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Bone fracture risk in patients with rheumatoid arthritis

A meta-analysis

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Abstract

Background: Patients with rheumatoid arthritis (RA) are predisposed to osteoporotic fracture. The present study aims to determine the association between rheumatoid arthritis (RA) and bone fracture risk, and in relation to gender and site-specific fractures.

Methods: Studies related to bone fracture in patients with RA were searched from databases including PubMed, EMBASE, and OVID from inception through April 2016. The quality of the studies was evaluated using the Newcastle-Ottawa Scale. Meta-analysis was performed with Stata13.1 software. The results were reported based on risk ratio (RR) and 95% confidence interval (95% CI) using a random effects model.

Results: The meta-analysis of 13 studies showed a significant higher risk of bone fracture in patients with RA than in patients without RA (RR = 2.25, 95% CI [1.76–2.87]). Subgroup analyses showed that both female and male patients with RA had increased risk of fracture when compared with female and male patients without RA (female: RR = 1.99, 95% CI [1.58–2.50]; male: RR = 1.87, 95% CI [1.48–2.37]). Another subgroup analysis of site-specific fracture also showed that RA is positively correlated with the incidence of vertebral fracture (RR = 2.93, 95% CI [2.25–3.83]) or hip fracture (RR = 2.41, 95% CI [1.83–3.17]).

Conclusion: RA is a risk factor for bone fracture in both men and women, with comparable risks of fractures at the vertebral and hip.

Abbreviations: 95% CI = 95% confidence interval, ACR = American College of Rheumatology, ARA = American Rheumatism Association, BMD = body mass density, BMI = body mass index, BMP-2 = bone morphogenetic protein 2, FRAX = Fracture Risk Assessment, HR = hazard ratio, IL = interleukin, MTX = methotrexate, NOS = Newcastle–Ottawa scale, OR = odds ratio, RA = rheumatoid arthritis, RANKL = nuclear factor kappa B ligand, RR = risk ratio, SMR = standard mortality rate, TNF-α = tumor necrosis factor-α.

Keywords: bone fracture, meta-analysis, osteoporosis, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA), a systemic autoimmune disorder that primarily affects the synovial tissues, is one of the most debilitating types of arthritis affecting approximately 1–2% of the world population. RA causes inflammation, pain, stiffness, swelling, and disability of the joint, thus limiting mobility in the affected joints and curtailing individuals with RA the ability to perform basic daily tasks. The onset of RA is typical during middle age, although reports have also suggested the development of RA at a younger age,[1] and the incidences of RA are 2 to 3 times more common in women than in men[2,3].

Patients with RA are at risk of osteoporosis and osteoporotic fractures.[4–6] Clinical studies have shown that the incidence of osteoporosis among RA patients is 1.9 times higher than among non-RA patients.[7] Bone loss in RA has been associated with many factors including chronic inflammation, use of glucocorticoids, and physical inactivity. The release of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) may cause the abnormal production of osteoclasts, thus disrupting the equilibrium between bone resorption and bone formation.[8–10] Secretion of receptor activator of nuclear factor kappa B ligand (RANKL) by activated T lymphocytes has also been observed to induce the differentiation of synovial macrophages into osteoclasts, leading to bone loss.[11,12] Oral glucocorticoids, clinical drugs commonly used to suppress RA-induced inflammation, can ironically promote the loss of bone mass by inhibiting the differentiation and activity of osteoblasts through the blockage of bone morphogenetic protein 2 (BMP-2) [13] or the Wnt/beta-catenine pathways.[14,15] Meanwhile, immobility resulting from RA-induced muscle pain, weakness, and swelling may increase the risk of falling by a

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certain extent,[16,17] thereby raising the rate of bone fracture. The mortality rate from osteoporotic fractures is higher than any other mortality including cervical cancer, uterine cancer, or breast cancer.[18] Therefore, the study of osteoporosis and osteoporotic fracture in RA patients is important for the early intervention and prevention of bone fracture.

Over the years, numerous observational studies have associated patients with RA with the increased risk of osteoporosis fracture involving mainly the hip or vertebral.[19–21] However, most clinical studies performed are either limited in sample size, restricted to certain subpopulation, or are fracture-site specific. The risk of bone fracture in RA patients has not been summarized and little is known whether the risk of fracture is site-specific. To the best of our knowledge, no meta-analysis has been performed to conclude the assessment of bone fracture risk in RA patients. Therefore, the present study aims to evaluate the overall risk of bone fracture associated with RA.

2. Materials and methods

This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[22] guidelines. As a meta-analysis study based on previous studies, ethical approval and informed consent were, therefore, not required.

3. Inclusion criteria

3.1. Participants

Subjects were eligible for inclusion if they were diagnosed with RA based on the diagnostic criteria published by the American Rheumatism Association (ARA)[23] or the American College of Rheumatology 1987 (ACR).[24] Eligibility of subjects was not restricted by race and sex. Subjects without RA and any other conditions that are known to affect bone mass are defined as the control group.

3.2. Studies outcomes

The primary outcome of interest is the incidence of bone fracture. The secondary outcome of interest is the incidence of hip fracture or vertebral fracture (also known as the spine fracture).

3.3. Types of studies

Only retrospective or prospective studies published in English or Chinese were included.

3.4. Exclusion criteria

The exclusion criteria were as follows:

(1) Studies on subjects without clearly defined diagnosis, and inclusion and exclusion criteria.
(2) Studies that reported the rate of mortality as outcome, that is, standard mortality rate (SMR).
(3) Studies with inaccurate or incomplete data and were unable to provide outcome.
(4) Studies published repeatedly.

3.5. Search strategy

We conducted a systematic search in PubMed, EMBASE, and OVID databases using the MeSH terms and free key words "rheumatoid arthritis" combined with "Fracture," to identify relevant studies published from inception through April 1, 2016. Language restrictions were not employed. We also searched the reference lists for full-text papers and all relevant publications were reviewed to identify any omitted studies.

3.6. Literature selection

Literatures were imported into EndNote software to check for completeness of volume, issue, and abstract. Important information was copied and edited; and, the literatures that met the criteria were retained. For the manuscripts that did not fulfill inclusion criteria, the original documents were read to determine eligibility; literatures were marked with "include," "pending," or "exclude" (with reasons). For articles marked with "pending," full-text articles were retrieved from references and further reviewed to determine eligibility.

3.7. Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the studies included. Specifically, the studies were evaluated on 8 items, categorized into 3 aspects: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. NOS employed the star system to provide a semi-quantitative appraisal for the overall quality of each cohort study. The highest quality studies were awarded up to 9 stars.

3.8. Data extraction

A self-designed data abstraction form was used to record the following information: first author and publication year, type of study, country where the study was conducted, inclusion criteria of participants, cases of RA, incidences of fractures in RA and non-RA participants, outcome measurement, confounders adjusted for, and matching baseline factors.

Data selection, evaluation, and extraction were performed by 2 independent investigators. Discrepancies were solved by discussion to consensus or by the assistance of a third investigator.

3.9. Outcome measurement

The primary outcome of interest for our study is the indicators associated with RA and bone fracture, which is calculated in risk ratio (RR), odds ratio (OR), and hazard ratio (HR) with 95% confidence interval (CI).

3.10. Statistical analysis

Statistical analysis was conducted using Stata13.1 software. All ratios (risk ratio (RR), odds ratio (OR), and hazard ratio (HR)) were combined to obtain an accurate and comprehensive statistical analysis.[25] Pooled RR and its 95% confidence interval (CI) were calculated. A chi-squared test (χ^2) was used to test the included studies for statistical evidence of heterogeneity, and the degree of heterogeneity among studies was assessed with I^2 statistic. When no significant heterogeneity was observed ($P > .1$, $I^2 \leq 50\%$), data were analyzed using the fixed-effects model. When heterogeneity was observed ($P \leq .1$, $I^2 > 50\%$), the studies were analyzed with the random-effects model. The sources of heterogeneity were evaluated by subgroup analyses (i.e., sex and site-specific fractures).

A sensitivity analysis was performed to assess the robustness of the overall effect size. The included studies were omitted one at a time and the pooled RRs were recalculated to determine if there was any change to the overall estimates.

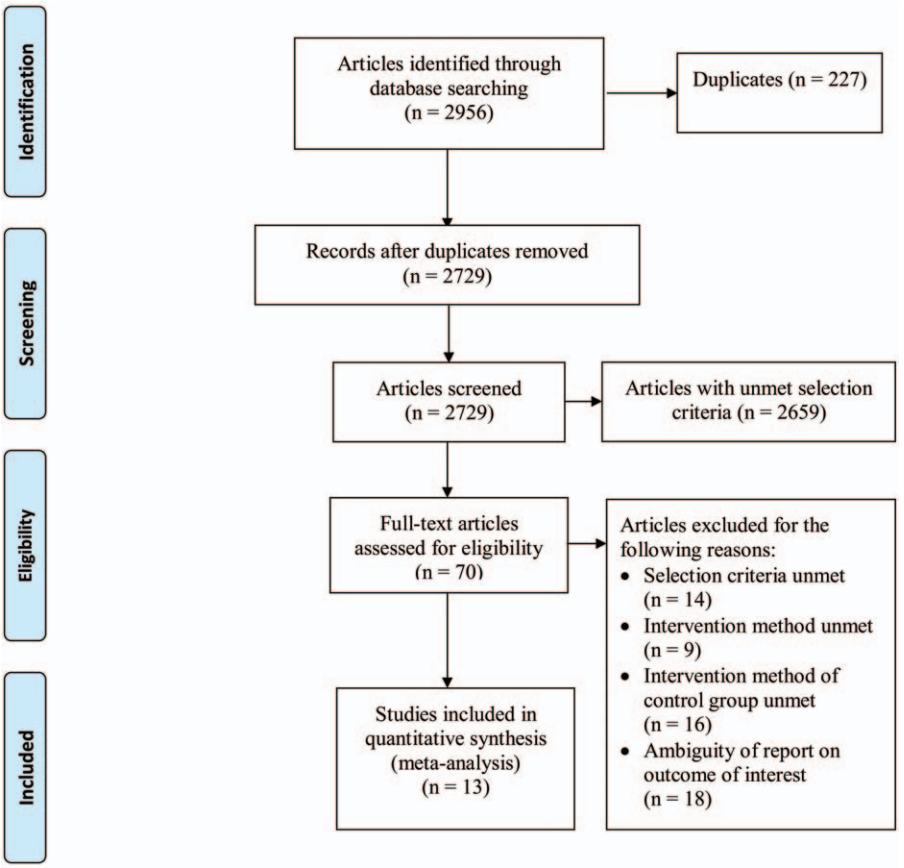

Figure 1. Study selection flow diagram.

Publication bias was assessed using the funnel plot. An asymmetry in the plot was further evaluated using Egger's test. $P < .05$ was considered to be significantly bias.

4. Results

4.1.1. Study selection

A total of 2956 articles were identified using the systematic literature search; 227 duplicates were removed, and 2659 articles did not meet the selection criteria. The remaining 70 full-text articles were retrieved for detailed evaluation. In total, 57 articles were excluded for the following reasons: did not fulfill selection criteria (n = 14), did not meet intervention method (n = 9), control group did not meet intervention method (n = 16), and ambiguous outcome (n = 18). Thus, 13 articles met the inclusion criteria for this meta-analysis (Fig. 1).[4,19–21,26–34]

4.2. Quality assessment

Individual studies were scored on the Newcastle-Ottawa Scale (NOS); 9 studies scored 8 out of 9,[4,19,21,26,27,30,31,33,34] 2 studies scored 7 out of 9,[28,32] and 2 studies scored 6 out of 9[20,29] (Table 1). Overall, the 13 included studies were considered as high-quality studies.

Table 1

Quality assessment of included studies.

	Selection				Comparability	Outcome			
Included studies	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at the start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up for of cohorts	Score
Spector et al 1993[33]	★	★	★	★	★★	★		★	8
Cooper et al 1995[27]	★	★	★	★	★★	★		★	8
Peel et al 1995[32]	★	★	★	★	★	★		★	7
Huusko et al 2001[29]	★	★	★	★		★		★	6
Ørstavik et al 2004[31]	★	★	★	★	★★	★		★	8
van Staa et al 2006[21]	★	★	★	★	★★	★		★	8
Weiss et al 2010[34]	★	★	★	★	★★	★		★	8
Kim et al 2010[19]	★	★	★	★	★★	★		★	8
Wright et al 2011[4]	★	★	★	★	★★	★		★	8
Ghazi et al 2012[28]	★	★	★	★	★	★		★	7
Amin et al 2013[26]	★	★	★	★	★★	★		★	8
Brennan et al 2014[20]	★	★	★	★		★		★	6
Liu et al 2014[30]	★	★	★	★	★★	★		★	8

Table 2

Characteristics of studies on the association between rheumatoid arthritis and bone fracture risk.

Author, year	Type of study	Region	Inclusion criteria of participants	No. of RA patients	No. of fracture in RA patients	No. of non-RA patients	No. of fracture in non-RA patients	Fracture site	Outcome measurement	Confounders adjusted for	Matching factors
Spector et al 1993[33]	Retrospective-cohort study	United Kingdom	The case groups were postmenopausal women aged 45–65 with RA who consecutively attended clinics in 5 London hospitals. All were white, were not taking replacement estrogens, and had agreed to have their bone density measured before entering the drug study. The controls were 713 postmenopausal women aged 45–65 not taking hormone replacements, who were obtained from the age-sex register of a large general practice in London.	Female 191	Female 18	Female 713	Female 44	Vertebral fracture	Female OR = 2.1 (1.2–3.7)	–	Age, years since the menopause, height, weight, and smoking habits.
Cooper et al 1995[27]	Case-control study	United Kingdom	The case group comprised 300 patients (60 men and 240 women) aged 50 years and over who were admitted sequentially to an orthopedic unit over an 18 month period with fracture of the proximal femur, and who were able to pass an abbreviated mental test. Patients in the study group were compared with 600 community controls (120 men and 480 women), residing in the same district, who were selected from the register of Hampshire Family Practitioner Committee.	Both 14 Male 1 Female 13	Both 300 Male 60 Female 240	Both 14 Male 2 Female 12	Both 600 Male 120 Female 480	Hip fracture	Both OR = 2.1 (1.0–4.7) Female OR = 2.4 (1.0–5.4) Male OR = 1.0 (0.1–11.0)	–	Sex and age within 4 years
Peel et al 1995[32]	Retrospective-cohort study	United Kingdom	The case group comprised 76 postmenopausal women with RA (ages 50–79 (mean 65 years), and 347 women from a population based group (ages 50–79 (mean age 64 years) as controls. There was no difference in menopausal age between the groups (mean time since menopause 16 years in the RA group compared with 18 years in the controls).	Female 76	Female 21	Female 347	Female 20	Vertebral fracture	Female OR = 6.2 (3.2–12.3)	–	Menopausal age
Huusko et al 2001[29]	Case-control study	Finland	All patients (373 [72%] women, 144 [28%] men) with acute hip fractures admitted to Jyväskylä Central Hospital in 1991–93 were selected from the hospital discharge register (mean age 78 years). Medical records of these patients were studied retrospectively for RA fulfilling the American Rheumatism Association criteria. The prevalence of RA in patients with hip fractures was compared with the prevalence rates of RA obtained from the nearby city of Tampere.	Both 29	Both 1051	Both 488	Both 141292	Hip fractures	Both RR = 3.26 (2.26–4.70)	Age, sex	
Ørstavik et al 2004[31]	Retrospective-cohort study	Norway	Patients were recruited from a representative subgroup of the RA register who had been part of an epidemiological study including BMD measurements 2 years previously, and year of birth between 1926 and 1948 (age at least 50 at study onset). A single control for each patient was randomly selected from the population register with Oslo.	Both 249	Both 10	Both 249	Both 2	Hip fractures	Hip fractures OR = 9.0 (1.2–394.5)	–	Age, sex, and residential area
Staa et al 2006[21]	Prospective-cohort study	United Kingdom	The study population consisted of all patients aged ≥40 years with at least 1 recorded diagnosis of RA during the period of the General Practice Research Database (for this study, data collection started in 1987 and ended in 2002). Each matched by age, sex, calendar time, and practice to 3 control patients.	Both 30262	Both 2460	Both 90783	–	Any fracture; Hip fractures; Spine fractures	Any fracture RR = 1.5 (1.4–1.6) Hip fractures RR = 2.0 (1.8–2.3) Spine fractures RR = 2.4 (2.0–2.8)	BMI, smoking, fracture history, fall history, general risk factors, and use in the prior 6 months of bisphosphonates, hormone replacement therapy, and thiazides.	Age, sex, calendar time, and practice

(*continued*)

Table 2

(continued).

Author, year	Type of study	Region	Inclusion criteria of participants	No. of RA patients	No. of fracture in RA patients	No. of non-RA patients	No. of fracture in non-RA patients	Fracture site	Outcome measurement	Confounders adjusted for	Matching factors
Weiss et al 2010[34]	Case-control study	Sweden	All individuals registered in the Swedish National Hospital Discharge Register with ICD-9 and ICD-10 codes of hip fractures or vertebral fractures in 1987 to 2004. Median age of the case group was 71 years. Each patient in the fracture cohort was matched with 7 controls. The controls did not have a hip or spine fracture at the time of the matching process or before.	–	–	–	–	Any fractures; hip fractures; vertebral fractures	Both Any fractures OR = 2.9 (2.8–3.1) Hip fractures OR = 2.9 (2.7–3.1) Vertebral fractures OR = 2.7 (2.1–3.4)	–	Sex, age, and residential area
Kim et al 2010[19]	Retrospective-cohort study	United States	Adults aged 18 years or older with at least 2 visits for RA identified with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD 9-CM) code 714.xx, were eligible for this study. Subjects who did not have a diagnosis of RA at any time during the entire study period were eligible to be part of the non-RA cohort for the period 1 January, 2001, to 30 June, 2008.	Both 47034	Both 872 Female 742 Male 130 Hip 311 Female 253 Male 58	Both 235170	Both 3096 Female 2653 Male 443 Hip 1027 Female 873 Male 154	Any fractures; hip fractures	Any fractures Both RR = 1.51 (1.40–1.63) Female RR = 1.49 (1.37–1.62) Male RR = 1.60 (1.32–1.95) Hip fractures Both RR = 1.62 (1.43–1.84) Female RR = 1.54 (1.34–1.77) Male RR = 2.05 (1.52–2.77)	–	Sex, age
Wright et al 2011[4]	Prospective-cohort study	United States	The Women's Health Initiative recruited 161,808 postmenopausal women aged 50–79 years from 40 centers across the country to participate in the clinical trials component. All women were followed for a mean of 7.80 ± 1.54 years.	Female 960	–	Female 83259	Female 12411 Spine 1126 Hip 775	Any fracture; Spine fracture; Hip fracture	Female Any Fracture HR = 1.49 (1.26,-1.75) Spine fracture HR = 1.93 (1.29–2.90) Hip fracture; HR = 3.03 (2.03–4.51)	Age; race; BMI; physical activity; assignment in the HT trial, DM trial, and CaD trial; hospitalizations; falls; smoking; hormone use; parental fracture >age 40; calcium & vitamin D intake; depression score; years since menopause; diabetic treatments; osteoporosis medication; general health score; fracture >55; and joint replacements	
Ghazi et al 2012[28]	Retrospective-cohort study	United States	Consecutive women (56.1 ± 14.2 years) with RA (mean disease duration, 14.9 ± 10 years) who fulfilled the American College of Rheumatology criteria and who attended the Rheumatology Department during a 6-month period, were recruited in the study. Controls (57.3 ± 13.9) randomly selected from the general population.	Female 101	–	Female 303	–	Vertebral fractures	Female OR = 6.5 (3.1–13.9)	BMI	Age

(*continued*)

Table 2

(continued).

Author, year	Type of study	Region	Inclusion criteria of participants	No. of RA patients	No. of fracture in RA patients	No. of non-RA patients	No. of fracture in non-RA patients	Fracture site	Outcome measurement	Confounders adjusted for	Matching factors
Amin et al 2013[26]	Perspective-cohort study	United States	A population-based inception cohort with RA from Olmsted County, Minnesota, 822 women (56± 16 years) and 349 men (58±14 years) diagnosed with RA between 1955 and 2007 (308 women and 110 men diagnosed before age 50) and an equal number of paired non-RA subjects. The median follow-up for each pair of women was 9 years (range: 4 days to 52 years) and for each pair of men was similarly 9 years (range: 16 days to 44 years).	Female 822 Male 349	Female 212 Male 68	Female 822 Male 349	Female 129 Male 43	Any fracture	Female HR=1.78 (1.43–2.21) Male HR=1.65 (1.13–2.42)	–	Sex, birth year
Brennan et al 2014[20]	Retrospective-cohort study	Australia	Women aged 35 years and older, residing in the Barwon Statistical Division (BSD) and clinically diagnosed with RA 1994–2001 were eligible for inclusion as cases (64 years). The control population comprised the entire female BSD population aged 35 years and older, excluding those individuals identified as cases (53 years).	Female 1008	Female 19	Female 172422	Female 1981	Any fracture	Female RR=1.43 (0.98–2.09)	Age	
Liu et al 2014[30]	Retrospective-cohort study	China	A total of 644 RA patients hospitalized from Jan. 2010 to Oct. 2013 were included. All patients were diagnosed as RA patients based on the criteria of American Rheumatism Association and European anti-RA association published in 2009. The patient population includes 119 men and 525 women aged from 16 to 83 years old (52.84±13.5). The course of disease ranges from 1 month to 42 years and the BMI of the patients is (22.14±8.3) kg/m. The patients have no long-term history of medications such as estrogens, androgens, anticoagulants, and drug affecting bone metabolism. The patients were diagnosed without renal dysfunction and thyroid and parathyroid related diseases. Meanwhile, 158 healthy population including 60 males and 98 females were chosen as the control group. The control group has an age range of 24–81 years old and BMI value of (23.94±3.0) kg/m.	Both 644	Both 107	Both 158	Both 6	Vertebral fractures	Both OR=4.716 (1.987–11.192)	Age, sex, BMI	Age, sex, BMI

–=Data not available, HR=hazard ratio, OR=odds ratio, RA=rheumatoid arthritis, RR=risk ratio.

4.3. Characteristics of included studies

A total of 13 studies that reported RR, OR, or HR were included in the meta-analysis to assess the association between RA and bone fracture. The studies were conducted in countries including the United States, United Kingdom, Sweden, Norway, Finland, Australia, and China. Various matching factors were considered when selecting controls, including age, sex, age or years of menopause, height, weight, body mass index (BMI), residential area, and smoking habits. Six studies[4,20,21,28–30] performed adjusted risks of fractures in RA patients to reduce potential confounders involving age, sex, BMI, smoking habits, previous history of fracture or fall, joint or hormone replacement therapy, and calcium, vitamin D, or other medication intake. The characteristics of each study are listed in Table 2.

4.4. Association of RA with bone fracture risk

The risk of a bone fracture was compared between the RA and non-RA patients. Meta-analysis showed strong heterogeneity ($P < .0001$, $I^2 = 96.5\%$) among the studies; thus, a random-effects model was employed to analyze the data. Our results show that patients with RA have a significantly higher risk of bone fracture compared to patients without RA (RR = 2.25, 95% CI [1.76–2.87]) (Fig. 2).

Studies have also suggested that RA affects more women than men. Therefore, we also performed subgroup analysis based on sex. Our results showed that the risks of bone fracture are significantly higher in both women and men with RA than in women and men without RA (women: RR = 1.99, 95% CI [1.58–2.50]; men: RR = 1.87, 95% CI [1.48–2.37]) (Fig. 3A).

Subgroup analyses of site-specific fractures were also performed. The pooled RR for 7 studies[4,21,28,30,32–34] related to the vertebral fracture was calculated. The result indicated a significant association between RA and the vertebral fracture (RR = 2.93, 95% CI [2.25–3.83]). Similarly, subgroup analyses of 7 studies[4,19,21,27,29,31,34] with hip fracture outcomes showed that RA is positively correlated with hip fracture (RR = 2.41, 95% CI [1.83–3.17]) (Fig. 3B).

4.5. Sensitivity analysis

Sensitivity analysis was performed to explore the heterogeneity among studies and to determine whether these factors would have an impact on the overall pooled estimates. Our sensitivity analysis showed that no individual studies significantly affected the pooled RRs (Fig. 4).

4.6. Publication bias

The funnel plot showed asymmetry, indicating the presence of potential publication bias (Fig. 5). Further analysis with Egger's test showed no evidence of publication bias ($P = .554$).

5. Discussion

RA is a common chronic inflammatory joint disease in adults. Progression of RA leads to local and systemic bone loss, and

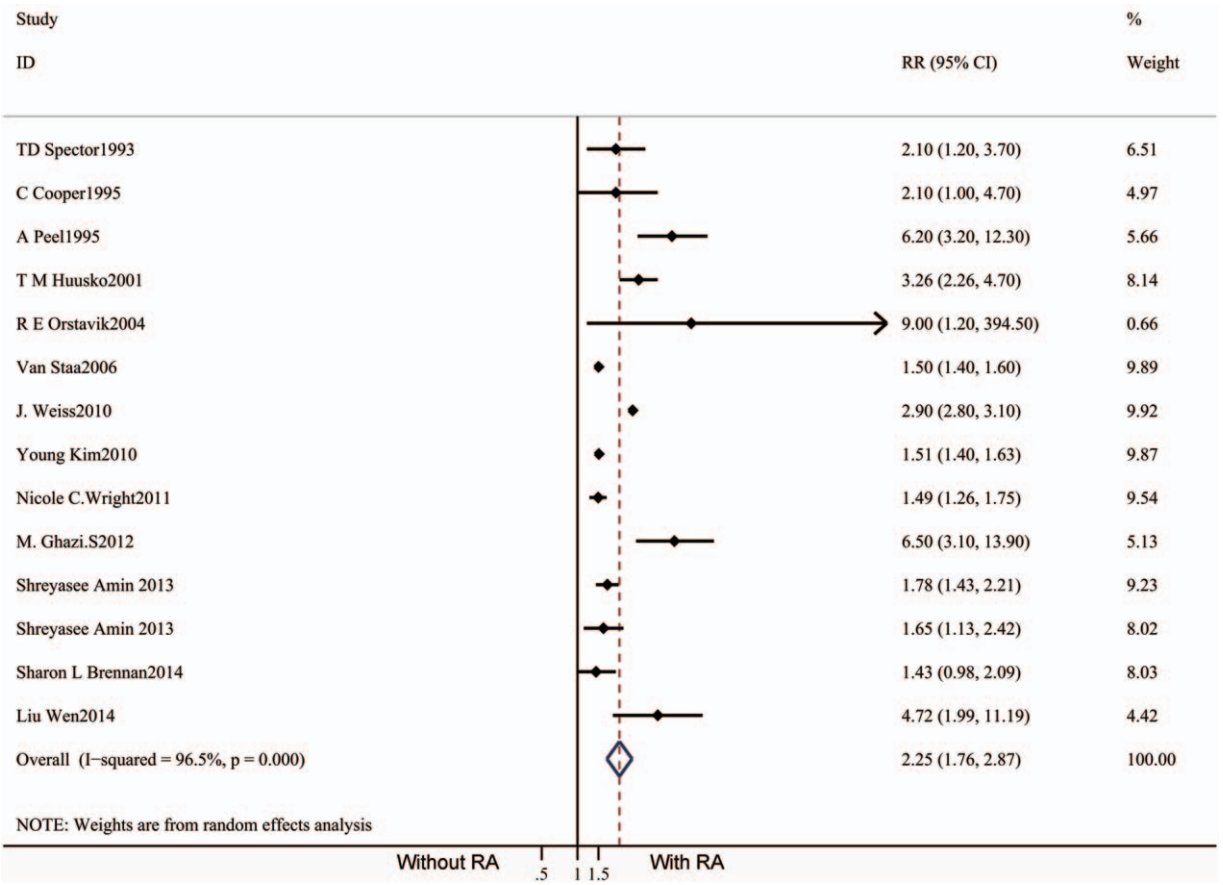

Figure 2. Forest plot for association between RA and the risk of bone fracture. RA = rheumatoid arthritis.

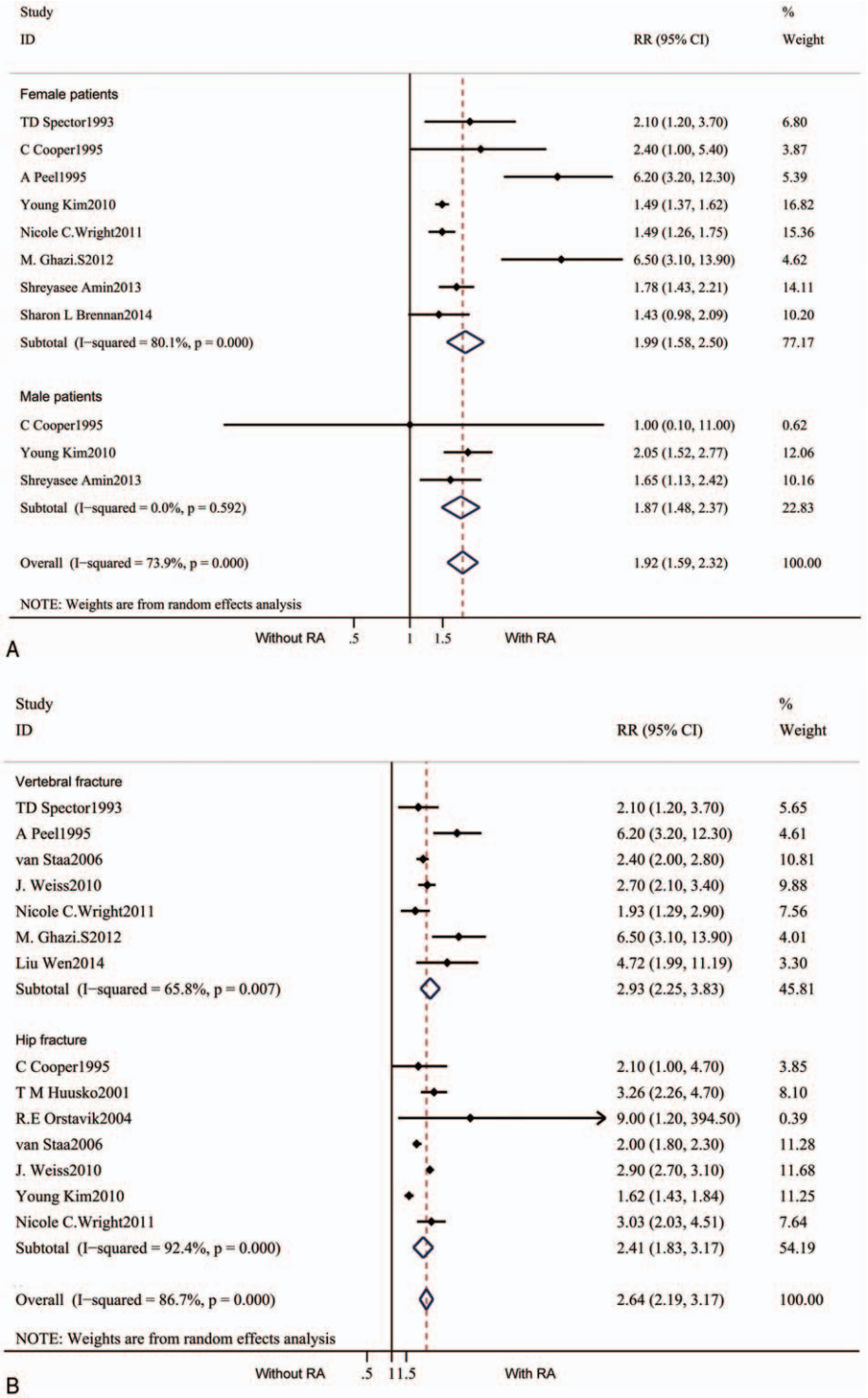

Figure 3. Forest plots for association between (A) female or male RA and the risk of bone fracture and (B) RA and site-specific fracture risk. RA = rheumatoid arthritis.

patients eventually develop osteoporosis.[4–6] Osteoporosis is a condition in which the bone decreases in strength and becomes vulnerable to fracture. The manifestation of the osteoporosis is due to the loss of bone mass and damage of fine structure in bone tissue which increases bone fragility. Our study, together with other studies,[19–21,35] demonstrate that patients with RA are at higher risk of osteoporotic fractures than patients with non-RA. Postmenopausal women are more prone to osteoporosis and it is estimated that osteoporotic fracture occurs at least once in approximately 50% of postmenopausal women and in over 20% of men over 50 years of age.[36,37] However, our results show a similar increased risk of fracture in men and women with RA than those without RA, further suggesting that RA is an independent risk factor for fracture. Although patients with

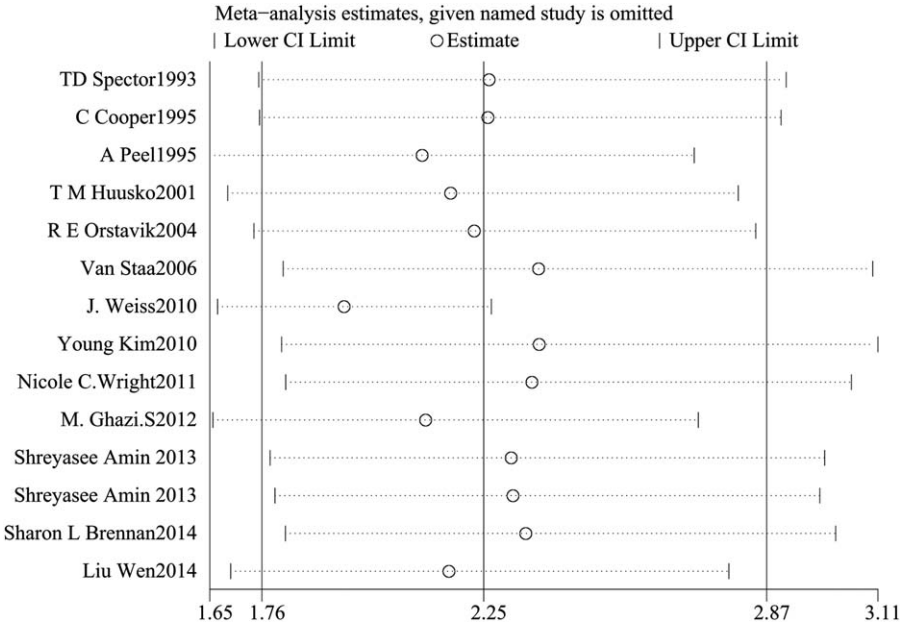

Figure 4. Sensitivity analysis of all included studies.

osteoporosis are prone to fractures mainly in the vertebral, hip, and forearm,[38,39] several studies have argued an increased risk of hip[21,27,29] or vertebral[20,21] fractures in RA patients. Our result show comparable risks of fractures at the vertebral and hip in RA patients, suggesting no specificity in the site fracture.

As fracture often reduces quality of life, fracture prevention is, therefore, crucial for patients with RA. First, the fracture risk should be carefully evaluated in RA patients. Although RA is an independent risk factor for fracture itself, chronic inflammation and glucocorticoid application may promote the development of osteoporosis.[40–42] Therefore, regular bone mineral density (BMD) measurement and fracture risk assessment using tools such as FRAX (Fracture Risk Assessment) algorithm should be performed for early detection of osteoporosis in RA patients.[43,44] Other skeletal or nonskeletal fracture risk factors, as well as other conditions such as age, gender, body mass index, cigarette smoking, high alcohol intake, inadequate physical activity, and family history of osteoporosis, that may lead to reduced BMD should be considered in the evaluation of fracture risk assessment in RA patients. For patients with high fracture risk, and those taking glucocorticoids particularly, prescription of calcium and vitamin D supplements, and treatments to control BMD loss, such as bisphosphonates, denosumab, and parathyroid hormone analogs should be considered.[44]

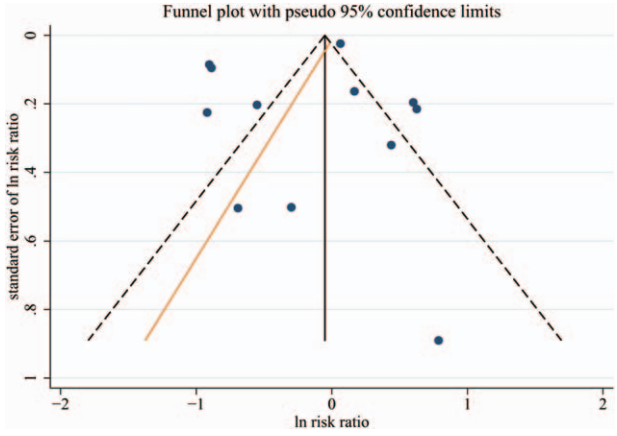

Figure 5. Funnel plot of included studies.

Second, chronic inflammation in RA should be controlled. For decades, prednisone, a corticosteroid drug, has been widely used to suppress inflammation, but the treatment itself could also enhance BMD loss.[45] Disease-modifying antirheumatic drugs such as methotrexate (MTX) are able to control RA disease activity and could be considered as a treatment option, as current clinic studies did not show the increased risk for osteoporosis and osteoporotic fracture in RA patients treated with MTX.[46] Newer inflammation-fighting drugs, such as TNF inhibitors etanercept and adalimumab, have also been reported to control inflammation without disrupting bone remodeling.[47,48] However, further investigations are warranted, as there are no data available to determine whether TNF inhibitors can minimize the risk for fracture.

Third, patients with RA should be assessed for fall risk regularly. Falls are the leading cause of fracture.[44] More than 95% of hip fractures resulted from falls.[49] Immobility resulting from pain, swelling, and lack of motor coordination in RA patients highly increases their risks of falling, thus increasing the risk for fracture. Taking certain preventive measures may help to reduce fall risk. Tai Chi[50] and regular weight-bearing exercises[51] such as walking and running may strengthen the bone and decrease BMD loss. Home safety assessment[50] and hip protectors[52] may reduce the risk of falling and fracture.

There are a few limitations in our meta-analysis. Heterogeneity was present among the 13 studies. Confounding factors such as age, sex, BMI, and postmenopausal status in RA and non-RA groups were not controlled at the same level. The confounders adjusted for are also different between studies. These differences attribute to a certain degree of bias when combined for the estimation of pooled RR. Moreover, the duration and severity of

RA were not considered when selecting subjects. This limitation could lead to the overestimation or underestimation of the associated indicator. In general, the risk of bone fracture increases with the duration and severity of RA. We also did not include BMD as one of our primary outcome of interest due to the limited studies available. The association of RA, osteoporosis, and bone fracture is thus not directly displayed. In addition, the treatment for RA patients was not taken into account in this study. Doses and duration of glucocorticoid might contribute to the difference in outcome measurement. The selection of participants, type of treatments given, confounder adjusted for, and matching factors between RA and non-RA patients are all possible sources contributing to the heterogeneity present among studies.

6. Conclusion

Our study concludes that RA is a risk factor for bone fracture in men and women, with a comparable risk of fracture at the hip and vertebral. Patients with RA are to be monitored more closely to control bone loss and prevent fracture.

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