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ORIGINAL ARTICLE

# Rheumatoid arthritis and risk of anxiety: a meta-analysis of cohort studies

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## Abstract

**Objectives** Rheumatoid arthritis (RA) may increase the risk of anxiety, but results from prior studies have no consensus. Our study aimed to evaluate the relationship between RA and incident anxiety by using a quantitative meta-analysis.

**Methods** A number of databases were used to gather relevant information; they included PubMed, EMBASE, and Web of Science, with the publication date of articles limited up to July 23, 2018. To evaluate their association, an odds ratio (OR) with 95% confidence interval (CI) was used. The random-effects model played a crucial role in calculating the pooled odds ratio, while subgroup analyses and sensitivity analyses were also performed.

**Results** A total of 10 studies, including 6201 cases of anxiety and 139,875 participants, met our inclusion criteria for this meta-analysis. All individuals were without anxiety at baseline. The follow-up period ranged from 1.0 to 9.2 years. Overall, the quantitative meta-analysis suggested that subjects with RA were associated with a significantly increased risk of anxiety incidence (OR, 1.20; 95% CI, 1.03–1.39) than those without.

**Conclusion** Results of this meta-analysis indicate that individuals with RA may confer an increased risk for the development of anxiety. Future studies should explore whether clinical manifestations of RA are modifiable risk factors for anxiety.

**Keywords** Anxiety · Meta-analysis · Rheumatoid arthritis

## Introduction

Rheumatoid arthritis (RA) is a common chronic autoimmune disease which involves the joints; as such, it has an occurrence in at least 1% of the general population [1]. It is characterized by synovitis of the joints and deterioration of the surrounding cartilage and soft tissue [2]. RA often presents two characteristic autoantibodies, anti-citrullinated protein antibodies and rheumatoid factor [3]. Symptoms such as stiffness, swelling, pain, and joint deformities can involve not only small joints in the hands and feet but also larger joints. RA may also involve extra-articular presentations such as cutaneous, gastrointestinal, pulmonary, renal, and cardiovascular diseases, which increases the burden of disease [4]. RA follows a progressive debilitating course which influences all aspects of one's life, like family life, social and work relationships, and psychological well-being in addition to physical symptoms [5].

The increased prevalence of psychiatric disorders in RA patients has been widely studied. The main psychiatric disorders reported in RA cases are anxiety, depression, and both [6]. The prevalence of anxiety in RA patients is a wide range in previous studies. One study has found significant anxiety disorder in approximately 20% of RA patients [7]. Another study reported that 26% of their studied RA population was classified as anxious [8]. Anxiety has been reported to be related to gender, age, marital status, pain, disease activity, and socioeconomic status in RA patients [8–10]. Interestingly, constant anxiety among RA patients may reduce their response to

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treatments, with the reduction in treatment effect as high as 50% as was the case with prednisolone in a recent study [11]. However, the results of other studies reported average levels of anxiety in persons with RA [12]. Consequentially, there still remains a variance about the association between RA and anxiety.

Whether RA independently increases anxiety incidence, or whether this relationship is confounded by traditional anxiety predispositions, it is unclear as previous studies have shown incoherent results [13]. Furthermore, small studies which were based on a small population led to imprecise and variable prevalence estimates [14]. In addition, past literature had no adequate evidence in the subgroup, such as study design (prospective vs retrospective), geographical area (Asia vs non-Asia), duration of follow-up (< 5 years vs ≥ 5 years), study quality (< 9 vs 9), and age (< 50 years vs ≥ 50 years). Thus, to obtain a more comprehensive estimate of the putative influence of RA on anxiety, we performed a meta-analysis of studies [15].

## Methods

The PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analysis)–recommended guidelines were followed in the production of this meta-analysis [16].

## Literature search

Researchers performed a systematic review of peer-reviewed papers from the databases of PubMed, EMBASE, and Web of Science with a restriction date placed only for articles published up to July 23, 2018. The database search keywords were "Arthritis, Rheumatoid" OR "Rheumatoid Arthritis" OR "RA" AND "Anxiety" OR "Social Anxiety" OR "Anxieties, Social" OR "Anxiety, Social" OR "Social Anxieties" OR "Hypervigilance" OR "Nervousness" AND "prospective studies" OR "cohort studies" OR "longitudinal studies" OR "follow-up studies." Retrieval of data was done through the usage of Medical Subject Heading (MeSH) terms in PubMed and EMTREE terms in EMBASE. Article search was limited only to those published in the English language. Additionally, reference lists of included studies were searched. The search was conducted by two independent investigators which featured components such as the literature search, title/abstract screening, the final decision on eligibility after full-text review, and data extraction. Another researcher was used to make final decisions in cases where disagreements were shown. The reviewers were blinded to the affiliated institution and publishing journal of potentially relevant research.

### Study selection

Studies were selected based on the following criteria: (1) community-based or population-based design (prospective and retrospective); (2) the original article was not found in reviews, posters, or abstracts; (3) at least a 12-month period of follow-up; (4) exposure was rheumatoid arthritis; and (5) odds ratios (ORs) and 95% confidence intervals (CIs) from reported quantitative estimates for anxiety which were related to RA, also hazard ratio/relative risks were equated to ORs, or sufficient original research data so that the variables could be calculated. Furthermore, exclusion criteria included (1) cross-sectional study design method; (2) animals or cell line studies, commentaries, meetings, meta-analysis, case reports or series, reviews, and editorials or manuscripts unrelated to the research topic; (3) shorter than a 12-month period of follow-up; and (4) there was insufficient raw data to estimate ORs and 95% CIs. EndNote was used to find and discard repeated data. Screening was done on titles and abstracts for eligible studies, while full-text was reviewed for potentially qualified studies. Authors were communicated with if there were multiple studies originating from the same research center in order to exclude overlapping samples.

### Data abstraction and quality assessment

Two of us (XJQ and LSC) independently extracted the data. If there was disagreement, another author (XWD) was consulted to resolve the disagreement. Data extracted from studies that fit the inclusion criteria: the first author's last name, year of publication, study design, country, location, size of participants, number of anxieties, sex, mean age, follow-up time, assessment of RA and anxiety, and study quality. To assess the quality of the included original articles, the Newcastle-Ottawa scale (NOS) was used [17]. The quality of studies was evaluated in the following three major components: selection of the study group (0–4 scores), quality of the adjustment for confounding (0–2 scores), and assessment of outcome or exposure in the cohorts (0–3 scores) (0 denoted non-compliance with any criteria, 9 denoted complete compliance with all criteria). Studies were graded from a high- to low-point scheme with a high-quality score if they met 7–8 points, medium if they met 4–6 points, and low if they met < 4 points.

### Statistical analysis

STATA software (version 12.0, Stata Corporation, TX, USA) was applied in all statistical analyses. Data analysis used ORs and 95% CIs. The RR and HR were directly regarded as OR. We converted these values in every study by using their natural logarithms, and the standard errors (SEs) were calculated from these logarithmic numbers and their corresponding 95% CIs [18]. Heterogeneity was considered significant when $I^2$

was > 50% and when $P$ was < 0.10. The random-effects model was used to determine the pooled outcome [19]. $P$ values were two-sided and $P < 0.05$ was viewed as statistically relevant.

To explore the possible sources of heterogeneity and to assess the potential impact of these factors on the occurrence of clinical outcomes, we further performed subgroup analysis by study design, geographical area, duration of follow-up, study quality, and age of participants. Furthermore, to test the robustness of the association, we calculated the effect of a single study on the overall estimate by implementing sensitivity analysis, which was carried out by continually removing each trial one at a time from the analysis.

## Results

### Search results

Primarily, the search identified 73 records from PubMed, 16 records from EMBASE, 458 records from the Web of Science, and 4 records from the reference lists of retrieved studies. The removal of duplicate papers allowed for a total of 485 studies to be suitably identified. Scanning of titles and abstracts resulted in the identification of 41 articles for full-text scrutiny. Thirty-one studies were excluded because they lacked necessary data ($n = 27$), were a meeting abstract ($n = 2$), were a review ($n = 1$), and reported not anxiety outcome ($n = 1$). Finally, there were ten cohort studies including 6201 cases of anxiety and 139,875 participants in the meta-analysis (Fig. 1) [20–29].

### Study characteristics

Table 1 shows the control features of the ten eligible studies and participants included in the present meta-analysis. These studies represented a total of 139,875 participants and were published between 2007 and 2018. Prospective cohort designs and retrospective cohort designs were used, being divided equally among the ten studies that were a part of the meta-analysis. Studies were conducted across three continents: five in Asia [21, 22, 25, 28, 29], four in Europe [20, 23, 26, 27], and only one in North America [24]. The average age range was from 41.5 to 61.1 years old. All studies did not have sex-specific data. The mean follow-up duration ranged from 1 to 9.2 years, where three studies were less than 5 years [20, 23, 26] and six studies were more than 5 years [21, 22, 24, 25, 27, 29]. The overall assessment of studies was good (range, 7–9).

### Quality assessment

According to the NOS criteria [17], the risk assessment of bias was carried out in the ten studies included (Table 2). The results indicated that the methodological quality of studies was satisfactory (range, 7–9 points).

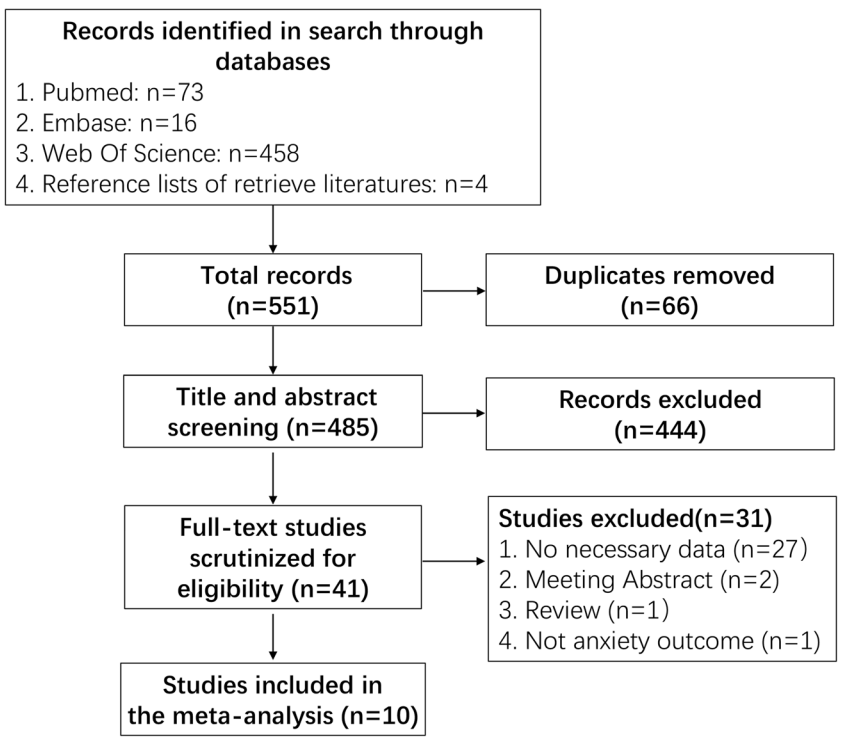


**Fig. 1** Flowchart depicting literature search and study selection. Flow diagram of systematic search in the 3 databases. After removal of duplicates, reviews, and quality control, 10 papers were suitable for analysis

**Table 1** Characteristics of studies included in this meta-analysis

| Author, publication (year) | Study design | Country/population | No. of participants | No. of anxiety cases | Se x | Age mean (year) | Follow-up duration (year) | Rheumatoid arthritis assessment | Anxiety ascertainment |
|---|---|---|---|---|---|---|---|---|---|
| Gåfvels et al. 2016 | Prospective | Sweden/Europe | 189 | 80 | M/F | 47.5 | 2 | 1987 ACR criteria | HADS-anxiety |
| Isik et al. 2007 | Retrospective | Turkey/Asia | 123 | 24 | M/F | 52.3 | 7 | American Rheumatism Association | HAMA and DSM-IV |
| Jamshidi et al. 2016 | Prospective | Iran/Asia | 414 | 348 | M/F | 45 | 5.9 | ACR criteria DAS 28 | Cattell's 40-item questionnaire |
| Kronisch et al. 2016 | Prospective | Scotland/Europe | 578 | 212 | M/F | 60.5 | 1 | 2010 ACR/EULAR RA criteria | HADS-anxiety |
| Marrie et al. 2018 | Retrospective | Canada/North America | 61,166 | NA | M/F | 53.7 | 9.19 | ICD-9-CM | Canadian Community Health Survey–Mental Health |
| Pu et al. 2018 | Retrospective | China/Asia | 161 | 102 | M/F | 47.1 | 6.57 | 1987 ACR criteria DAS28 | HAMA |
| Van't Land et al. 2010 | Prospective | Netherlands/Europe | 7076 | 881 | M/F | 41.5 | 1 | National Comorbidity Survey Replication | CIDI version 1.1 |
| Verstappen et al. 2007 | Prospective | Netherlands/Europe | 112 | NA | M/F | 56.5 | 7.1 | NA | PSHAQ |
| Watad et al. 2017 | Retrospective | Israel/Asia | 69,755 | 4494 | M/F | 61.1 | NA | ICD-9 | ICD-9 |
| Zhang et al. 2017 | Retrospective | China/Asia | 301 | 60 | M/F | 53.7 | 7.2 | ACR criteria | HADS-anxiety |

*ACR*, American College of Rheumatology; *EULAR*, European League Against Rheumatism; *HADS*, Hospital Anxiety and Depression scale; *HAMA*, Hamilton Anxiety Scale; *DSM-IV*, Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition; *DAS 28*, Disease Activity Score 28; *CIDI version 1.1*, Composite International Diagnostic Interview version 1.1; *PSHAQ*, Psychological Functional Health Assessment; *ICD-9*, International Classification of Diseases-9; *NA*, not available; *M*, male; *F*, female

**Table 2** Quality scores of included studies

| Study | Selection | Comparability | Outcome/ exposure | Total |
|---|---|---|---|---|
| Gåfvels et al. 2016 | 3 | 1 | 3 | 7 |
| Isik et al. 2007 | 4 | 1 | 3 | 8 |
| Jamshidi et al. 2016 | 3 | 2 | 3 | 8 |
| Kronisch et al. 2016 | 3 | 1 | 3 | 7 |
| Marrie et al. 2018 | 4 | 2 | 3 | 9 |
| Pu et al. 2018 | 3 | 1 | 3 | 7 |
| Van't Land et al. 2010 | 4 | 2 | 3 | 9 |
| Verstappen et al. 2007 | 4 | 1 | 3 | 8 |
| Watad et al. 2017 | 4 | 2 | 3 | 9 |
| Zhang et al. 2017 | 4 | 1 | 3 | 8 |

## Rheumatoid arthritis and risk of anxiety

The ORs of anxiety incidence in respect of RA from a single study and the combined OR are presented in Fig. 2. The evaluation of individual studies showed a positive relationship between RA and the risk of anxiety in eight of the ten included studies. RA patients, when compared with non-RA subjects in the meta-analysis, had a significantly higher risk for development of anxiety based on the ten studies [20–29] (combined OR, 1.20; 95% CI, 1.03–1.39). The studies substantially portrayed heterogeneity ($P = 0.000$; $I^2 = 95.4\%$). The forest plots of ORs and 95% CI for anxiety occurrence and RA are shown in Fig. 2.

## Subgroup analysis

We next performed a subgroup analysis based on the ten studies [20–29] to further elucidate the role of RA in anxiety. The pooled OR for anxiety stratified by study design, geographical area, duration of follow-up, study quality, and age of participants was presented in Fig. 3. In Fig. 3, the pooled estimate of multivariate ORs of anxiety incidence was 1.33 (95% CI, 1.15–1.54) in the subgroup of prospective study and the estimated OR for studies from non-Asia (such as Europe or North America) was 1.30 (95% CI, 1.16–1.47). In addition, increases in anxiety events were found in the overall subgroup meta-analysis by duration of follow-up (< 5 years), study quality (9 points), and age (< 50 years).

## Sensitivity analysis

Sensitivity analysis was performed by omitting one study at a time and reassessing the summary OR for the remaining studies. This indicated that the risk of anxiety did not vary substantially with the exclusion of any individual study and demonstrated that the results of the present meta-analysis were stable (Fig. 4).

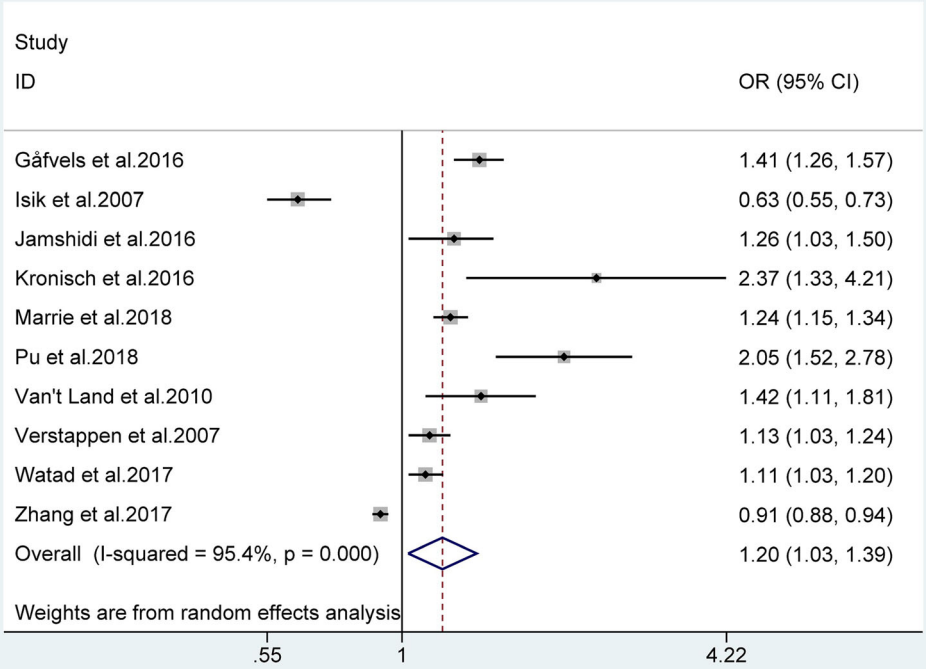


**Fig. 2** Meta-analysis of the association between RA and anxiety incidence. There was a highly significant difference between the two groups ($P = 0.021$, $< 0.05$). The random-effects model was used. OR, odds ratio; CI, confidence interval

## Discussion

With the involvement of ten cohort studies that included 139,875 participants and 6201 cases, a remarkably positive relationship could be drawn between RA and risk of anxiety. These results implied that individuals with RA might have a higher prevalence of anxiety than without.

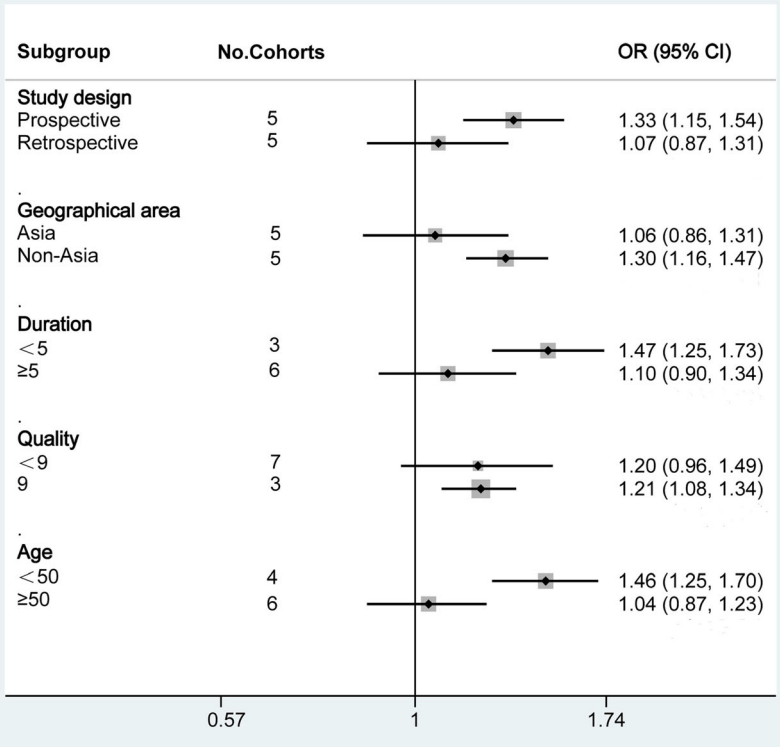


**Fig. 3** Analyses of subgroups relating RA to anxiety. The random-effects model was applied. OR, odds ratio; CI, confidence interval

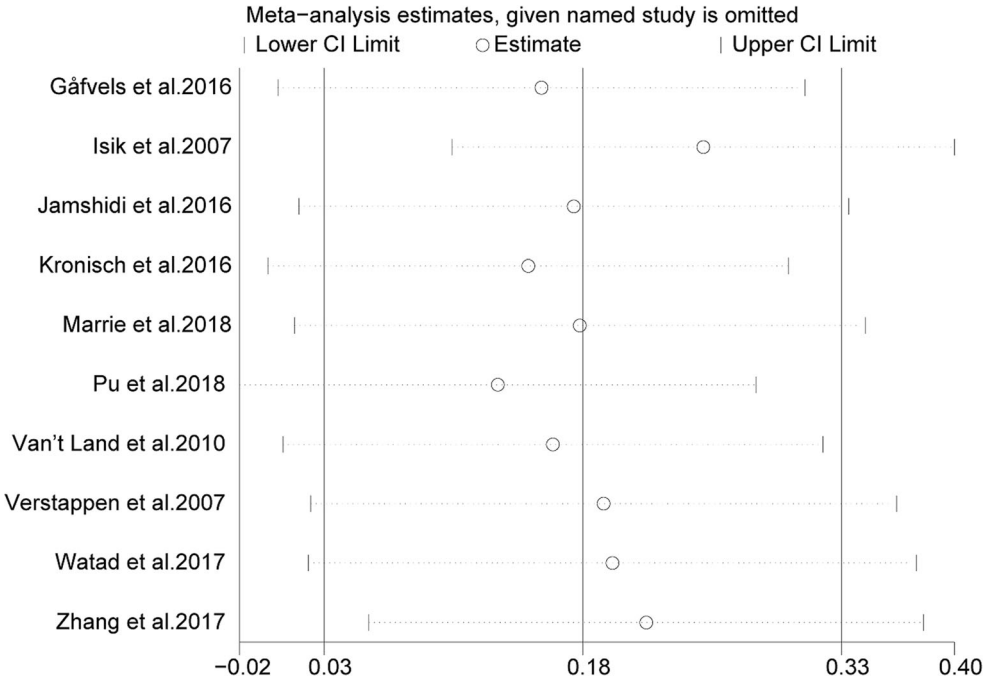


**Fig. 4** Sensitivity analysis results of the given named study omitted

Anxiety leads to adverse consequences. We have found that concomitant anxiety and RA can disproportionately worsen several outcomes [30]. It results in sleep disorders, early awakenings, insomnia, and dreaminess. Moreover, patients suffering from anxiety are often less compliant with treatment and may underestimate its effectiveness [31]. Utilization of health resources is increased among RA patients with anxiety, which lead to increased medical spending [32]. Besides, it has been noted that inattention and memory loss are attributed to anxiety. In addition, patients with anxiety may also increase sick leave and interfere with work productivity [31].

RA patients with anxiety have a poorer long-term health outcome, including increased mortality, more morbidity, and increased pain [33], which interfere with well-being and normal functioning and contribute to a decline in quality of life [34]. Therefore, anxiety morbidity is important as a target for prevention and control not only in its own right but also because it can improve the overall health as well as the quality of life in those patients [35]. Functional impairment, pain, low socioeconomic status, disease activity, and poor clinical status have all been reported to be associated with risk of anxiety in RA patients [36]. It is important for clinicians to better understand the mental distress of RA. On the one hand, it is convenient to predict who may be susceptible to developing such a disorder. On the other hand, knowledge of psychological factors related to increased vulnerability to such diseases can provide a basis for targeted intervention. Furthermore, the identification of risk factors is relatively difficult and is more complex, but it is meaningful to the earlier detection or even prevention of those psychiatric symptoms [37].

The reason for the anxiety prevalence in persons with RA was not well understood, but several explanations were possible. First, in prior research, arthritis and mood disorders were thought to have the same pathogenesis, as anxiety seemed to be particularly prevalent in autoimmune diseases like arthritis [38]. The biological basis of anxiety in RA patients is complex. Some molecules, such as pro-inflammatory cytokines, tend to rise in RA subjects, which have confirmed the association between anxiety and pain in RA patients. El-Tantawy and coworkers found a significant correlation between anxiety and serum levels of TNF-alpha, IL-1beta, and IL-18 in the RA patients [39]. Liu and collaborators found higher serum levels of IL-6, IL-17, and TNF-α in RA patients than those of healthy controls [40]. Moreover, both decreased [41] and increased [42] the serum levels of immunoglobulin (Ig) were reported in cases with psychiatric disorders, in comparison with the healthy control subjects. It has been suggested that the increase in serum levels of IgG and IgM may play an important role in the etiology and pathogenesis of mental diseases [42] and that the increase in serum levels of IgM may be a marker pointing to schizoaffective disorder. In Isik et al's study [21], the establishment of decreased serum levels of IgG and IgA levels in anxiety RA patients may support the relationship between mental disorders and the immune system. Second, Van Dyke et al. summarized a number of RA-associated conditions such as handicaps; low income and painful spells might play a role in the development of anxiety [6]. Finally, It was reported that usage of steroids, especially at a high-dose and in a long-term [43], disease-modifying antirheumatic drugs [44], and non-steroidal anti-inflammatory drugs [45] in RA cases led to psychiatric side effects.

Therefore, there are many potential causes why individuals with RA may have progressive anxiety during the course of the disease [46].

In conjunction with the association between the trends of RA and anxiety disorder, the management of psychological distress should occur as soon as possible [47]. For one thing, the persons are supposed to enhance and promote their awareness that disease knowledge is of great significance for us. People with a high level of disease knowledge were coping better and had less anxiety than those with a low level of disease knowledge [48]. For another, it is particularly important to properly treat arthritis. RA is a chronic disease with many clinical manifestations, including pain, stiffness, joint damage, and the progression of the disease, which adversely affect the well-being and normal functioning. It has been reported that clinical manifestations of RA can be modified with appropriate treatments and, consequently, the incidence of anxiety was decreased. RA therapies have been shown to improve patient's quality of life by reducing the burden of disability, pain, and fatigue in early and established RA patients [49]. In particular, patient-reported results including anxiety have been shown to improve for RA patients achieving remission [49].

Heterogeneity may come from multiple sources; therefore, subgroup analysis and sensitivity analysis were implemented to probe potentially perplexing factors that explained the high-level between-study heterogeneity. In Fig. 3, the subgroup analysis showed that the relations were still significant in different subgroups except in the retrospective study, Asian population, equal or greater than 5 years of duration, less than 9 points of quality, and the older subgroup ($\geq$ 50 years). Thus, the significant heterogeneity might be attributable to study design, geographical area, duration of follow-up, study quality, and age of participants. Furthermore, to some extent, differences in environmental factors, unhealthy lifestyles, psychological status, selective bias, and research methods might lead to the heterogeneity. However, individual study has little influence on overall RR or 95% CI in the sensitivity analysis (Fig. 4). In addition, the existence of confounding factors could not be completely removed in the study populations, but these eligible ten studies of our paper were high-quality score (7–9 points) and met the strict inclusion criteria. In short, even though there was remarkable evidence to suggest heterogeneity among individual studies, the outcome of our meta-analysis remains credible.

Focus can be placed on a number of limitations that were encountered throughout the meta-analysis. First of all, heterogeneity was notably observed throughout the expanse of the studies, which might have caused inconsistencies in study designs, sample sizes, geographical areas, durations of follow-up, analysis strategies, study qualities, and participants' essential features. For example, prospective and retrospective were equally divided among the ten cohort studies which were included. To solve this problem, however, we carried out a subgroup analysis and adopted the random-effects models to determine the overall estimate of variability. Second, it would be interesting to identify whether the RA-anxiety association differed by anxiety sub-types (e.g., mild, moderate, and severe), but few data were available for a stratified analysis. Third, our paper included a small number of studies. We only included ten studies for meta-analysis of RA and risk of anxiety disorder. The limited number of included studies was so few that we were only able to include a small number of moderators in the subgroup analysis. These relatively small numbers of studies that provided data of patient-related moderators made it difficult to make further analysis (such as meta-regression and publication bias). Meanwhile, several studies with relatively small sample sizes were included in the present meta-analysis, which might have a significant impact on the credibility of their results. Fourth, lingering confounding factors are notably present when carrying out observational studies. The observation in most of the studies included in this paper was adjusted for a wide range of potential confounding factors of anxiety disorder, but some literature reported no estimated risk adjusted for confounding factors. In addition, other confounding factors (e.g., low education, poor health-care, unhealthy lifestyles, evaluation of participants, or low socioeconomic status) may have affected the association of RA with the risk of anxiety. Finally, selective bias and language bias might affect the overall results. Included studies were taken from Asian countries (5 studies), European countries (4 studies), and one study was taken from North America; there is no relevant report from any Oceanian and African populations. Furthermore, we conducted searches on three major electronic databases (PubMed, EMBASE, and Web of Science) with the limitation of English language–based articles. Thus, some literature published in other non-English languages (such as Russian and Korean) may have been missed. These limits highlight the need for continued investigations into the relationship between RA and anxiety disorder.

In conclusion, clear observation was made throughout this meta-analysis of cohort studies to highlight the evident association of RA and an increased risk of anxiety. The positive relationship between RA and anxiety might play an important role in public health practices and in guiding clinical applications. Further studies, particularly randomized-controlled studies of drugs that improve the clinical manifestations of RA, should explore whether or not clinical manifestations of RA are potentially modifiable risk factors for anxiety.

**Author contributions** XJQ, XLZ, and LSC contributed to the conception and design, acquisition of data, analysis of data, and writing the original draft. JWH, LY, JF, and RWZ performed the literature search and interpreted data. CY and XLZ reedited this manuscript. XWD contributed to supervision, writing, review, and editing. All authors reviewed the manuscript.

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## Compliance with ethical standards

**Disclosures** None.

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