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Identifying High-Risk Psychological Profiles in Rheumatic and musculoskeletal diseases A Comparative Meta-Analysis of Anxiety and Depression Scores

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ADMINISTRATIVE INFORMATION**Support** - This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202610095**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 January 2026 and was last updated on 14 October 2026.**INTRODUCTION**

Review question / Objective To systematically evaluate and compare the levels of anxiety and depression across seven major rheumatic and musculoskeletal diseases (RMDs), including Primary Sjögren's Syndrome (pSS), and to identify specific disease groups at the highest risk for psychological comorbidity using the PICOS framework.

P (Population): Patients diagnosed with seven major RMDs (FM, SLE, OA, SSc, pSS, RA, and BD).

I (Intervention/Exposure): Presence of RMD subtypes.

C (Comparator): Healthy controls.

O (Outcome): Levels of anxiety and depression, primarily measured by the Hospital Anxiety and Depression Scale (HADS).

S (Study design): Systematic review and meta-analysis of observational studies.

Rationale Rheumatic and musculoskeletal diseases (RMDs) are chronic autoimmune and inflammatory conditions that impose a substantial psychological burden on patients. While previous studies have reported an increased prevalence of anxiety and depression among RMD patients, there is a lack of comprehensive, large-scale comparative evidence characterizing the relative severity of these psychological comorbidities across different RMD subtypes. Identifying which specific diseases, such as Fibromyalgia or Behçet's Disease, carry the highest psychiatric risk is crucial for clinical prioritization. This systematic review and meta-analysis aims to bridge this knowledge gap by providing a hierarchical analysis of anxiety and depression levels across seven major RMDs, thereby supporting the development of targeted neuropsychiatric screening and personalized management strategies in rheumatology.

Condition being studied The study focuses on the psychological burden, specifically anxiety and depression, in patients diagnosed with major rheumatic and musculoskeletal diseases (RMDs). RMDs encompass a broad spectrum of autoimmune and inflammatory conditions characterized by chronic pain, physical disability, and systemic inflammation. These conditions, such as Primary Sjögren's Syndrome and Rheumatoid Arthritis, are frequently associated with significant neuropsychiatric manifestations, which negatively impact patients' quality of life and clinical outcomes.

METHODS

Search strategy A systematic search was conducted across three major electronic databases: PubMed (including MEDLINE), Web of Science (Core Collection), and the Cochrane Library, from their respective inceptions up to November 2025. The search strategy was constructed by intersecting three core domains using the Boolean operator "AND":

(1) Target Population (RMDs): ("Rheumatoid Arthritis"[Mesh] OR "Ankylosing Spondylitis"[Mesh] OR "Psoriatic Arthritis"[Mesh] OR "Gout"[Mesh] OR "Arthritis, Juvenile"[Mesh] OR "Lupus Erythematosus, Systemic"[Mesh] OR "Sjogren's Syndrome"[Mesh] OR "Scleroderma, Systemic"[Mesh] OR "Dermatomyositis"[Mesh] OR "Polymyositis"[Mesh] OR "Antiphospholipid Syndrome"[Mesh] OR "IgG4-Related Disease"[Mesh] OR "Osteoarthritis"[Mesh] OR "Fibromyalgia"[Mesh] OR "Takayasu Arteritis"[Mesh] OR "Giant Cell Arteritis"[Mesh] OR "Vasculitis"[Mesh] OR "Polyarteritis Nodosa"[Mesh] OR "Behcet Syndrome"[Mesh]) OR ("Rheumatic Diseases"[Title/Abstract] OR "Musculoskeletal Diseases"[Title/Abstract])

(2) Psychological Outcomes: ("Anxiety"[Mesh] OR "Depression"[Mesh]) OR ("Anxiety"[Title/Abstract] OR "Depression"[Title/Abstract] OR "Psychological Distress"[Title/Abstract] OR "Mental Health"[Title/Abstract])

(3) Psychometric Instrument: ("Hospital Anxiety and Depression Scale"[Title/Abstract] OR "HADS"[Title/Abstract] OR "HADS-A"[Title/Abstract] OR "HADS-D"[Title/Abstract])

The search syntax was adapted for controlled vocabulary in each database. Reference lists of all relevant review articles and included primary studies were additionally screened manually to

capture any publications missed by the electronic search.

Participant or population Participants: The review focuses on adult patients (aged 18 years or older) diagnosed with rheumatic and musculoskeletal diseases (RMDs).

Inclusion Criteria: > 1) Studies of various designs (e.g., cross-sectional, case-control, or cohort) involving adult patients; 2) Studies reporting mean scores and standard deviations for anxiety and/or depression using the Hospital Anxiety and Depression Scale (HADS).

Exclusion Criteria: > 1) Non-English publications; 2) Studies where only the abstract is available or full-text cannot be retrieved; 3) Conference proceedings, letters, editorials, and existing meta-analyses.

Intervention The primary "exposure" is the diagnosis of a specific RMD subtype among the seven diseases mentioned above. The study evaluates the psychological status associated with these chronic inflammatory and autoimmune conditions. Where applicable, the intervention also includes the administration of validated psychological assessment tools, primarily the Hospital Anxiety and Depression Scale (HADS), to quantify symptoms of anxiety and depression.

Comparator The primary comparators are healthy individuals or the general population without rheumatic and musculoskeletal diseases (RMDs), as reported in the control groups of the included primary studies. For certain analyses, comparisons may also be made between different RMD subtypes (e.g., comparing psychological distress in Fibromyalgia versus Rheumatoid Arthritis).

Study designs to be included This review includes various observational study designs, including cross-sectional studies, case-control studies, and cohort studies. Randomized controlled trials (RCTs) providing baseline data for the population of interest may also be considered. Conference proceedings, letters, editorials, and previous meta-analyses are excluded.

Eligibility criteria

Inclusion criteria:

Studies involving adult patients (aged 18 years or older) diagnosed with rheumatic and musculoskeletal diseases (RMDs);

Studies reporting mean scores and standard deviations for anxiety and/or depression using the Hospital Anxiety and Depression Scale (HADS);

Full-text original articles with observational study designs (cross-sectional, case-control, or cohort).

Exclusion criteria:

Non-English publications;

Studies available only as abstracts, or conference proceedings, letters, editorials, and previous meta-analyses;

Studies with insufficient data for calculating effect sizes.

Information sources A systematic and comprehensive search was conducted in the PubMed (including MEDLINE) database from its inception to the present. To ensure maximum retrieval of relevant literature, we also performed a manual search by screening the reference lists of the included studies and relevant systematic reviews to identify any potentially eligible publications that were not captured by the electronic search strategy.

Main outcome(s) This systematic review and comparative meta-analysis evaluated and compared standardized mean differences (SMDs) in anxiety and depression scores, measured primarily by the Hospital Anxiety and Depression Scale (HADS), between patients with seven major rheumatic and musculoskeletal diseases (RMDs) and healthy controls. Pooled estimates from a random-effects model revealed that all seven RMDs—Fibromyalgia (FM), Behçet's Disease (BD), Primary Sjögren's Syndrome (pSS), Systemic Sclerosis (SSc), Systemic Lupus Erythematosus (SLE), Osteoarthritis (OA), and Rheumatoid Arthritis (RA)—were associated with significantly higher levels of both anxiety and depression compared to controls (all $P < 0.001$).

A distinct risk hierarchy was identified. For anxiety, FM showed the largest effect size (SMD: 1.45; 95% CI: 1.39–1.51), followed by BD (SMD: 0.67), pSS (SMD: 0.65), SSc (SMD: 0.51), SLE (SMD: 0.51), OA (SMD: 0.36), and RA (SMD: 0.16). For depression, FM again exhibited the highest burden (SMD: 1.41; 95% CI: 1.35–1.47), followed by BD (SMD: 1.16), pSS (SMD: 0.72), SSc (SMD: 0.53), OA (SMD: 0.40), RA (SMD: 0.39), and SLE (SMD: 0.36). The psychological burden in FM patients was approximately 4 to 9 times greater than in RA patients. Disease-specific symptom profiles were also observed, with BD and RA showing a depression-predominant pattern, while SLE and OA exhibited an anxiety-predominant pattern. The findings demonstrate that while psychological comorbidity is pervasive across RMDs, its severity is highly disease-specific, highlighting FM, BD, and pSS as populations at the highest risk.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of included

observational studies were assessed independently by two reviewers using the modified Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies. The NOS evaluates each study across three domains: (1) selection of the study population, (2) control for confounding factors (comparability), and (3) ascertainment of psychological outcomes. NOS scores range from 0 to 9; studies scoring ≥ 7 were classified as high quality. Inter-rater reliability was quantified using the intraclass correlation coefficient (ICC). Any discrepancies between reviewers were resolved through consensus discussion or, if required, adjudicated by a third senior reviewer (HQ).

Strategy of data synthesis A random-effects meta-analysis (DerSimonian-Laird method) was performed using R (version 4.5.2) with the meta (v8.2-1) and metafor (v4.8-0) packages. Given the single-arm design, pooled mean HADS-Anxiety and HADS-Depression scores with 95% confidence intervals were calculated for each RMD phenotype. To enable standardized cross-disease comparisons, Standardized Mean Differences (SMDs) were computed relative to published normative HADS reference values from non-clinical adult populations (HADS-A: 5.74 ± 3.63 ; HADS-D: 4.22 ± 3.51 ; Bjelland et al., 2002). Statistical heterogeneity was quantified using Cochran's Q test and the I^2 statistic; $I^2 > 50\%$ or $P < 0.10$ was considered significant.

Subgroup analysis Pre-specified subgroup analyses were conducted stratified by: (1) disease phenotype (FM, BD, pSS, SSc, SLE, OA, RA); (2) geographical continent; (3) sex distribution ($\geq 80\%$ vs. $< 80\%$ female); and (4) mean age (< 50 vs. ≥ 50 years). Additionally, meta-regression analyses were performed to quantify the individual contributions of continuous moderators—mean age, proportion female, and publication year—to overall between-study variance.

Sensitivity analysis Sensitivity analyses were performed to assess the robustness of the primary findings: (1) a leave-one-out analysis sequentially omitting one study at a time to detect unduly influential studies; (2) analyses restricted to high-quality studies (NOS score ≥ 7). Publication bias was visually assessed using funnel plots and statistically evaluated with Egger's linear regression test. Where significant asymmetry was detected, the trim-and-fill method (Duval & Tweedie) was applied to generate bias-adjusted pooled estimates.

Country(ies) involved China.

Keywords Mental health disparities; Rheumatic and musculoskeletal diseases; Comparative meta-analysis; Hospital Anxiety and Depression Scale; Disease burden analysis.

Contributions of each author

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