

Increased risk of vertebral fracture in patients with rheumatoid arthritis

A meta-analysis

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Abstract

The relationship between rheumatoid arthritis and risk of vertebral fracture has been reported by several observational studies. However, there is no higher-level evidence study, such as meta-analysis, that has investigated the relationship, and its mechanisms are not yet fully clear. This meta-analysis aimed to provide a summary of an observational study of the relationship between rheumatoid arthritis and the risk of vertebral fractures.

Relevant studies were identified by searching PubMed and EMBASE databases (up to August 1, 2016). We included published observational studies (cohort or case-control design) evaluating the relationship between rheumatoid arthritis and the risk of vertebral fractures. Two reviewers searched and abstracted the data independently. Relative risks (RRs) with 95% confidence intervals (CIs) were used throughout the whole analysis.

Seven observational studies (2 cohort studies, 2 nested case-control studies, and 3 case-control studies) were included in this meta-analysis. The results showed that the pooled RR of vertebral fracture for individuals with rheumatoid arthritis was 2.34 (95% CI 2.05–2.63, $I^2=35.4\%$, P for heterogeneity=0.16). Further subgroup analysis by sex showed that the pooled RRs for both women and men, and only women were 2.14 (95% CI 1.47–2.8, $I^2=48.5\%$, P for heterogeneity=0.12) and 2.39 (95% CI 2.07–2.70, $I^2=34\%$, P for heterogeneity=0.22), respectively. Subgroup analysis by study design showed that the pooled RRs for cohort studies, nested case-control studies, and case-control studies were 2.31 (95% CI 1.95–2.67, $I^2=4.8\%$, P for heterogeneity=0.31), 1.89 (95% CI 1.01–2.77, $I^2=72.1\%$, P for heterogeneity=0.06), and 2.62 (95% CI 2.04–3.91, $I^2=26.1\%$, P for heterogeneity=0.26), respectively.

Based on our meta-analysis, rheumatoid arthritis should be regarded as an independent risk factor of vertebral fracture. Further studies are needed to institute prevention and treatment strategies.

Abbreviations: CI = confidence interval, GC = glucocorticosteroid, HR = hazard ratio, IL = interleukin, OR = odds ratio, RR = relative risk.

Keywords: meta-analysis, rheumatoid arthritis, risk, vertebral fracture

1. Introduction

Vertebral fracture is one of the most common fractures associated with osteoporosis, which is a major cause of back pain, restricted activity, disability, and decreased lifespan.^[1,2] The prevalence of vertebral fracture is nearly 20% in older people.^[1,2] In the United

States, the government spends over \$1 billion for vertebral fractures annually.^[1,3] Identifying the potential risk factors is important for the prevention and treatment of vertebral fractures. Several risk factors for vertebral fracture such as diabetes mellitus,^[4] proton pump inhibitors use,^[5] and risedronate use^[6] have been identified by meta-analysis.

Rheumatoid arthritis is a chronic and autoimmune joint disease that is associated with subchondral bone and cartilage degradation and progressive bone loss.^[7] Osteoporosis is a “silent” complication of rheumatoid arthritis, which may lead to fractures.^[8] Many observational studies suggested that patients with rheumatoid arthritis had an increased risk of vertebral fracture.^[9–15] However, small sample size and low level of evidence made the relationship less meaningful. To our knowledge, there was no meta-analysis on the association between rheumatoid arthritis and vertebral fracture risk. We therefore performed this meta-analysis to evaluate the relationship between rheumatoid arthritis and the risk of vertebral fractures using data from published observational studies.

2. Materials and methods

This meta-analysis was performed according to the MOOSE guidelines and the PRISMA statement.^[16,17] Because our study was performed based on previous studies, so the ethical approval and informed consent were not required.

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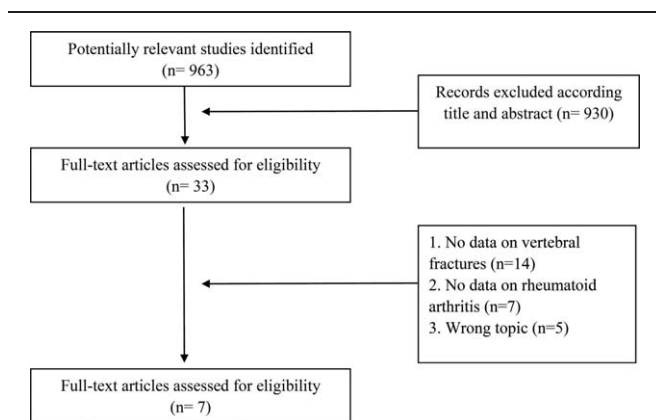


Figure 1. Flowchart for study selection.

2.1. Search strategy and data sources

The MEDLINE and EMBASE databases were searched for published observational studies (including cohort studies and case-control studies) that investigated the relationship between rheumatoid arthritis and the risk of vertebral fracture (up to August 1, 2016, with English restriction). Medical Subject Headings (MeSH) and free text, such as “rheumatoid arthritis” and “fracture,” were used for searching. In addition, manual searches for the references of all relevant studies and the abstracts of meetings related to osteoporosis and rheumatology were performed to identify additional studies.

2.2. Study selection

The articles were evaluated by the 2 independent reviewers. Two independent reviewers resolved the discrepancies by arbitration and reached a consensus on study searching, study inclusion, and interpretation of data after discussion. Studies were included in the present meta-analysis if they met the following inclusion criteria: an observational study (including cohort studies and case-control studies); reported adult population; reported rheumatoid arthritis and the risk of vertebral fractures as the outcome; and reported risk estimates, such as relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs) with 95% confidence intervals (CIs). The studies were excluded if they did not meet the inclusion criteria. If different articles came from the same source, the most detailed one with greatest degree of control for potential confounders will be taken into account.

2.3. Data extraction

The data were extracted by 2 independent reviewers (BC and GC) using a standardized data collection form for analysis. The

reliability was checked by a third reviewer (YF). The standard data extracted form included the first author’s last name, publication year, country where the study was performed, design of observational study, number of subjects, number of rheumatoid arthritis and vertebral fractures, fracture ascertainment, and RR estimates with corresponding 95% CIs. The reviewers extracted the RRs and 95% CIs that reflected the greatest degree of control for potential confounders. The study quality was assessed using the 9-star Newcastle–Ottawa Scale. A third reviewer was involved to resolve disagreement regarding the abstracted data.

2.4. Statistical analyses

The RRs were used as the mean of measuring association across studies in this meta-analysis. The multivariable-adjusted HRs or ORs were transformed into RRs according to prior publications.^[18,19] The Cochrane Q test and the Cochran I^2 statistics were used to estimate heterogeneity across including studies.^[20] According to Higgins et al,^[21] the reviewers considered I^2 values <30% as having low heterogeneity, 30% to 50% as having moderate heterogeneity, and >75% as having high heterogeneity. The subgroup analyses were performed by sex and study design. The publication bias was assessed using Begg test and Egger test.^[22,23] Sensitivity analysis involved removing any included study and assessing whether the results would be affected significantly. All statistical tests were performed using the STATA software (version 12.0; StataCorp, College Station, TX) and $P < 0.05$ was considered to be statistically significant.

3. Results

Figure 1 shows the procedure of the study selection. A total of 963 studies were included from the initial database search. After title and abstract assessment, 930 studies were excluded because of duplicate and not satiating inclusion criteria, and 33 articles remained. After assessment of the full text, 7 studies were included in the current meta-analysis.

3.1. Characteristics of the included studies

Table 1 shows the characteristics of the included observational studies. Two cohort studies, 2 nested case-control studies, and 3 case-control studies were included in this meta-analysis, with 631,210 participants, 11,523 vertebral fractures, and 31,989 rheumatoid arthritis. Three studies included both men and women, and 4 studies included only women. The studies were performed across 4 different countries (3 studies from the United Kingdom and 1 each from Sweden, France, and Japan). The fractures were identified using verified self-reporting of fracture experience and radiological diagnosis.

Table 1

Characteristics of the included studies.

Study, y	Country, design	Sex/age, y	No. of subjects	No. of VF, RA	Fracture Ascertainment	Relative risks (95% CI)
Spector et al, 1993	UK, case-control	Women, 45–65	862	62, 191	Verified radiological records	2.1 (1.2–3.7)
Peel et al, 1995	UK, nested case-control	Women, 50–79	423	41, 76	Verified radiological records	6.2 (3.2, 12.3)
van Staa et al, 2006	UK, cohort	Both ≥ 40	121143	2460,30262	Verified radiological records	2.4 (2.0, 2.8)
Weiss et al, 2010	Sweden, case-control	Both median 71.5	423710	6216, 191	Verified radiological records	2.7 (2.1, 3.4)
Wright et al, 2011	United States, cohort	Women 50–79	84255	2559, 960	Verified self-report, radiological records	1.93 (1.29, 2.90)
Ghazi et al, 2012	France, case-control	Women 56.1 ± 14.2	404	35,101	Verified radiological records	6.5 (3.1, 13.9)
Okano et al, 2016	Japan, nested case-control	Both mean 59	413	150, 208	Verified radiological records	1.72 (1.04–2.83)

RA=rheumatoid arthritis, VF=vertebral fracture.

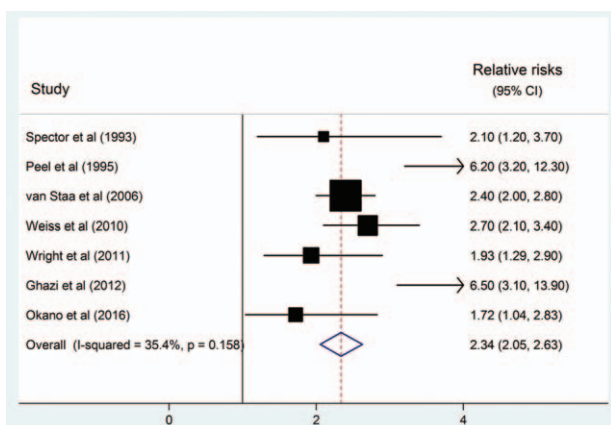


Figure 2. Adjusted relative risk (RR) of rheumatoid arthritis and the risk of vertebral fractures.

3.2. Rheumatoid arthritis and the risk of vertebral fracture

Figure 2 shows the results of the relationship between rheumatoid arthritis and the risk of vertebral fractures. A meta-analysis with a fixed-effect model showed a significant increase in the risk of vertebral fractures in patients with rheumatoid arthritis (RR 2.34, 95% CI 2.05–2.63), with no heterogeneity across studies ($I^2=35.4\%$, P for heterogeneity = 0.16). The Begg test and Egger test showed no evidence of publication bias ($P=0.45$ for Begg test and $P=0.37$ for Egger test). Sensitivity analysis showed that excluding any study from the meta-analysis did not change the results substantially (Fig. 3).

3.3. Subgroup analysis for the relationship between rheumatoid arthritis and the risk of vertebral fracture

The subgroup analyses were assessed by sex and study design for the relationship between rheumatoid arthritis and the risk of vertebral fractures. In the subgroup analysis by sex (Fig. 4), the RRs were 2.14 (95% CI 1.47–2.8) for both men and women, with no heterogeneity across studies ($I^2=48.5\%$, P for heterogeneity = 0.12) and 2.39 (95% CI 2.07–2.70) for only women with no heterogeneity across studies ($I^2=34\%$, P for heterogeneity = 0.22).

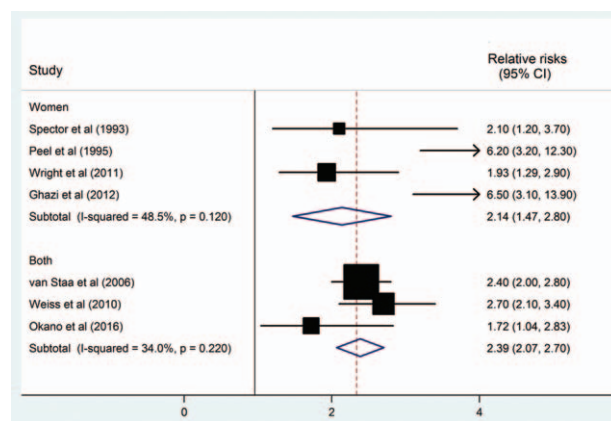


Figure 4. Subgroup analysis of sex for the relationship between rheumatoid arthritis and the risk of vertebral fractures.

In the subgroup analysis by study design (Fig. 5), the RRs were 2.31 (95% CI 1.95–2.67) for cohort studies with no heterogeneity across studies ($I^2=4.8\%$, P for heterogeneity = 0.31), 1.89 (95% CI 1.01–2.77) for nested case-control studies with moderate heterogeneity across studies ($I^2=72.1\%$, P for heterogeneity = 0.06), and 2.62 (95% CI 2.04–3.91) for case-control studies with no heterogeneity across studies ($I^2=26.1\%$, P for heterogeneity = 0.26).

4. Discussion

The present meta-analysis summarizes the results of 7 observational studies (including 2 cohort studies, 2 nested case-control studies, and 3 case-control studies), with a total of 631,210 participants, 11,523 vertebral fractures, and 31,989 rheumatoid arthritis. Our meta-analysis showed that the pooled RR of vertebral fracture in patients with rheumatoid arthritis was 2.34 (95% CI 2.05–2.63, $P < 0.0001$). Further subgroup analyses by sex and study design all found a similar relationship. Therefore, our meta-analysis strongly supports the relationship between rheumatoid arthritis and vertebral fracture risk.

A common complication of rheumatoid arthritis is bone loss or bone erosion.^[24,25] In the early stage of rheumatoid arthritis,

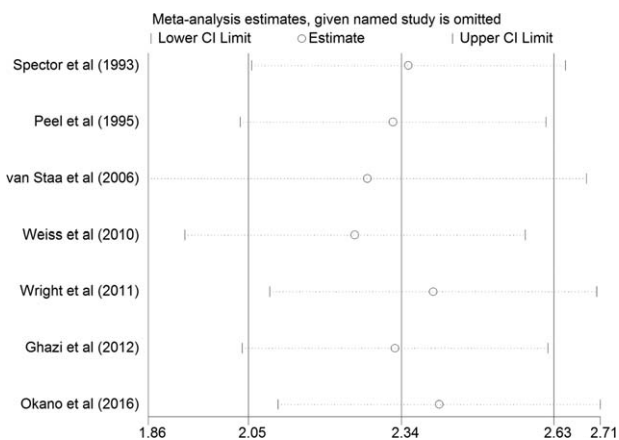


Figure 3. Sensitivity analysis of rheumatoid arthritis and the risk of vertebral fractures (excluding any study from the meta-analysis that did not change the results substantially).

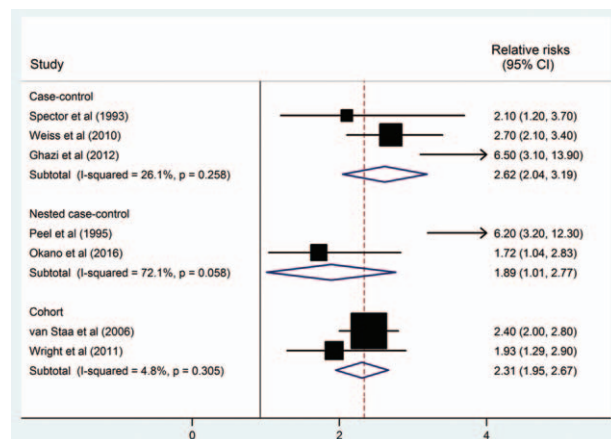


Figure 5. Subgroup analysis of study design of the relationship between rheumatoid arthritis and the risk of vertebral fractures.

cortical bone and subchondral bone erosion is obvious.^[24–26] Ultimately, cancellous bone is also lost. The vertebral skeleton is affected by systemic and local bone loss, and results in increased vertebral fracture risk. If rheumatoid arthritis is not detected and treated early, bone erosions and bone loss will progress rapidly.^[27–29] Thus, identifying the relationship between rheumatoid arthritis and vertebral fracture risk is important, and early treatment of rheumatoid arthritis and related bone loss is a critical objective in caring for patients with rheumatoid arthritis.^[25,27–29] However, a care gap in the management of osteoporosis and related fracture for patients with rheumatoid arthritis remains.^[30]

Several plausible mechanisms have been proposed for the associations between rheumatoid arthritis and vertebral fracture risk. First, during the progress of bone loss in rheumatoid arthritis, osteoclasts and osteoblasts may play a foundational role. Osteoclasts mediate bone loss at the pannus–bone interface and in subchondral locations. The differentiation and function of osteoclasts are regulated by the nuclear factor kappa B (RANK) ligand (RANKL) pathway.^[31] The RANKL can bind RANK and promote osteoclastogenesis. In rheumatoid arthritis, the RANK/RANKL pathway is activated, resulting in disturbed bone remodeling.^[31] Moreover, in synovial tissues affected by rheumatoid arthritis, the ratio of RANKL/osteoprotegerin mRNA expression is increased.^[31] An animal experiment showed that in tumor necrosis factor (TNF)-related activation-induced cytokine/RANKL knockout mice, induction of serum transfer arthritis did not lead to focal articular bone loss.^[32] Furthermore, on the site of bone erosion due to rheumatoid arthritis, the expression of Runx2 and alkaline phosphatase from osteoblasts is minimal, which may inhibit the osteoblasts from repairing the bone erosions caused by rheumatoid arthritis.^[26,28] Therefore, with physiologic bone remodeling, bone resorption and bone formation are balanced; however, this balance is altered in favor of bone resorption in patients with rheumatoid arthritis.^[24]

Second, the synovial tissue in rheumatoid arthritis is a rich source of proinflammatory cytokines with osteoclastogenic activity, including interleukin (IL)-1, IL-6, and IL-17, tumor necrosis factor, and macrophage colony-stimulating factor. These proinflammatory cytokines expressed in the bone microenvironment of rheumatoid arthritis may influence osteoclast differentiation and osteoblast activity.^[24,33–36]

Third, osteopenia and osteoporosis are the most common characteristics of rheumatoid arthritis. Haugeberg et al^[37] performed a cross-sectional study, and their results showed that compared with the control group, the prevalence of osteoporosis was increased 2-fold in 394 female rheumatoid arthritis patients. Another study investigated by the same team showed that compared with the control group, a 2-fold statistically significant increased frequency of reduced bone mass (Z score ≤ 1 SD below control) was found for both the spine and the hip in male rheumatoid arthritis patients.^[38] Moreover, in a Korean cohort study, a large percentage (90.8%) of rheumatoid arthritis patients had osteoporosis and osteopenia.^[39] Moreover, due to steroid use, patients with rheumatoid arthritis were more prone to secondary osteoporosis.^[29] Ioannidis et al conducted a 10-year prospective observational cohort study including 9263 ambulatory men and women, and their results showed that glucocorticoid treatment was associated with an increased 10-year incidence of fracture risk [HR for nonvertebral fracture 1.5, 95% CI 1.1–2.0, prior glucocorticoid treatment vs never glucocorticosteroid (GC) treatment].^[40]

Our study has several advantages. First, through a comprehensive search of studies, we included a substantial number of

subjects and fracture cases (up to 631,210 participants with 11,523 vertebral fractures and 31,989 rheumatoid arthritis), which significantly increased the statistical power of this meta-analysis. Second, the quantitative assessment of the analysis was based on all types of observational studies (including 2 cohort studies, 2 nested case-control studies, and 3 case-control studies), and the cohort and nested case-control studies may minimize the selection or recall bias. Third, 2 independent reviews performed the data extraction and analysis, and also quality assessment, and a third reviewer confirmed the reliability.

Despite these advantages, our meta-analysis has some limitations. First, the confounding factors were inherent in the studies included in the meta-analysis, which may have exaggerated or underestimated the risk estimates. Second, there was no description in the articles of the medicine(s) used, whether antirheumatic or antiosteoporosis drugs, which might have a part in the causal pathway of the studied relationship. Third, we did not conduct a subgroup analysis on the duration or stage of rheumatoid arthritis; some reports indicated that the duration of rheumatoid arthritis may offer a potential insight on these issues. Finally, geographical distribution was limited to European countries; only 1 study was performed in Asia and none of the data were from other regions, such as the United States. Further studies should include patients of other ethnic groups, which may offer a better understanding of the relationship between rheumatoid arthritis and vertebral fracture risk.

5. Conclusions

The power of our meta-analysis supports the association between rheumatoid arthritis and the risk of vertebral fracture. Based on our meta-analysis, rheumatoid arthritis should be regarded as an independent risk factor of vertebral fracture. Further studies are needed to institute prevention and treatment strategies.

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