18.39–59.21) and 15.31 (95% CI 10.43–22.47) per 1000 person-years, respectively. Patients with RA had a higher risk of overall (RR 1.52, 95% CI 1.07–2.14) and fragility (RR 1.61, 95% CI 1.44–1.79) fractures. Subgroup analyses suggested a higher risk of fragility fractures among female patients (31.03 vs. 23.75 per 1000 person-years). The pooled site-specific incidence rates of vertebral, hip, forearm, and proximal humeral fractures were 7.51 (95% CI 3.27–17.23), 4.33 (95% CI 2.26–8.27), 3.40 (95% CI 2.27–5.10), and 1.86 (95% CI 1.36–2.53) per 1000 person-years, respectively. Clinical vertebral fractures were underestimated compared with radiographic screening (4.29 vs. 42.40 per 1000 person-years). Predictors of fractures included both traditional OP risk factors and RA-specific factors.

Conclusions Patients with RA are at high risk of incident overall and fragility fractures. Consideration of vertebral imaging for patients with additional OP risk factors, including RA-specific risk factors, may help with early OP diagnosis and timely intervention.

Keywords Fracture incidence · Fragility fracture · Meta-analysis · Osteoporosis · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by chronic symmetrical polyarthritis and extra-articular manifestations. Patients with RA may develop a number of skeletal complications, including periarticular osteopenia, subchondral bone erosion, joint fusion, generalized bone loss, and fragility fractures [1, 2]. The association between RA and fracture has been attributed to chronic systemic inflammation, immobility, reduced physical activity, increased fall risk, vitamin D deficiency and glucocorticoid use [1, 3]. In the widely used fracture risk assessment tool (FRAX), rheumatoid arthritis has been included as an independent clinical risk factor for the estimation of 10-year risk of major osteoporotic and hip fractures [4]. As one of the most common comorbidities in RA, the presence of fragility fracture may affect treatment strategies for individual patients and result in decreased quality of life, disability, hospitalization, and shortening of life expectancy [5, 6]. Early diagnosis of osteoporosis and timely intervention can prevent subsequent fractures [7]. Therefore, assessment of fracture risk is of vital importance in the management of patients with RA.

Risk for fracture among patients with RA has been quantified primarily by individual observational studies, which differ significantly in study design, source of participants, sample size, and type of fractures, and reported results with a high degree of heterogeneity [8–11]. A recently published meta-analysis of 13 observational studies indicated that compared to general population, patients with RA are at higher overall risk for fractures, as well as increased risk for site-specific fractures of the vertebrae and hip [12]. These studies have led to a better understanding of the association between RA and fracture, as well as the relative risk of fracture in this population. However, the absolute risk of fractures in RA patients has not been well studied due to the high variability among existing studies, and the sources of this high between-study heterogeneity also remain unclear. More reliable and comprehensive estimates of the fracture incidence are of great importance for the prevention and early management of this common comorbidity. Therefore, we conducted a systematic review and meta-analysis of published cohort studies to investigate the incidence rates of fractures in RA patients, as well as the potential sources of heterogeneity among studies. Pooled incidence rates were separately calculated for (1) all fractures, (2) fragility fractures, and (3) fractures at the four major osteoporotic fracture (MOF) sites (vertebrae, hip, forearm, and proximal humerus). For available studies, risk estimates of overall and fragility fractures were combined in the meta-analysis, and reported predictors of fractures were also summarized.

Methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13].

Eligibility and exclusion criteria

We included studies which met the following inclusion criteria: (1) prospective or retrospective cohort studies, (2) carried out in adult RA patients with or without control groups, (3) reporting on incident fractures (all fractures, fragility fractures, or fractures at MOF sites). Studies only assessing prevalence of fracture in RA patients were excluded. If multiple articles were derived from the same population and reported on the same outcomes, the latest publication was included.

Information sources and search strategy

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to September 2017 to identify all potential studies reporting incidence of fractures among patients with RA. The major search terms we used included "rheumatoid arthritis," "fracture," "vertebral deformity," "cohort," "follow up," "longitudinal," "prospective," "long term," "incidence," and "observational study." Reference lists of identified studies, relevant original studies, reviews, and textbooks were also searched manually for additional articles. For conference abstracts and papers that we could not find full texts, we also tried to contact the authors for additional data. No restrictions were placed on ethnicity, language, or publication type. The following search strategy was performed on EMBASE as an example:

1. "rheumatoid arthritis":ti,ab OR "ra":ti,ab
2. "fracture*":ti,ab OR "vertebral deformit*":ti,ab
3. "cohort" OR "longitudinal" OR "prospective" OR "follow-up" OR "follow up" OR "followup" OR "observation" OR "observational stud*" OR "long term" OR "long-term" OR "longterm" OR "incidence" OR "incident"
4. #1 AND #2 AND #3

Study selection

Two investigators (SYJ and LYP) independently reviewed the titles and abstracts identified in the search and retrieved full articles to determine eligibility of each study. Disagreements or uncertainties were resolved at each step by consensus.

Data extraction

Data were extracted by two reviewers (SYJ and CY) independently from selected articles using a standardized form. Discrepancies were resolved by discussion with a third reviewer (YHW). For each eligible study, the following data were collected: authors, year of publication, geographic region where study was performed, type of study design, number of RA patients, number of controls (if applicable), age and sex distribution, use of glucocorticoids, person-years or mean duration of follow-up, reported fracture types, number of incident fractures, and associated risk factors. When available, data on fragility fractures and/or fractures at the four MOF sites (vertebrae, hip, forearm, and proximal humerus) were collected. For all studies that included control groups, risk estimates [relative risks (RRs) or hazard ratios (HRs)] of fracture in RA patients were also extracted.

Study quality assessment

The quality of selected observational studies was assessed independently by two investigators using the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Data synthesis and analysis

The outcomes in this meta-analysis included the incidence rates of all fractures and fragility fractures among patients with RA, and we also analyzed site-specific incidence rates of major osteoporotic fractures. Pooled incidence rates were calculated across studies based upon the log-transformed incidence rates and standard errors ($1/\sqrt{\text{fractures}}$) using the generic inverse variance method. For studies not providing incidence rates directly, we calculated the fracture incidence rate per 1000 person-years by dividing the number of incident fractures by the person-years contributed by all RA patients followed up in the study. If not reported, we calculated the number of person-years using the mean duration of follow-up. Exact 95% confidence intervals (CIs) for incidence rates were calculated for studies that did not provide CIs. Furthermore, to evaluate fracture risk in RA patients compared with controls, pooled RRs of both all fractures and fragility fractures were calculated by combining risk estimates from all available cohorts.

We employed a random-effects model to account for heterogeneity between studies in our sample when estimating the common effect size. Statistical evidence of heterogeneity across studies was examined using the Cochrane Q test and the I^2 statistic [14]. To identify potential sources of heterogeneity in fracture incidence rates, we conducted subgroup analyses for the following study characteristics: geographic region (North America, Europe, or Asia), sex (only women or mixed), mean or median follow-up period, percentage of patients receiving glucocorticoid (GC) treatment, and sample size (< 1000 or ≥ 1000). Cumulative meta-analyses were conducted by adding the studies successively according to the year of publication to identify potential change in fracture risk over time. For the incidence of fragility fractures, subgroup analysis was performed based upon the definition used to identify fragility fractures (site of fracture or cause of fracture). For vertebral fractures, subgroup analysis was also conducted based upon detection method (clinical fractures or radiographic). Differences between subgroups were examined using the Chi-square test [15]. Sensitivity analyses were performed by serially excluding each study to evaluate its influence on the overall results. Publication bias was assessed using funnel plots and Egger's test. All analyses were performed using Stata Version 14.0 (StataCorp, Texas, USA), and a P value of less than 0.05 was considered statistically significant.

Results

Study characteristics

Of the 2390 articles identified initially by our database search, 23 cohort studies reported in 25 articles (3 articles reported data on different fracture sites from the same cohort [9, 16, 17]) met all eligibility criteria and were included in subsequent analyses. The study selection process and reasons for exclusion are shown in Fig. 1.

The main characteristics of the 25 selected articles are summarized in Table 1. These studies were published between 1993 and 2017. Among the 23 reported cohorts, seven were conducted in the USA, eight in Europe, six in Asia, and one in Australia. Gregson et al. carried out their study in multiple countries. The number of enrolled patients with RA ranged from 96 to 47,034. Differences were observed in the baseline characteristics of participants across the studies, including age, gender distribution, and use of glucocorticoids.

As is shown in Table 1, the included studies reported different types of fractures as outcomes. Among the 25 studies, 10 studies [10, 18, 21, 22, 26, 27, 29, 30, 33, 35] reporting data on all fractures and 10 studies [8, 18, 24, 25, 27, 28, 32–34, 36] reporting data on fragility fractures were further included in the meta-analyses for pooled incidence rates of all fractures and fragility fractures. Of the studies reporting data on fragility fractures, three defined fragility fractures based on the cause of fracture (low-trauma or low-energy), and six defined them based on the site of fracture (spine, hip, forearm, proximal humerus, with or without pelvis). No detailed definition for fragility fractures was presented by Suzuki et al. in their study [36]. As for the four typical sites of major osteoporotic fractures, we identified 12 studies [17, 18, 20–22, 25–28, 32, 33, 35] reporting data on vertebral fractures, 8 on

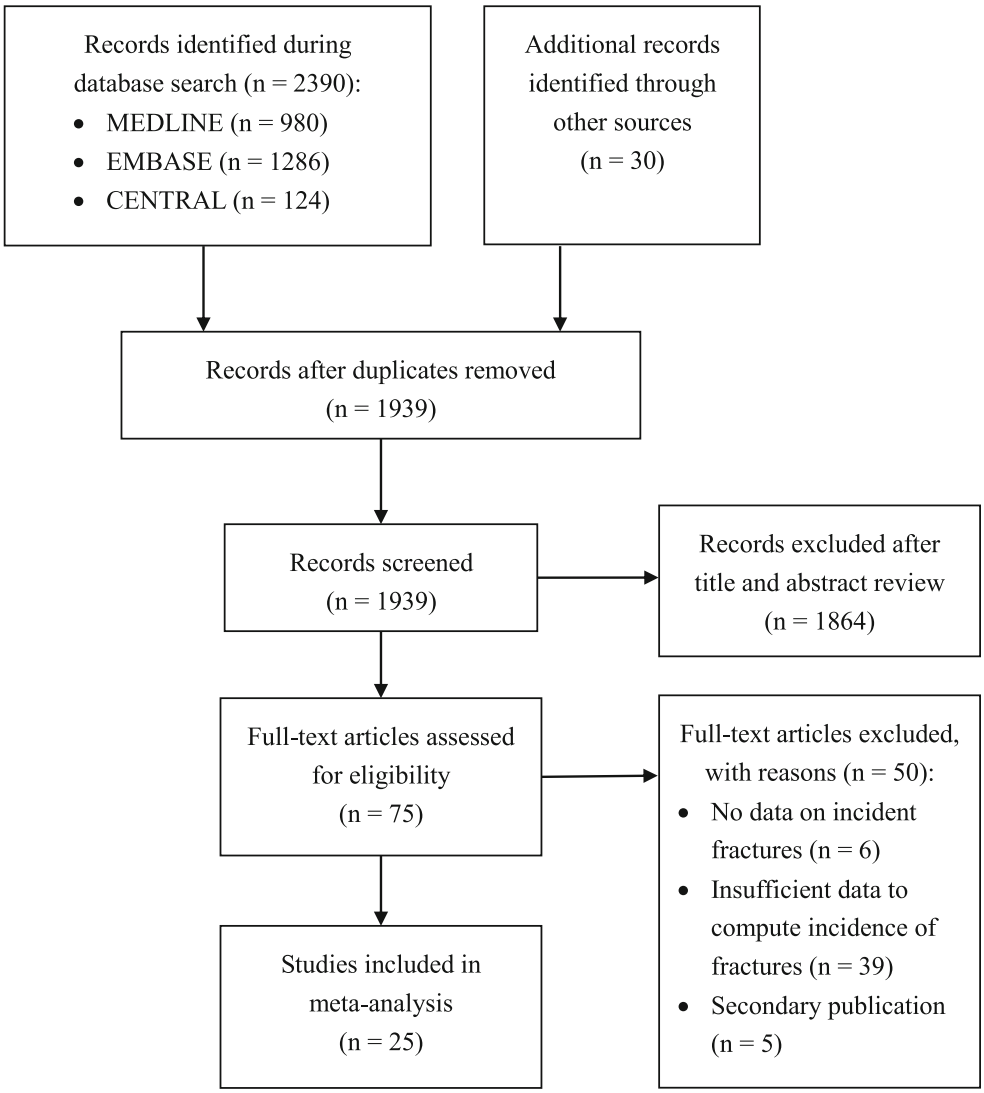


Fig. 1 Study identification and selection process

radial fractures [9, 18, 19, 23, 26, 27, 31, 33] and 6 on humeral fractures [16, 18, 19, 23, 26, 27], which were included in site-specific analyses. Among the 15 studies reporting on hip fractures [9, 11, 18, 19, 22, 23, 25–28, 31–35], two studies [34, 35] from the UK were based on two large primary care databases that have approximately 50–60% overlap, so the one providing more recent data from a larger population was included in the analysis to avoid potential overlap [35]. Among the 23 cohorts, 11 had control groups consisting of matched non-RA participants [8, 11, 19, 23, 25, 27, 29–31, 34, 35]. Risk estimates of all fractures and fragility fractures were reported by three [29, 30, 35] and four studies [8, 23, 25, 27], respectively. Although there was no control group enrolled in the Korean cohort reported by Kim et al. [33], the standard incidence ratio (SIR) of fractures in RA patients was calculated using data from the general population. Thus, three studies [29, 30, 35] were selected for the meta-analysis of all fracture risk, and 5 [8, 23, 25, 27, 33] were selected for the meta-analysis of fragility fracture risk.

Incidence of fractures in RA patients

Incidence rates of all fractures varied widely across the 10 selected cohorts, ranging from 6.94 to 86.27 per 1000 person-years (Fig. 2a). The pooled incidence rate was 33.00 (95% CI 18.39 to 59.21) per 1000 person-years, with significant between-study heterogeneity ($I^2 = 99.7\%$, $P < 0.001$). No significant temporal trend in incidence of all fractures was identified in the cumulative analysis (Fig. 1a in Online Resource 2). We further combined the risk estimates of all fractures from cohorts with control groups (Fig. 3a). The pooled RR for all fractures in RA was 1.52 (95% CI 1.07 to 2.14). Subgroup analysis of the 2 studies including only women participants was performed, and the pooled RR for all fractures in women with RA was 1.77 (95% CI 1.19 to 2.64).

As for fragility fractures, incidence rates from the 10 included cohorts varied from 5.57 to 31.78 per 1000 person-years (Fig. 2b). The pooled incidence rate was 15.31 (10.43 to 22.47) per 1000 person-years, and significant heterogeneity

Table 1 Characteristics of all included studies

Author, year	Country	Participants		Baseline age (year) *	Female (%)	Follow-up (year)**	GC in RA (%)	Fracture ascertainment	Fracture type	Quality score[¶]
		RA	Control							
Michel, 1993 [18]	USA, Canada	1110	–	54 ± 0.4	79.2	8.4[a]	58	Self-report	All, fragility (hip, wrist, shoulder, pelvis, spine)	4
Orstavik, 2004 [19]	Norway	249	249	63.0 ± 6.8;50–72	100.0	16.6[a]	69.5	Self-report	Fragility (low-trauma) non-vertebral	7
van Staa, 2006 [8][†]	UK	30,262	90,783	≥ 40	71.1	4.3[a]	24	ICD codes	Fragility (radius/ulna, humerus, rib, femur/hip, pelvis, vertebrae)	8
Arai, 2006 [20]	Japan	112	–	50–64	100.0	4.0[a]	45.5	Radiologic reports	Radiographic vertebral[f]	4
Katayama, 2008 [21]	Japan	138	–	64.6; 50–79	79.7	2.5[a]	100 (≥ 1 year)	Medical records; radiologic reports	All non-vertebral, radiographic vertebral[f]	7
Coulson, 2009 [22]	USA	8419	–	NR	100.0	NR	NR	Self-report	All, vertebral, hip	4
Kim, 2010 [23]	USA	47,034	235,170	55 (46–64)	72.6	1.6[b]	38.7	ICD codes	Fragility non-vertebral (hip, wrist, humerus, and pelvis)	8
Mazzantini, 2010 [24]	Italy	365	–	NR	66.3	14.2[a] (≥ 10)	81.3	Medical records	Fragility (low-trauma)	5
Wright, 2011 [25]	USA	960	83,295	64.8 ± 7.1; 50–79	100.0[c]	7.8[a]	NR	Self-report	Fragility (spine, arm, elbow, tailbone, hip, upper and lower leg, and foot)	6
Vis, 2011 [26]	Norway, UK, Netherlan-ds	102	–	61 ± 6; 50–70	100.0[c]	5.0[a]	64	Medical records; radiologic reports	All, fragility (low-trauma) non-vertebral, radiographic vertebral[f]	3
Amin, 2013 [27]	USA	1171	1171	W 56 ± 16 M 58 ± 14	70.2	9[b]	67.8	Medical records	All, fragility (non-pathologic low-trauma), MOF (hip, spine, wrist, shoulder)	8
Kawai, 2013 [28]	USA	17,549	–	58 (48–69)	86.3	2[a]	57.9	Medical records	Fragility (low-trauma)	8
Brennan, 2014 [29]	Australia	1008	172,422	64; ≥ 35	100.0	1.0[a]	NR	Radiologic reports	All	6
Gregson, 2014 [30]	International	341	6123	≥ 55	100.0[c]	3[a]	NR	Self-report	All	4
Ochi, 2015 [9][‡]	Japan	9987	–	55.7 ± 13.5	82.0	5.7[a]	44.3	Self-report with medical records	Fragility (low-trauma) non-vertebral	5
Ishida, 2015 [17][‡]	Japan	10,469	–	55.6[d]	81.9[d]	5.8[a]	43.7[d]	Self-report with medical records	Vertebral (low-trauma)	5
Lin, 2015 [11]	Taiwan	33,366	NR	NR	NR	NR	51.6	Insurance database[e]	Hip (non-pathologic)	7
Yamamoto, 2015 [31]	Sweden	8517	741,598	61.2 ± 11.0; ≥ 45	70	NR	NR	ICD codes	Hip, distal radius	7
Ochi, 2016 [16][‡]	Japan	11,907	–	56.6	82.0	5.6[a]	44.2	Self-report with medical records	Humerus (low-trauma)	5
Balasubramanian, 2016 [32]	USA	42,127	–	49.6; 18–64	74	1.6[a]	83.4	ICD codes	Fragility (hip, radius/ulna, pelvis, humerus, femur, vertebral)	7
Kim, 2016 [33]	Korea	3557	–	54.2	85.7	1.5[b]	73.2	Self-report	All, fragility (vertebrae, clavicle, humerus, wrist, femur, ankle)	6
Klop, 2016 [34][†]	UK	11,582	38,755	62.9 ± 11.4; 40–90	67.8	9.0[b]	15.6	Medical records	Fragility (hip, spine, forearm, humerus)	7
Ogdie, 2017 [35]	UK	39,306	821,834	58.7 ± 15.3	69.2	6.3[a]	29.3	ICD codes	All, hip, vertebral	9
Roubille, 2017 [10][§]	France	602	–	48 ± 12	79.1	6.0[a]	64.1	Medical records	All	6

Table 1 (continued)

Author, year	Country	Participants		Baseline age (year) *	Female (%)	Follow-up (year)**	GC in RA (%)	Fracture ascertainment	Fracture type	Quality score[¶]
		RA	Control							
Suzuki, 2017 [36]	Japan	96 (OP)	–	70.0 ± 0.8	100[c]	2.0[a]	21.9	Medical records	Fragility non-vertebral and vertebral	4

MOF, major osteoporotic fracture; *OP*, osteoporosis

*Data are presented as mean ± SD, median (interquartile range) or range

**Data are presented as [a] mean or [b] median

[†] Two cohort studies based on the same database GPRD/CPRD in the UK but having separate follow-up periods (1987 to 2002 vs. 2004 to 2013) reporting on non-overlapping fracture cases

[‡] Studies from the IORRA cohort with data on different fracture sites ascertained by self-reports and confirmed with medical records

[§] Only enrolled patients with early RA (disease duration < 6 months)

[¶] Detailed assessment is presented in Online Resource 1

[c] Postmenopausal women

[d] Data derived from 10,240 patients

[e] Medical records from the National Health Insurance Research Database (NHIRD) in Taiwan, data in which is refreshed every year

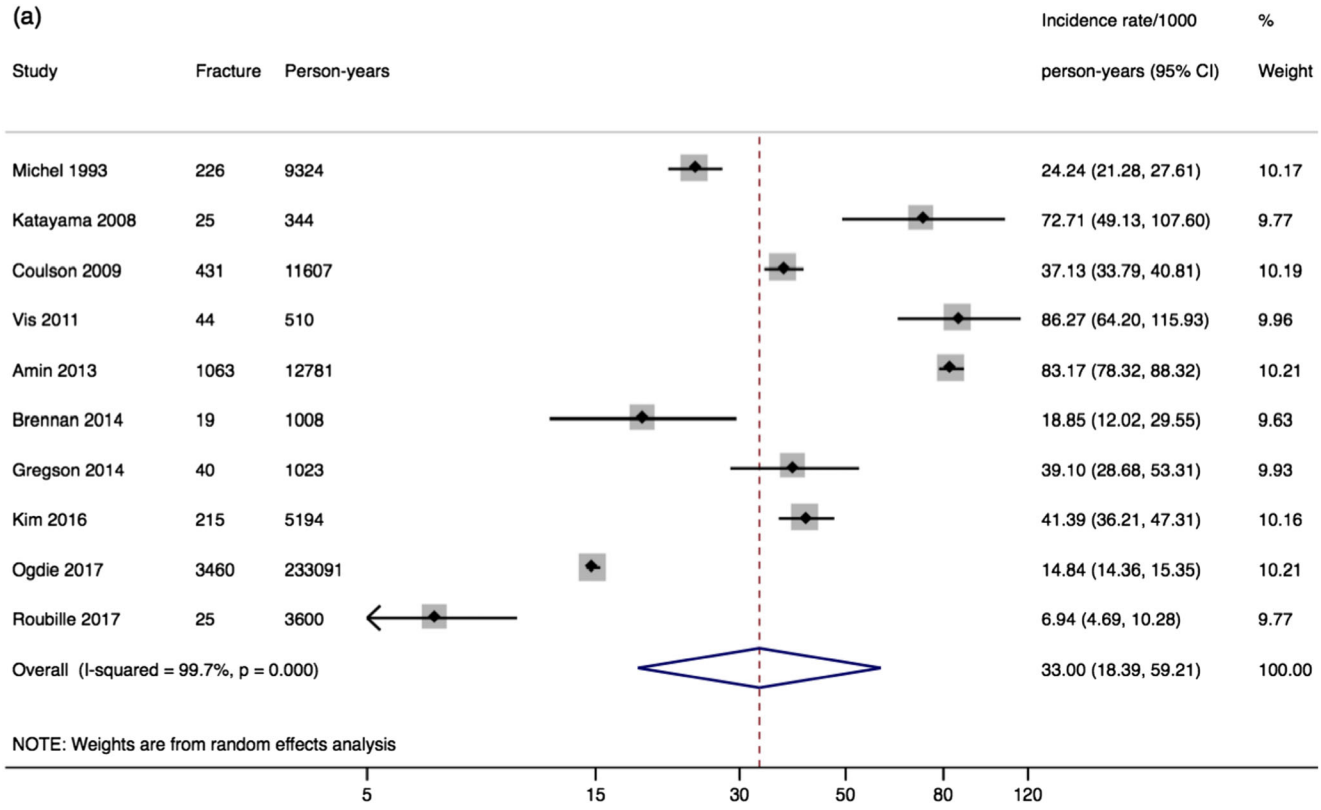
[f] Radiographic vertebral fractures were diagnosed through X-ray screening

was also noted ($I^2 = 99.3\%$, $P < 0.001$). According to subgroup analyses by study characteristics shown in Table 2, the pooled incidence rate of fragility fractures was likely to be higher in studies conducted in Asia than in North America or Europe. The pooled incidence rate of fractures among women with RA was significantly higher than that among men [31.03 (95% CI 28.75 to 33.50) vs. 23.75 (19.59 to 28.78) per 1000 person-years, $P = 0.011$]. None of the other selected study characteristics were significantly associated with the pooled incidence rate and capable of explaining the observed heterogeneity. The cumulative analysis showed no apparent temporal change in the incidence of fragility fractures (Fig. 1b in Online Resource 2). Pooled risk estimates showed that patients with RA were at increased risk of developing fragility fractures compared with non-RA controls (RR 1.61, 95% CI 1.44–1.79) (Fig. 3b). Subgroup analyses by sex or definition of fragility fracture showed no significant changes in heterogeneity.

In addition, site-specific incidence rates of major osteoporotic fractures were also calculated in the subgroup analyses (Table 2 and Online Resource 3). The pooled incidence rate of vertebral fractures was 7.51 (95% CI 3.27 to 17.23) per 1000 person-years. In the subgroup analysis based upon vertebral fracture detection method, the pooled incidence rate of radiographic fractures was significantly higher than that of clinical fractures [42.40 (95% CI 32.47 to 55.36) vs. 4.29 (1.69 to 10.89) per 1000 person-years, $P < 0.001$]. Significant between-study heterogeneity was noted in the overall analysis and the clinical subgroup, but not in the radiographic subgroup ($I^2 = 0\%$). The pooled incidence rates of fractures at the hip, forearm, and proximal humerus were 4.33 (95% CI 2.26 to 8.27), 3.40 (2.27 to 5.10), and 1.86 (1.36 to 2.53) per 1000 person-years, respectively. There was notable heterogeneity across studies for all three fracture sites (hip: $I^2 = 99.7\%$, $P < 0.001$; forearm: $I^2 = 95.6\%$, $P < 0.001$; humerus: $I^2 = 77.9\%$, $P < 0.001$).

Sensitivity analysis

After we serially removed each study from the analysis, pooled incidence rates ranged from 29.67 to 39.06 per 1000 person-years for all fractures and from 14.03 to 17.37 per 1000 person-years for fragility fractures (Online Resource 4). Removal of the study by Roubille et al. [10], which included only early RA patients with disease duration less than 6 months, resulted in a notably higher incidence rate of all fractures (39.06 per 1000 person-years). As for fracture site-specific incidence rates, the results ranged from 6.39 to 9.15 per 1000 person-years for vertebral fractures, from 3.67 to 4.85 for hip fractures, from 3.10 to 3.87 for forearm fractures, and from 1.65 to 2.08 for fractures at the proximal humerus. After we excluded the study by Ogdie et al. [35], the incidence rate of



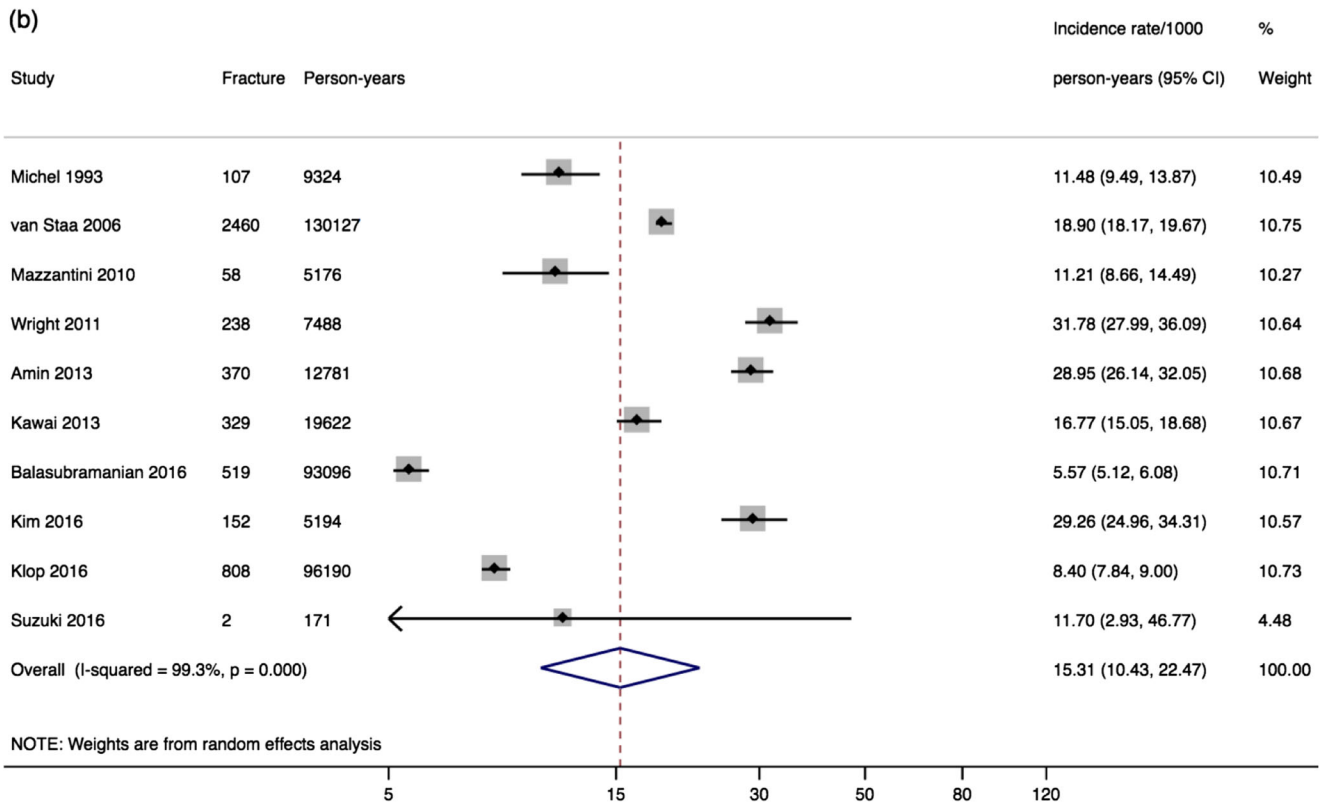


Fig. 2 Pooled incidence rates of fractures among patients with RA. **a** All fractures. **b** Fragility fractures

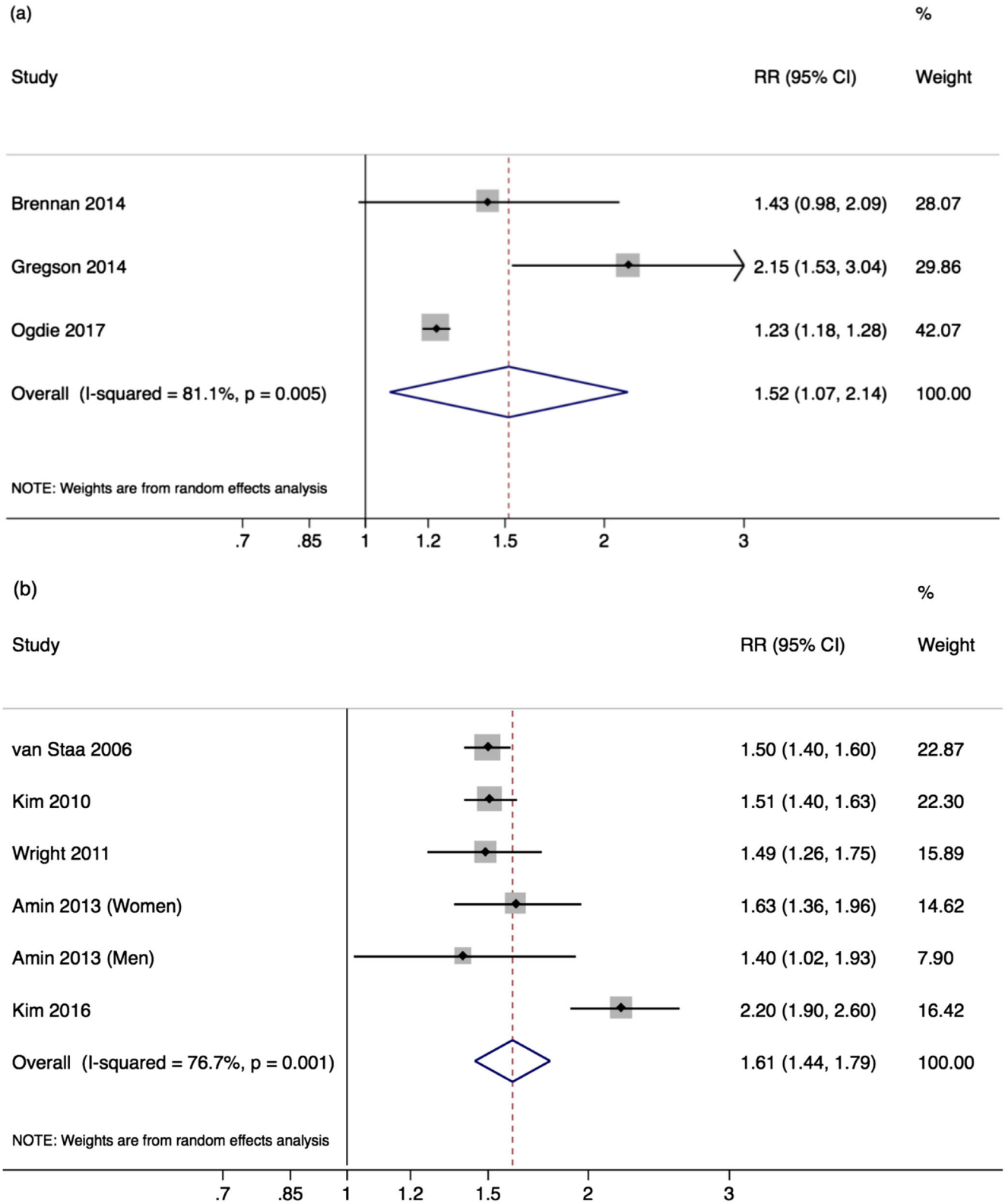


Fig. 3 Meta-analysis of fracture risk in RA patients compared to non-RA controls. **a** All fractures. **b** Fragility fractures

vertebral fractures increased substantially (9.15 per 1000 person-years). According to the authors, the detection method for vertebral fractures used in their study (clinical fractures identified using diagnosis codes) likely contributed to under reporting of vertebral fracture occurrence. Removal of the study by Lin et al. [11], which reported

Table 2 Subgroup analysis of the incidence rate of fragility fractures, by study characteristics and major osteoporotic fracture site

	No. of studies	No. of RA patients	Incidence rate/1000 person-years (95% CI)	I^2 (%)	*P* value	*P* value*
Total	10	108,779	15.31 (10.43–22.47)	99.3	< 0.001	
Geographic region						
North America	5	62,917	15.81 (7.67–32.59)	99.5	< 0.001	0.374
Europe	3	42,209	12.14 (6.43–22.90)	99.5	< 0.001	
Asia	2	3653	24.21 (11.69–50.13)	39.8	0.198	
Sex						
Women	4	4927	31.03 (28.75–33.50)	0.0	0.556	*0.011*[b]
Men	2	857	23.75 (19.59–28.78)	0.0	0.635	
Mixed only[a]	6	102,995	11.14 (6.98–17.78)	99.4	< 0.001	
Fracture ascertainment method						
Self-reports only	3	5627	22.09 (12.37–39.47)	97.6	< 0.001	0.158
With other methods	7	103,152	12.91 (8.09–20.62)	99.4	< 0.001	
Definition of fragility fractures						
Fracture sites	6	89,598	14.52 (8.62–24.47)	99.6	< 0.001	0.576
Low-trauma	3	19,085	17.79 (10.95–28.90)	97.4	< 0.001	
Percentage of GC treatment						
≥ 60%	4	47,220	15.17 (5.67–40.61)	99.0	< 0.001	0.792
< 60%	5	60,599	13.12 (8.41–20.48)	99.6	< 0.001	
Sample size						
≥ 1000	7	107,358	14.63 (9.38–22.81)	99.5	< 0.001	0.752
< 1000	3	1421	17.19 (7.01–42.15)	96.2	< 0.001	
Site-specific analyses of MOFs						
Vertebral	13	125,020	7.51 (3.27–17.23)	99.5	< 0.001	
Clinical	10	124,668	4.29 (1.69–10.89)	99.6	< 0.001	*< 0.001*
Radiographic	3	352	42.40 (32.47–55.36)	0.0	0.873	
Hip	15	213,454	4.33 (2.26–8.27)	99.7	< 0.001	
Forearm	9	71,727	3.40 (2.27–5.10)	95.6	< 0.001	
Humerus	7	61,573	1.86 (1.36–2.53)	77.9	< 0.001	

GC, glucocorticoid; *MOF*, major osteoporotic fracture; *RA*, rheumatoid arthritis

**P* values in this column represent differences between the categories within each subgroup. Significant results (*P*<0.05) were presented in italic letters

[a] Studies that included patients of both sexes but did not provide data separately

[b] *P* value for the difference between men and women

data from an annually refreshed insurance database and is therefore somewhat different from typical cohort studies, led to a much lower incidence rate of hip fractures (3.67 per 1000 person-years).

Assessment of publication bias

Publication bias was investigated using funnel plots and the Egger test. Visual inspection of the funnel plots revealed mild to moderate asymmetry (Online Resource 5). According to Egger's test, there was no evidence of publication bias in studies reporting on all fractures ($P = 0.348$), fragility fractures ($P = 0.928$), vertebral fractures ($P = 0.790$), hip fractures ($P = 0.140$), forearm fractures ($P = 0.873$), and fractures at the proximal humerus ($P = 0.282$).

Predictors of fractures

A summary of significant predictors of fractures in multivariate analyses or adjusted analyses reported by the included studies is presented in Table 3. Though predictors varied across studies, some of them remained consistent, including traditional factors such as older age [10, 16–18, 23], female gender [10, 17, 18, 23], low body mass [8, 18], known diagnosis of osteoporosis or lower bone mineral density (BMD) at the hip [18, 26], history of prior fracture [16, 17, 23, 26, 33], and use of oral glucocorticoids [8, 16–18, 22, 23, 28, 32]. However, bisphosphonates and other osteoporosis drugs, which were used to protect patients from fractures, were also positively correlated with fractures in some studies [16, 17, 23, 33]. As for RA-specific factors, disease duration [8, 18], disease activity [measured with the disease activity score 28

Table 3 Predictors of fractures reported by the included studies

Author, year	Significant predictors of fractures
Michel, 1993	Older age, years taking prednisone, previous diagnosis of osteoporosis, disability, lack of physical activity, female sex, disease duration, impaired grip strength, low body mass
van Staa, 2006	> 10 years' duration of RA, low body mass, use of oral glucocorticoids
Coulson, 2009	Menopausal status, mHAQ, prednisone
Kim, 2010	Older age, female sex, oral glucocorticoid use, osteoporosis drugs, SSRIs, anticonvulsants, and opioids, history of Parkinson's disease, prior fall and fracture, hospitalization, number of physician visits and prescription drugs, comorbidity index
Vis, 2011	BMD of the total hip, history of fracture
Amin, 2013	Extra-articular manifestations, major joint surgeries
Kawai, 2013	> 10 mg/d GC use
Ishida, 2015	Older age, female sex, DAS28, HAQ-DI, history of any prior fracture, baseline daily prednisolone dose, bisphosphonate use
Ochi, 2016	Older age, CRP level, history of fracture, daily prednisolone dose, oral bisphosphonate
Balasubramanian, 2016	Daily use of corticosteroid, accumulative dose of corticosteroid
Kim, 2016	Older age, history of fracture, higher HAQ, use of bisphosphonate
Roubille, 2017	Older age, female sex

CRP, C-reactive protein; *DAS28*, disease activity score 28; *GC*, glucocorticoid; *HAQ-DI*, health assessment questionnaire-disability index; *mHAQ*, modified health assessment questionnaire score; *SSRI*, selective serotonin reuptake inhibitor

(DAS28) or serum C-reactive protein (CRP) level] [16, 17], and factors related to function and quality of life [impaired mobility, disability, or higher Health Assessment Questionnaire (HAQ) score] [17, 18, 22, 33] were found to be significant predictors of fractures.

Discussion

Fragility fracture is one of the most prevalent comorbidities among patients with RA, and is associated with poor prognosis [6, 11]. Although numerous studies have demonstrated the increased risk of fractures in this population, the absolute fracture risk has varied widely among studies and has not been well studied via meta-analyses. To our knowledge, this is the first systematic review and meta-analysis to investigate the pooled incidence rates of fractures in RA patients and also to evaluate fragility fractures separately as a special subgroup. In the present study, the pooled incidence rates of fractures were estimated among over 280,000 patients with RA across 23 cohort studies. We found that fragility fractures were likely to account for approximately half of all fractures in RA patients (15.31 per 1000 person-years vs. 33.00 per 1000 person-years).

Our study further examined potential sources of heterogeneity between studies included in our meta-analysis that may influence the stability of calculated incidence rates. Subgroup analyses suggested that women with RA have a higher risk of fragility fractures, consistent with previous results from the general population [37]. Although the definition of fragility fractures varied across studies based on either fracture site or cause of fracture, incidence rates of fractures were similar between these two subgroups. Other potential sources of between-study heterogeneity included ethnicity, history of fractures, the geographic region where the study was carried out, and fracture ascertainment method. Regarding the latter, according to a study by Chen et al. [38], validity of self-reported fractures varied significantly by fracture site [highest for the wrist (81%) and lowest for the spine (51%)]. In the present study, there was no statistically significant difference in the pooled incidence rates between categories within these subgroups. It is possible that our ability to detect differences within these subgroups were limited by power in certain cases, or that differences were obscured by heterogeneity from other sources. Future efforts to standardize study designs between cohorts across different countries are necessary to enable better comparison of incidence of fracture rates among RA patients from different geographic regions and ethnicities. In addition, our study did not find evidence for change in fracture incidence over time. More studies are necessary to evaluate the presence of potential temporal trends in fracture risk, for example, as a result of changes over time in therapeutic strategies in RA and earlier control of inflammation.

Among the four MOF sites, the spine was the most commonly affected site in our study, almost accounting for half of all fragility fractures (7.51 vs. 15.31 per 1000 person-years). Subgroup analysis based upon vertebral fracture detection method demonstrated that compared with radiographic screening, clinical detection based on symptoms could result in a marked underestimation of vertebral fractures (42.40 vs.

4.29 per 1000 person-years). This finding was generally consistent with previous epidemiological studies, which indicated that more than three quarters of vertebral fractures remained undiagnosed without spine imaging [39], and much lower heterogeneity existed among studies around the world reporting on incidence of radiographic fractures [37]. Since the presence of vertebral fracture is diagnostic of osteoporosis (OP) regardless of bone mineral density [40] and an independent predictor of future fractures [41], our results support the important role of vertebral imaging for fracture risk assessment in the management of RA patients in the appropriate clinical setting. Both the standard semi-quantitative grading system by Genant and the vertebral fracture assessment (VFA) are validated tools for vertebral imaging in RA patients [42]. For the general population, guidelines (e.g., the 2014 US National Osteoporosis Foundation guidelines) have been published emphasizing the importance of identifying vertebral fractures and recommend more frequent use of vertebral imaging for fracture risk assessment in patients with older age, decreased BMD, height loss, and use of GCs [40, 41]. Future studies are needed to evaluate the cost-effectiveness of these existing strategies in patients with RA and develop guidelines applicable for this population.

Based upon the cohorts in our meta-analysis that included control populations, we calculated the relative risks of both all fractures and fragility fractures in individuals with RA compared with those without RA. Like previous studies, we found that fracture risk is increased among patients with RA [8, 23, 25, 27]. Xue and colleagues published a meta-analysis of 13 observational studies (including seven case-control studies and six cohort studies) with the goal of comparing fracture risk between patients with RA and controls. Their results demonstrated that men and women with RA are at higher risk of both overall fractures (RR 2.25, 95% CI 1.76–2.87) and site-specific fractures at two MOF sites [vertebral (including studies that defined vertebral fractures either clinically or radiographically): RR 2.93, 2.25–3.83; hip: RR 2.41, 1.83–3.17] [12], which was consistent with another meta-analysis by Chen et al. focusing on vertebral fractures (RR 2.34, 2.05–2.63) [2]. Differences in RR between meta-analyses may be attributable to differences in criteria for study inclusion (e.g., all observational studies in previous meta-analyses or only cohorts in the present study). Our study provides meaningful added context because we took into account the spectrum of fracture definitions adopted by the studies included, and quantified the specific increased risk associated with fragility fracture defined both by site of fracture and cause of fracture.

A number of risk factors have been shown to predispose patients with RA to incident fractures. We summarized predictors of fracture identified by each study and found that traditional risk factors for fragility fracture in the general population [40] (e.g., older age, female sex, low body mass, low BMD, lack of physical activity, and history of prior fracture or fall) were commonly associated with increased fracture risk among patients with RA. Several RA-related clinical characteristics were also frequently reported as predictors of fractures, including disease duration and disease activity level, likely reflecting the association between chronic inflammation and bone loss. This association has been attributed to the impact of inflammatory mediators on bone remodeling, which results in increased bone resorption and impaired bone formation by affecting the differentiation and activity of osteoclasts and osteoblasts [3]. Measures of functional disability and quality of life, as reflected in different versions of the HAQ, are directly related to level of physical activity and immobilization, and may in turn reflect fracture risk in RA patients [17, 33]. As for the influence of medications, long-term GC treatment is an independent risk factor for fracture, and the importance of the prevention of glucocorticoid-induced osteoporosis (GIOP) in rheumatology has been well-established [43]. In most of the studies included, GC-related factors were reported as predictors of fractures [8, 16–18, 22, 23, 28, 32]. A few studies did not find an association; however, this may be due to insufficient statistical power [26, 33] or the relative safety of low-dose GC therapy in patients with early RA [10]. We attribute the association found between bisphosphonate use and fracture risk to indication bias [33]. Due to insufficient data regarding the association between other RA treatments and fracture rates, we did not conduct a summary of the influence of DMARDs or biologic therapies on fracture rates in this review.

Currently, a number of fracture risk assessment tools are applied in clinical practice, and among them, the FRAX tool is the most widely used [44]. FRAX includes demographic factors as well as disease-related factors such as RA and use of GCs. Unfortunately, while glucocorticoids have a dose-dependent impact on fracture risk, this risk factor is only accounted for in a binary fashion in FRAX. In 2011, Kanis et al. proposed that for individuals receiving the equivalent of more than 7.5 mg prednisone/day, the FRAX-generated fracture risk should be increased by 15% for MOFs and 20% for hip fractures [45]. This recommendation has recently incorporated into the "2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis" [43], which may improve adoption of this adjustment in clinical practice. Unfortunately, FRAX does not take into account other RA-related clinical risk factors such as disease activity, duration, and functional disability. Furthermore, for patients with RA who are younger (FRAX applies only to individuals aged 40–90 years) or not treated with GCs, but have increased fracture risk [25, 27], additional studies are needed to develop new strategies to improve the ability of clinicians to assess fracture risk.

Our study has limitations that warrant mention. Data provided in this review were derived from studies that varied in study design, study population, sources of data, ascertainment of fractures, and reported fracture types. The significant heterogeneity across studies remained even after subgroup analyses examining several key study characteristics. It is possible that the heterogeneity is multifactorial in nature or that individual subgroup analyses were underpowered to show the full impact of certain study characteristics. Furthermore, due to the limited number of included studies available for certain subgroup analyses (e.g., studies reporting separate data on male patients), this review mainly provides data on the incidence of fractures in the overall population of patients with RA. Pooled incidence rates of fractures for subgroups of patients may be unstable and should be interpreted with caution. Finally, although publication bias was not identified by Egger's test, the funnel plots still revealed mild to moderate asymmetry. Therefore, publication bias may exist in this study despite our attempts to minimize this during the search and screening process.

Conclusions

This systematic review and meta-analysis found that patients with rheumatoid arthritis are at higher risk of both overall incident fracture and fragility fracture. The pooled incidence rates of all fracture and fragility fracture were 33.00 and 15.31 per 1000 person-years, respectively. The vertebral spine is the most common site of fragility fracture; therefore, more active identification of patients who may benefit from vertebral imaging may help with early diagnosis and intervention. In addition to traditional OP risk factors, RA-specific factors including duration of RA, disease activity, and HAQ score should also be considered during the assessment of fracture risk. Finally, when appropriate, FRAX scores should be adjusted for patients receiving GC therapy.

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Compliance with ethical standards

Conflicts of interest None.

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