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REVIEW ARTICLE

Prevalence, Severity, and Measures of Anxiety in Rheumatoid Arthritis: A Systematic Review

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Objective. Many studies have reported high rates of anxiety in adults with rheumatoid arthritis (RA). The aim of this systematic review was to examine those findings and determine the overall prevalence, severity, and commonly used measures of anxiety in individuals with RA.

Methods. Six databases were searched from January 2000 without restrictions on language/location, study design, or gray literature. All identified studies that examined anxiety prevalence and severity in adults with RA, as assessed with clinical diagnostic interview and/or standardized self-report measures, were considered for inclusion. Quality assessment of included studies was conducted using a modified Newcastle-Ottawa Evaluation Scale, and the findings were synthesized via a narrative approach.

Results. Across the 47 studies (n = 11,085 participants), the sample size ranged from 60 to 1,321 participants with seven studies including healthy controls or groups with other health conditions. The studies were conducted across 23 countries, and anxiety prevalence ranged from 2.4% to 77%, predominantly determined with standardized self-report measures, of which Hospital Anxiety and Depression scale was used most frequently; only eight studies used a clinical diagnostic interview to confirm a specific anxiety diagnosis. Notable associations with anxiety in RA were physical disability, pain, disease activity, depression, and quality of life.

Conclusion. The reported prevalence of anxiety in RA varied widely potentially because of use of different self-report measures and cutoff points. Such cutoff points will need to be standardized to clinical thresholds to inform appropriate interventions for anxiety comorbidity in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic disease, manifesting primarily in the joints, that can lead to severe disability.[1] The global prevalence of RA is between 0.5 and 1.3%.[1–3] Although there have been considerable improvements in the management of RA, the rates of morbidity and mortality and the costs of care remain high.[4] The cooccurrence of depression in an autoimmune, inflammatory disease such as RA may be indicative of shared pathophysiologic mechanisms, as well as an indication of the impact of RA on quality of life (QoL).[5] A similar association may apply to anxiety in RA.[6] Anxiety is commonly accompanied with a presentation of depression, which increases accumulative comorbidity burden. Further, anxiety presentation may include physiological symptoms that can exuberate or add to the presentation of RA symptoms. Although many studies have identified comorbidity of anxiety in RA, there has been no comprehensive systematic review of its prevalence,

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The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social care.

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SIGNIFICANCE & INNOVATIONS

- Anxiety is highly prevalent in rheumatoid arthritis (RA) and associated with poorer clinical status and outcomes.
- The prevalence of anxiety in RA ranged considerably across studies, potentially because of varying case definition cutoff points for possibility or probability of anxiety presentation.
- Anxiety in RA is predominantly assessed with measures that are indicative of anxiety symptoms but not diagnostic of specific anxiety disorders that differ in presentation and treatment requirements.
- Further work is required to arrive at consensus on the case definition cutoff points when self-report measures are used to assist clinicians in how to manage anxiety in RA and when to refer patients for a formal psychological assessment and treatment.

severity, and specific types of anxiety (ie, generalized anxiety disorder [GAD]).

Two recent systematic reviews[7,8] have, to a degree, explored anxiety in RA but were narrow in scope. In the first, the focus was on the prevalence of various comorbidities in RA, of which anxiety was found to be the most prevalent comorbid condition (62%) followed by hypertension (38%) and depression (32%) with the remaining 11 conditions ranging in prevalence from 2.3% (stroke) to 15% (thyroid disease).[7] Similar findings in relation to comorbid psychiatric conditions in RA are commonly reported across studies, with the lifetime and annual prevalence rates of both depression and anxiety being significantly higher in RA compared with the age-matched populations, particularly in the 25- to 44-year-old age group, and in women.[9] In the second systematic review,[8] the focus was on the relationship between anxiety and disease activity and QoL, which was explored across 20 studies. It was reported that anxiety was associated with higher disease activity, particularly in early stages of RA, and with lower QoL.

Although the first review confirmed comorbidity of anxiety in RA, the second review highlighted the potential impact of anxiety on RA disease activity and overall QoL; neither of these reviews aimed to capture prevalence or severity of anxiety in RA. There is a recognition of both depression and anxiety being commonly present in RA, and although the prevalence rates of depression have been systematically reported, the same has not been the case for anxiety. The objectives of this systematic review were, therefore, to identify both prevalence and severity of anxiety, and how it was measured across studies, and associations between anxiety and the range of demographic, clinical, psychological, and other reported factors, in individuals with RA.

MATERIALS AND METHODS

Eligibility criteria. The following criteria determined studies' inclusion: (1) an adult sample of older than 18 years with a confirmed diagnosis of RA as defined by the American College of Rheumatology, (2) reported anxiety prevalence and severity using a clinical diagnostic interview and/or standardized self-report measure, (3) participants sampled from inpatient or outpatient settings, and (4) sample size of greater than or equal to 50. Studies were excluded if they had (1) insufficient demographic and clinical details on RA sample, (2) no standardized measure of anxiety, (3) community samples/settings (as diagnosis of RA could not be confirmed), and (4) English version of study (original or translated) not available.

Information sources. The following databases were included in the search: CINAHL, Embase, PsycINFO, Medline, Scopus, and Web of Science with search period commencing from January 1, 2000, to December 31, 2021. There was no restriction in study design or language of publication, and conference abstracts and poster presentations were included if they contained sufficient study details to meet inclusion criteria. An example of an electronic search strategy is provided in the Supplementary Appendix, Table 1.

Search strategy and selection and data collection processes. This systematic review included the following six stages: (1) systematic search of the literature based on a combination of key words and relevant index terms, (2) screening of titles, (3) screening of abstracts based on a predetermined inclusion and exclusion criteria, (4) examination of full-text articles against the predetermined inclusion and exclusion criteria, (5) quality assessment based on modified Newcastle-Ottawa Quality Assessment Scale (NOS),[10,11] and (6) synthesis of the findings across the included studies. This systematic review's protocol, data extraction, and the reporting followed the approached detailed in the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[12] Each of the six stages of this systematic review involved at least two authors, and all authors were involved in at least three of the six stages of the systematic review. Authors undertook this work independently. Any inter-rater disagreements were resolved through discussion, rereview, and consultation with the first author.

Data items. The key data extracted from each study included country location, study design, clinical setting, sample size, demographic variables (at minimum gender and age), anxiety measure(s) and cutoff points, and any identified demographic, clinical, psychological, or other variables associated with anxiety. Outcome measures were (a) anxiety (general or specific) prevalence as determined via a clinical diagnostic interview used to determine specific types of anxiety disorders or a self-report

measure with a defined threshold to identify elevated levels of anxiety symptoms and (b) anxiety severity levels as determined by the clinical diagnosis or self-report measures as defined by case definition cutoff points. In cases of longitudinal studies or pre-post intervention studies, only baseline data were extracted.

Study risk of bias assessment. Quality assessment was conducted with a modified NOS (Supplimentary Appendix, Table 2). The NOS is an instrument originally developed by Wells and colleagues to evaluate the design quality of studies included in meta-analyses and systematic reviews by identifying risk of bias at the study design level.[11] The modified NOS included seven questions to assess the risk of bias across the following four domains: selection bias, performance bias, detection bias, and information bias. Scores on the modified NOS ranged from 0 (high risk of bias) to 18 (low risk of bias) and were grouped into following quality categories: studies scoring (0–6, low; 7–12 moderate; 13–18 high). Authors evaluated the 47 studies in pairs, with two authors rating each study independently, and then discussing any discrepancies with one another, or a third reviewer, if necessary, to derive a final score.

Synthesis methods and statistical analyses. Given the variations across studies in their approach to assessment of anxiety and determination of its severity, it was decided that a meta-analysis was not possible without significantly reducing the number of studies that could be included. Subsequently, a narrative, summative approach was undertaken to synthesize the data, and statistical analyses were limited to a descriptive presentation of findings across included studies. Each study was profiled across key data items and then synthesized in terms of the assessment measures (diagnostic interviews or self-report measures) and a range of cutoff point scores to define anxiety. Prevalence and severity were summed across all studies, followed with an examination of anxiety associations with demographic, clinical, psychological, and other factors.

Reporting bias and certainty assessment. To avoid exclusion of relevant articles based on availability or language, authors of non-English publications were contacted to request access and/or English translation where possible, with two follow-up emails over a period of two months. To identify potential reporting biases and certainty assessments across studies, the process of review included considerations of confounding variables and interactions between anxiety and demographic, clinical, psychological, and other variables. Additionally, self-report measures were reviewed in terms of their prevalence of use and how case definition and severity of anxiety presentation was determined across those studies.

The following can be obtained by contacting the corresponding author: template data collection forms, data extracted from included studies, data used for all analyses, and any other materials used in the review.

RESULTS

Study selection. The initial search yielded 1,777 articles. Of these, 685 were duplicates and were removed. Titles were then screened for potential inclusion, resulting in 322 articles progressing to abstract screening. Of the 322 abstracts, 167 were retained for full-text review based on predetermined criteria, resulting in final 47 studies being included in the review. The full selection process is summarized in Figure 1.

Study characteristics. The 47 studies included are presented in Appendix Supplementary Table 3. The sample size across those studies ranged from 60 to 1,321 with an overall RA sample total of 11,085. These studies were conducted across 23 countries, most commonly in the United Kingdom (9 studies) and Turkey (7 studies). All studies were conducted in outpatient settings. All but one study[13] included both male and female participants, with 36 studies having 75% or more of the sample being female. Across 47 studies, participants' mean age ranged from 40 to 71 years of age. Only one study[14] did not provide age for the RA sample but rather a combined age range for all included arthritis conditions. Further, 37 studies were cross-sectional and 10 were longitudinal studies. Seven of the 47 studies included comparison groups (other musculoskeletal conditions and health controls).

Risk of bias. The risk of bias scores for included studies are presented in Table 1. Overall, the included studies had a moderate risk of bias. Total scores ranged from six to 17, with most of the studies scoring between 9 to 15 with the average score for all included studies being 11. Only three studies had a score indicating a low risk of bias, with two scoring 15[15,16] and one scoring 17.[17] Two studies had a high risk of bias with scores of 6.[14,18] Most studies had a representative RA sample and an adequate sample size. However, most studies (78%)[13–15,18–51] received lower scores on the domain of assessing anxiety because they used self-report measures, which provide a valuable indication of the anxiety symptoms but not a confirmatory diagnosis of anxiety, which can only be established through a formal clinical assessment. Overall, six studies[15,17,23,30,36,37] provided sufficient data on anxiety and adjusted for confounding variables that may influence anxiety in patients with RA. Most studies reported on examining at least one association (demographic, clinical, psychological or other) with anxiety, except five studies.[32,42,44,48,58] Ten studies[14,18,19,27,29,32,35,36,44,54] did not include consideration of the implications of comorbidity of anxiety and RA on either condition.

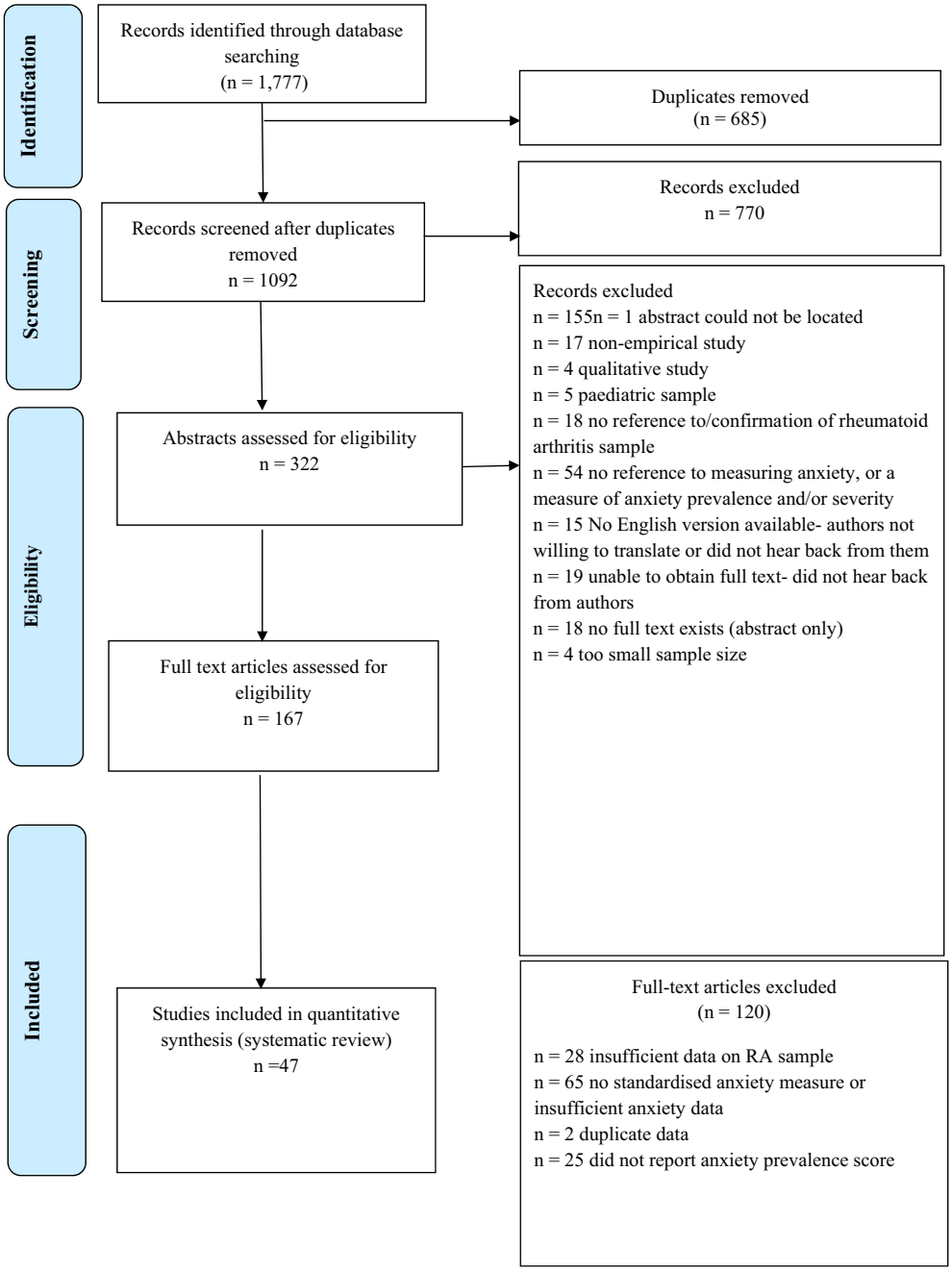

Figure 1. Flowchart: Database Search and Studies Selection.

Synthesis of measures. All 47 studies reported the prevalence of participants meeting the threshold for anxiety using either a diagnostic interview or a standardized self-report measure (Supplementary Table 3). Further details of diagnostic or self-report measures used and the scores across those are presented in Table 2. Self-report measures were used in 39 studies, and 27 of these studies provided a mean score for anxiety, four provided a median score, and 12 reported only on the number of participants meeting the threshold for anxiety.

Of the 47 studies, eight used a diagnostic interview (Diagnostic and Statistical Manual of Mental Disorders [DSM] or International Classification of Diseases) only to detect anxiety. Two used both a diagnostic interview and a self-report measure.[54,56] In the 41 studies that used self-report measure, multiple measures were used: Beck Anxiety Inventory (BAI), Cattell, Depression Anxiety Stress Scales (DASS), Endler Multidimensional Anxiety Scales, GAD, Hospital Anxiety and Depression Scale (HADS), Hamilton Anxiety Rating Scale (HAM-A), Overall Anxiety Severity and Impairment Scale, Patient-Reported Outcomes

Table 1. Modified Newcastle-Ottawa Scale assessment of 47 studies

Author, year (ref.)	Selection (6 points)		Exposure (3 points)	Comparability (6 points)		Interpretation (3 points)	Total (18 points)
	S1	S2	E1	C1	C2	I1	
Abda et al, 2016 (13)[a]	1	3	1	3	2	2	12
Anyfanti et al, 2016 (14)[b]	2	2	1	1	0	0	6
Barlow et al, 2002 (19)[c]	3	1	1	2	2	0	9
Cordingley et al, 2014 (20)[a]	2	3	1	2	2	2	12
Covic et al, 2012 (21)[b]	2	2	1	3	0	2	10
Cunha et al, 2016 (22)[b]	2	1	1	1	2	1	8
DiRenzo et al, 2019 (23)	2	2	1	3	3	3	14
Dirik and Karanci, 2010 (24)[b]	3	2	1	2	3	3	14
El-Miedany et al, 2002 (52)[b]	2	1	2	0	3	2	10
Fifield et al, 2001 (53)[a]	1	3	2	3	0	1	10
Fragoulis et al, 2020 (15)	2	3	1	3	3	3	15
Gåfvels et al, 2011 (18)[a]	3	1	1	1	0	0	6
Hattori et al, 2018 (25)[b]	3	3	1	1	3	3	14
Hitcheon et al, 2020 (5)	2	2	3	3	1	0	11
Ho et al, 2011 (26)[b]	3	1	1	2	3	1	11
Inanc et al, 2014 (27)[a]	2	1	1	2	2	0	8
Isik et al, 2007 (56)[b]	2	1	3	2	2	3	13
Jamshidi et al, 2016 (28)[b]	2	3	1	2	1	2	11
Juárez-Rojop et al, 2020 (50)	2	2	1	2	2	2	11
Karahan et al, 2016 (29)[b]	3	2	1	3	2	0	11
Katchamart et al, 2019 (30)	2	3	1	3	3	2	14
Kekow et al, 2011 (31)[b]	3	3	1	1	1	1	10
Ko et al, 2020 (32)	2	3	1	2	1	0	7
Lapčević et al, 2017 (33)[b]	2	3	1	1	2	3	12
Liu et al, 2017 (34)[b]	2	3	1	1	2	3	12
Lok et al, 2010 (17)[c]	3	3	2	3	3	3	17
Mangelli et al, 2002 (35)[a]	3	2	1	2	1	0	9
Matcham et al, 2016 (36)[b]	3	1	1	3	3	0	11
McBain et al, 2013 (37)[a]	3	1	1	3	3	3	14
McQuillan et al, 2003 (60)[a]	3	3	3	3	1	1	14
Mella et al, 2010 (38)[b]	2	1	1	1	1	1	7
Mok et al, 2012 (16)[a]	3	3	2	3	2	2	15
Monaghan et al, 2007 (39)[a]	3	2	1	1	3	2	12
Nas et al, 2011 (40)[a]	3	3	1	1	3	1	12
Ng et al, 2019 (41)	3	3	1	2	3	2	14
Rice et al, 2016 (42)[a]	3	2	1	3	1	2	12
Ryan and McGuire, 2016 (43)[a]	3	3	1	1	1	1	10
Sharpe and Schrieber, 2012 (44)[a]	3	2	1	1	0	0	7
Soósová et al, 2011 (45)[b]	2	1	1	3	1	2	10
Soósová et al, 2016 (46)[b]	3	2	1	2	1	2	11
Tiosana et al, 2020 (47)	1	1	1	2	3	3	11
Treharne et al, 2005 (48)[a]	2	2	1	2	1	1	9
Uda et al, 2021 (51)	2	3	1	1	3	3	13
Uguz et al, 2009 (57)[b]	3	1	2	2	2	2	12
Uguz et al, 2015 (58)[a]	3	1	3	1	1	1	10
Wan et al, 2016 (55)[a]	3	2	2	2	2	2	13
Zyrianova et al, 2006 (49)[b]	3	1	1	1	2	1	9
Average score and range across four categories and the total	(Average score = 4.51; range 1–6)						(Average score = 11.13; range 6–17)

[a] Anxiety as secondary outcome.
[b] Anxiety specifically as primary outcome.
[c] Psychological well-being as primary outcome.

Measurement Information System (PROMIS), Spielberger's State-Trait Anxiety Inventory, and Zung Self-Rating Anxiety Scale. The most frequently used self-report measure was the HADS (24 studies), followed by the GAD-7 and BAI (four studies respectively).

Case definition thresholds. Of the 47 studies, 39 used self-report measures with varying case definition cutoff points. Of the 24 studies using the HADS, four studies used both a possible (≥8) and a probable (≥11) threshold for anxiety,[21,25,37,54] 11 studies[18,19,26,30,31,35,38,43,50,51,55] used possible (≥8)

Table 2. Summary of anxiety measures, anxiety prevalence and anxiety severity across 47 studies.

Study ref	Measure	Definition	Threshold	No. of studies	No of participants	Prevalence Range %
Studies using diagnostic assessment						
56	DSM-IV	Any anxiety	Meets diagnosis	1	82	13.4
53	DSM-IV	GAD	Meets diagnosis	1	415	5
16, 17	SCID-I	GAD and other specified anxiety disorders	Meets diagnosis	2	400	5 (GAD)
54, 57, 58	SCID-I	Any anxiety disorder (unspecified)	Meets diagnosis	3	294	19.3 – 22.9
54, 57	SCID-I	GAD	Meets diagnosis	2	233	7.3 – 16.9
52	ICD-10	Anxiety disorder unspecified	Meets diagnosis	1	80	70
Studies using self-report scales						
29, 45, 46, 49	BAI	Mild Moderate Severe	≥ 8 ≥ 16 ≥ 26	4	418	15.5 – 29.7 8.9 – 44.8 8.9 – 29.3
28	Cattell	Moderate Neurotic Needs psychotherapy	≥ 4 ≥ 7 ≥ 9	1	414	38.9 28 17.1
21, 22	DASS42	Severe	≥ 14	2	249	7.8 – 37.5
22	DASS42	Extremely severe	≥ 25	1	80	25
42	DASS21	Mild Moderate Severe Extremely severe	≥ 4 ≥ 8 ≥ 13 ≥ 26	1	163	19.6 16.0 4.9 9.8
60	EMAS	Mild to moderate	≥ 40	1	415	3
54	GAD-2	Possible	≥ 3	1	150	20.7
32, 33, 36, 54	GAD-7	Moderate	≥ 10	4	863	9.8 – 36.2
18, 19, 21, 25, 26, 30, 31, 35, 37, 38, 43, 50, 51, 54, 55	HADS	Possible anxiety	≥ 8	15	4,044	11.5 - 58
24, 27, 40	HADS	Probable anxiety	≥ 10	3	625	2.6 - 39
15, 20, 21, 25, 37, 39, 41, 44, 48 ,54	HADS	Probable anxiety	≥ 11	10	3,879	2.4 – 48.7
56	HAM-A	Mild	≥ 6	1	82	3
56	HAM-A	Mild to moderate	≥ 15	1	82	8
14, 47	HAM-A	Moderate to severe	≥ 18	2	249	12.1 – 32.9
54	OASIS	Probable	≥ 8	1	150	22.7
23, 54	PROMIS	Mild	≥ 55.4	2	346	18 – 22.7
23	PROMIS	Moderate to severe	≥ 62.3	1	196	9
13	STAI	Average Above average Severe	≥ 25 ≥ 36 ≥ 52	1	200	11 77 12
34	ZSRAS	Mild to moderate	≥ 50	1	297	47.5

threshold, three studies[24,27,40] used higher possible (≥10) threshold, and six studies[15,20,39,41,44,48] used probable anxiety threshold (≥11).

Of the remaining studies (n = 15) using self-report measures, the BAI and GAD-7 were each used in four studies. For the BAI, the four studies reported on all three thresholds (≥8, ≥16, ≥26), which reflected mild, moderate, and severe anxiety.[29,45,46,49] Studies using the GAD-7 used a single threshold of greater than or equal to 10,[32,33,36,54] whereas of the three studies using HAM-A, one reported two thresholds (≥6, ≥15),[56] and two reported one, but higher threshold (≥18).[14,47] The other studies included multiple thresholds (DASS42,[21,22]; DASS21,[42]; PROMIS,[23,54]) or single (Cattell[28]) thresholds for case definition. In eight studies, anxiety was determined using diagnostic interviews.[16,17,52–54,56–58] Of those, five studies reported on criteria being met for GAD.[16,17,53,54,57]

Prevalence of anxiety. The prevalence of anxiety across the 47 studies ranged from 2.4% to 77%, noting that two studies reported significantly higher prevalence rates (70%, 77%)[13,52] compared with the other studies at the upper prevalence range. Prevalence based on studies using clinical diagnosis of anxiety disorders ranged from 5 to 70%.[16,17,52–54,56–58] Specifically, prevalence rates for GAD using the DSM-IV 5%–13.4% or the Structured Clinical Interview for DSM Disorders (SCID) (5% – 16.9%)[17,54,57] were lower than the rates reported for "any anxiety disorder" (13.4%– 22.9% SCID)[54,56–58] and 70% on International Classification of Diseases, Tenth Revision.[52] The prevalence of anxiety was higher when using self-report measures ranging from 2.4% to 77% and varied across studies, measures, and case definition cutoff points. Across most studies using self-report measures, application of more stringent cutoff points resulted in lower prevalence rates (Table 2).

Severity of anxiety. Across the studies, self-report measures included cutoff points, which were indicative of case definition as well as of severity of anxiety symptoms. For example, on the HAM-A measure, the mean score ranged between 8.37 and 17.78, with the scores of greater than or equal to 6, indicating minor anxiety symptoms, and those of greater than or equal to 15, indicating major anxiety symptoms. For the BAI, the mean score ranged between 17.53 and 21.91, exceeding the moderate anxiety symptoms cutoff score of greater than or equal to 15. On the PROMIS, mean scores ranged between 58.4 and 65, indicating moderate to severe anxiety symptoms based on the cutoff score of greater than or equal to 55.4. Similarly, the DASS measure includes cutoff scores for mild, moderate, severe, and extremely severe. Therefore, studies that used those scales provided levels or intensity of symptoms with higher cutoffs, suggesting more severe anxiety presentation.

Anxiety and associated variables. Of 47 studies, 18 reported on associations between anxiety and demographic variables. Anxiety was associated with sex, being reported as higher in female participants in five studies.[22,24,31,37,52] Age was reported to be associated with anxiety in four studies,[15,31,34,36] in three of these this association was with younger participants[15,31,36] and in one study the association was with older participants.[34] Other demographic variables reported to be associated with anxiety included not being married,[28,30,34] not being employed,[33] lower education level,[33,46] lower socioeconomic status,[50] lower income,[22,26,34] and higher use of social security assistance.[17]

The inclusion and measurement of clinical variables varied considerably across the studies. The following variables were found to be associated with higher levels of anxiety: greater disease activity,[26,27,30,31,34,36,41,47,50,52] greater functional disability,[15,19,22,28,30,40,45,46,51] longer disease duration,[30,46,52,56] pain,[19,22,27,28,31,43,45,46,55] fatigue,[31,33] use of medication for pain,[26] use of anti-tumor necrosis factor medications,[57] rheumatoid factor seropositivity,[52] presence of nodules,[52] inflammation measured by erythrocyte sedimentation rate,[26] lower levels of immunoglobulin A,[56] and overall worse physical health.[26]

In relation to other comorbid psychiatric conditions, 27 studies examined an association between anxiety and depression, with 14 of those reporting depression to be significantly associated with anxiety.[19,23,24,26,29,33,34,36,43,45,46,52,55,60] Other variables associated with higher levels of anxiety included worse QoL,[16,23,26,29,31,40,55] poorer coping,[24] decreased social support,[17,24,26,34,45,55] and self-efficacy,[24,34] poorer well-being,[35] less optimism,[37] reduced autonomy,[43] greater pain catastrophizing,[43] alexithymia (difficulties in identifying and describing emotions),[29,43] poorer illness perceptions,[20] increased perceived severity of RA,[24] greater sexual dysfunction,[13] and loss of social desire and satisfaction.[13]

DISCUSSION

Based on the 47 studies included in this review, anxiety is highly prevalent in RA, with rates ranging from 2.4% to 77%, although two studies[13,52] had significantly higher prevalence rates (70% and 77%) compared with the rest of the studies in which the highest prevalence was 58%. When based on the eight studies that used clinical interviews to determine presence of a specific anxiety disorder such as GAD, the prevalence was considerably lower, ranging from 5% to 16.9%. However, presence of anxiety symptoms, even when not at clinically diagnosed level, may have impact on the overall management of RA and should therefore be regularly screened for and treated as necessary.

In summary, when studies have used clinical assessment, a diagnosis of a specific anxiety condition is possible as is a confirmation of severity of anxiety symptoms. When studies have used self-report measures, higher scores were indicative of presence and severity of anxiety symptoms that may warrant a referral for a formal diagnostic assessment and if necessary, a psychological or pharmacological treatment. Anxiety is an umbrella term for broad anxiety symptoms and for several different clinical types of anxiety in which most of the studies included did not specifically identify. Further, the use of lower threshold cutoff points means that the reported prevalence rates are capturing presence of anxiety symptoms with different severity cutoff point indicators. Use of severity indicators in some of the measures can be useful and informative to the clinicians who require an efficient screening measure to determine if there is a presence of psychological distress that should be considered in the overall management of RA.

In terms of associations with demographic, clinical, psychological, and other factors, the strongest links were found between anxiety and higher levels of depression (14 studies), functional disability (12 to 9 studies), pain (10 to 9 studies), RA disease activity (9 to 10 studies), and lower levels of QoL (7 studies). Similar associations (functional disability, disease activity, and QoL) were reported in other reviews.[6,8] The comorbidity between anxiety and RA may be due to complex and bidirectional psychological and disease-related pathways that include dysregulated inflammatory responses, ongoing presence of pain and fatigue that may impact affective states, or cognitive and behavioral responses to the presence of a chronic disease.[6] In turn, symptoms of anxiety can subsequently contribute to the worse QoL[16] and RA treatment outcomes.[31]

Based on the number of studies that have considered the presence of anxiety in RA, it is apparent that this comorbidity is well recognized. Further research should, however, focus on using clinical diagnostic interviews to determine which particular type of anxiety is most commonly present in RA, as the vast majority of studies have measured anxiety symptoms but not anxiety disorders, therefore capturing a broad range of presentations from contextual physiologic symptoms of anxiety to specific anxiety disorders.[61]

Clinical diagnostic confirmation may address the heterogeneity observed across studies regarding potentially elevated prevalence rates of anxiety based on the use of self-report measures[54] and may, in turn, better inform treatment considerations.

Self-report measures capture anxiety symptoms, not specific anxiety disorders, but even subclinical anxiety presentation may have detrimental effects on RA health outcomes.[23,62] It is therefore important to identify the presence of anxiety symptoms in RA as part of routine RA management, and when necessary, refer for clinical assessment of those symptoms. Future research should also consider how people living with RA experience the impact of anxiety symptoms or anxiety disorders on their RA symptoms.

This review has identified several limitations across the 47 studies including (1) predominant reliance on anxiety self-report measures, with varying case definition cutoff points, which are indicative of anxiety and are therefore effective screening tools but not necessarily diagnostically specific, which is important to determine at more severe symptoms presentation; (2) methodologic approaches that increased risk of bias with only six studies being in the top third of the quality assessment scores; (3) predominantly female samples that may be somewhat greater than expected on the basis of male:female ratio in RA; (4) limited management of associated and confounding factors; (5) limited demographic data with only a few studies having included participants' race, ethnicity and education level, thus making it unclear if the findings are broadly applicable across populations; and at systematic review level: (6) selection of only studies available in English language; and (7) evaluation being based on a qualitative, narrative approach.

In summary, this systematic review has identified anxiety to be commonly comorbid with RA and associated with poorer clinical outcomes, such as RA disease severity, pain, and physical disability, as well as depression and lower QoL. Effective screening for anxiety is therefore important to undertake, which can be done with the use of standardized self-report scale with recommended cutoffs scores for case definition in RA. Those specific cutoff point recommendations are available but not uniformly applied across studies. For clinicians, it is critical to know when the presence of anxiety symptoms is something to monitor for a time being and when it is at the level of severity that requires a referral to a mental health practitioner for specific treatment. The treatments for anxiety range from self-care programs to more specific clinical interventions, such as cognitive behavior therapy, which is highly effective.[21,63]

Based on the findings in this systematic review, further research should consider what may be most optimal screening measures for clinicians to use and the resources they may need to understand the potential impact of anxiety on RA and the support those patients may need in managing this comorbidity. Therefore, more research is needed to address how anxiety, at both clinical and subclinical level, may be best managed for those living with RA to minimize the poorer health outcomes associated with this comorbidity.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Meade had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Meade, Katz, Manolios, Conaghan.
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