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META-ANALYSIS

Prevalence of Insomnia in Rheumatoid Arthritis Patients: Systematic Review and Meta-Analysis

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Abstract

Introduction: Insomnia poses a significant challenge for individuals with rheumatoid arthritis (RA), impacting their daily lives. We address insomnia in RA patients, considering the multifaceted factors contributing to disrupted sleep patterns, such as pain, inflammation, and psychological aspects.

Aim of the work: To identify the frequency of insomnia in patients with rheumatoid arthritis. This study is a crucial step toward understanding and addressing the sleep challenges faced by RA patients.

Methods: In accordance with PRISMA guidelines, we systematically searched databases like PubMed, Web of Science, and Scopus. Eligible studies, identified through screening and quality assessments, were subjected to data extraction. We employed random and fixed effects models to assess heterogeneity and potential publication bias.

Results: The literature search yielded 1,117 articles, with ten studies meeting the inclusion criteria. The prevalence of diagnosed insomnia in RA patients was notably high at 45%, significantly surpassing that of the general population (5.6%). Subgroup analyses addressed heterogeneity, indicated by an I² value of 99.85%. The study's robust methodology and adherence to PRISMA guidelines contribute to its academic credibility.

Conclusion: This research underscores the frequency of insomnia in RA patients (45%), emphasizing the demand for heightened awareness and efficient screening tools. The potential impact of this study is significant, as it advocates for referral to specialized sleep clinics for tailored interventions, presenting an avenue for mitigating future comorbidities and addressing inflammation-related indicators.

Keywords: Insomnia; rheumatoid arthritis; sleep disturbance

1. Introduction

Insomnia has turned into a significant problem for patients who have rheumatoid arthritis (RA). Rheumatoid arthritis is a Persistent condition in which Synovitis is a defining feature. It is estimated that more than 60% of those patients experience sleep difficulties, with Insomnia being the most common complaint.¹ Insomnia significantly impacts the life quality of individuals with rheumatoid arthritis, with difficulty falling, remaining asleep, or experiencing unsatisfying sleep are defining symptoms. The signs of rheumatoid arthritis, such as joint pain and stiffness, can make it difficult for individuals to find a comfortable sleeping position and stay asleep throughout the night.^{2,3} The PainPain and discomfort associated with rheumatoid arthritis can also lead to sleep disruption,

resulting in a brutal sequence of pain and sleep deprivation.⁴ Moreover, the inflammatory process involved in rheumatoid arthritis can influence many body systems. This could additionally interrupt regular sleep-wake sequences and add to sleep difficulties in individuals with rheumatoid arthritis.^{5,6,7,8} Additionally, the psychological impact of prolonged ailment like rheumatoid arthritis can also contribute to sleep disturbances. Overall, rheumatoid arthritis has a significant impact on sleep patterns, with Insomnia being a common and troublesome symptom experienced by individuals with the condition. The precise mechanisms underlying the connection between chronic pain (CP) and rheumatoid arthritis (RA) with Insomnia remain unclear, likely involving multiple factors. For instance, the somatic PainPain connected to CP could interrupt sleep by heightening internal arousal levels.^{9,10}

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Both CP and sleep disruptions are linked to various brain-related changes, including abnormal central nervous system (CNS) activity, physical alterations (like hippocampal withering), dopaminergic shifts, and reduced agents that control neuronal endurance and development.^{11,12} CP remains linked to modifications in the inflammatory reactions in CNS, vital for regulation of sleep cycles.¹³ On an emotional level, abnormalities like depression,^{14, 15} and pain before bedtime¹⁶ may aid sleep disorders in those experiencing discomfort. Furthermore, CP-related habits, like diminished energy levels and afternoon snoozing, could also participate.¹⁷ While extensive research explores sleep disorders in individuals with PainPain,^{18,19,20} Most of the literature relies on personal estimations like bedtime diaries, rating scales, and questionnaires,¹⁹ which are susceptible to incorrect recollection and recollection distorts, diminishing their dependability.²¹ More accurate data regarding the Insomnia in RA patients is warranted.²²

Top of Form

We aim to explore the frequency of Insomnia in rheumatoid arthritis patients.

2. Patients and methods

We Conducted This systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²³ Strictly following the methods outlined in the Cochrane Handbook of Systematic Reviews and Meta-analysis of Interventions (version 6.4).²⁴

Search strategy, Selection criteria, and Data Extraction

On January 20, 2023, we extensively and systematically searched central online archives of PubMed, Web of Science, and Scopus. They were using a search strategy based on the PICO framework. We scrutinized the source list of the encompassed papers and pertinent systematic reviews to identify any potentially omitted eligible studies. Subsequently, duplicate entries were eliminated, followed by a thorough title and abstract screening utilizing the Rayyan platform. Reports were deemed suitable if they met the inclusion criteria. Observational reports (Cohort, case-control, crosssectional) on rheumatoid arthritis patients with Insomnia were included. We excluded RCTs, non-English studies, Conference abstracts, Protocols without full-text papers, and studies on other sleep disorders. An Excel spreadsheet was created for data extraction and provided access to all involved authors. The entire author team actively participated in extracting data for each study. We extracted the succeeding data from each study: (1) characteristics of the included studies and

populations, (2) primary and secondary outcomes, and (3) risk of bias assessment. This systematic review comprised six stages: (1) conducting a systematic literature search based on a combination of keywords and relevant index terms; (2) screening titles; (3) screening abstracts employing pre-determined inclusion and exclusion criteria; (4) evaluating full-text articles against the pre-determined criteria; (5) performing a quality assessment using the modified Newcastle-Ottawa Quality Assessment Scale²⁵; and (6) synthesizing findings across the included studies. At each of the six stages, at least two authors were involved, with all authors participating in at least three stages independently. Any disagreements among raters were resolved through discussion, re-review, and consultation with the first author.

RISK OF BIAS ASSESSMENT

Independent Dual reviewers used the Newcastle-Ottawa Scale (NOS) to assess the encompassed studies and determine the risk of bias in the included observational papers. ²⁵ They evaluated papers across various questions and categories of the scale. Each study, numbered within the Selection and Outcome categories, is eligible to receive no more than a single star. In cases of conflicting opinions between reviewers, disagreements were resolved through discussion.

Data extraction, preparation, analysis

Two reviewers independently assessed the included studies. The extraction of information from each study followed a structured approach encompassing paper and patient details (country, sample size, age, sex), disease-related particulars (RA diagnosis, duration), and insomnia-related data (total patients, sleep latency or Athens Insomnia Scale (AIS) usage). Supplementary variables potentially influencing the RA-Insomnia relationship were also obtained for additional analysis. These encompassed factors connected to Insomnia prevalence among RA patients. The computation of combined prevalence estimates, accompanied by a 95% confidence interval (CI), utilized a random-effect model. Heterogeneity was assessed through I², and statistical analyses were conducted using open meta-analyst software. Diagnosed Insomnia in RA was quantified for (a) any diagnosed Insomnia, (b) definite diagnoses of insomnia or sleep latency, and (c) Insomnia detected via AIS criteria. Unfortunately, only two studies were investigated using a crosssectional design. Populace base rates from large-scale epidemiological studies were obtained for comparison using Fischer exact tests.²⁶All effect sizes from separate papers underwent weighting through their variance inversed, earlier to computing mean effect sizes. Probability (p-values) were computed to assess the statistical significance of Hedge g effect sizes. Heterogeneity evaluation involves the Q-statistic, in which

significant values point to an inconsistency in reported effect sizes among studies. I² measured the ratio of variability non-attributable to errors in sampling, with values indicating low, moderate, or high levels of heterogeneity (25%, 50%, and 75%, respectively). Given the anticipated heterogeneity in chronic pain (CP) conditions, a random-effects model was applied to address within-study and between-study variances. Subgroup analyses explored heterogeneity based on methodological and sampling variables²⁶. While Q and I² analyses might be underpowered with limited studies or sample size, RA was deemed associated with Insomnia when statistically significant ($p < 0.05$).

3. Results

Literature search results

The initial search yielded 1,117 articles. Of these, 137 were duplicates and were eliminated. Titles and abstracts were then vetted for potential inclusion, from which 28 papers progressing to full text review based on pre-determined criteria while 952 were removed, resulting in final 9 studies existing in the review. The complete screening procedure is summarized in (Figure 1).

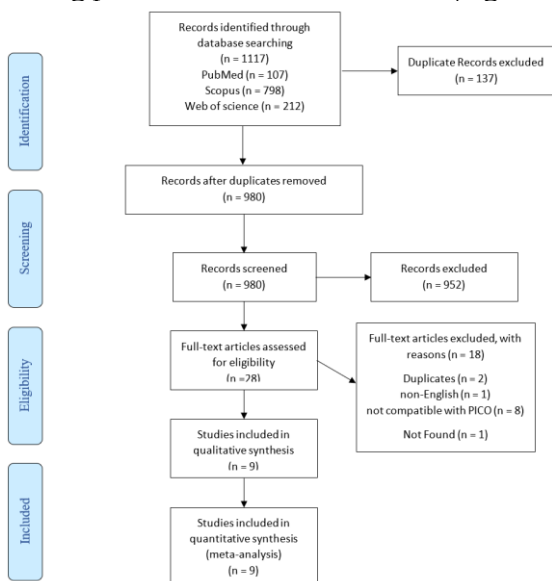


Figure 1. PRISMA flowchart with selected

Table 1. Included studies Quality Appraisal according to Adapted Newcastle-Ottawa scale (NOS)

STUDY	NEWCASTLE-OTTAWA SCALE			SCORE
	SELECTION	COMPARABILITY	EXPOSURE	
BELT, 2009	★★★★☆	★★★	☆☆☆☆	6
CHUNG, 2018	★★★★★	★★☆	★★★★☆	8
GUO, 2016	★★★★★	★★★	★★★★☆	4
KWIATKOWSKA, 2019	★★★☆☆	★★★	☆☆☆☆	6

studies to be included in the study.

Study Characteristics:

The 9 papers analysed are presented in Supplementary file 1 Table. The sample size in those papers fluctuated from 68 to 65,754, with an overall RA sample total of 70,388. These studies were conducted across ten countries, most commonly in the US (2 studies). All studies were conducted in outpatient settings except for two studies (Gun, 2016 and

Morse, 2023) which were survey-based. Females were predominant in all the studies except for Morse et al., 21 (9%). Across the ten studies, participants mean age fluctuated from 48.1 to 65.8 years of age. Only two studies (McBeth, 2022 and Vazquez, 2023) did not provide age for the RA sample but rather a combined age range for all included arthritis conditions. Further, four studies were cross-sectional, two were longitudinal cohorts, and three were case-control studies.

Risk of bias and applicability assessments

The quality of the included studies was calculated according to the Newcastle-Ottawa Scale (NOS) to determine bias risk in cohort, cross-sectional and case control papers.²⁵ . Summary of the appraisal is shown in Table 1.

LYNE, 2022	★★★★☆ / ★☆☆ / ☆☆☆★	4
MCBETH, 2022	★★★★★ / ★☆☆ / ☆☆☆★	4
VASQUEZ, 2023	☆★★★★ / ★☆☆ / ☆☆☆★	3
MORSE, 2023	★★★★★ / ★☆☆ / ★☆☆★	7
MUSTAFA, 2019	☆☆★★★★ / ★☆☆ / ★☆☆★	6

outcomes	(inconsistency)	99.83 to	0.0030
Prevalance of Insomnia	95% CI for I2	99.87	

The observed prevalence rates of diagnosed Insomnia in the RA sample were noteworthy (45%) of individuals diagnosed with RA experienced some form of Insomnia, a proportion significantly surpassing that of the general population, which stood at 5.6%Top of Form

We employed both random and fixed effects in our analysis. The aggregated random effects analysis revealed a prevalence of Insomnia, derived from nine studies encompassing a total of 70,369 patients, to be 45.050% (95% CI: 21.249 to 70.127) Figure2. The observed heterogeneity was notably high, with an I2 value of 99.85%. On the other hand, the pooled fixed effects estimate for Insomnia prevalence was 0.463 (95% CI: 0.415 to 0.516).In the assessment conducted through Egger test, the derived intercept was established at 24.3579, complemented by a 95% CI spanning from 11.4066 to 37.3093. Notably, the statistical significance associated with this outcome was determined to be P = 0.0030. Concurrently, the investigation employing Begg test revealed Kendall Tau as -0.2778, with the consequential significance level registering at P = 0.2971 Table 2. This meticulous analysis contributes crucial insights to the body of knowledge, addressing the nuanced facets of our research in a manner consistent with academic standards.

4. Discussion

This report is the foremost systematic review and meta-analysis to assess the prevalence of Insomnia in people with RA. We found that 45.05% of RA patients had Insomnia. Previous literature (incorporated in our meta-analysis) stated an elevated prevalence of Insomnia in RA patients with interstitial lung disease (ILD) compared with non-ILD RA patients.²⁷ People with Insomnia, in general, were found to have higher levels of inflammatory particles in their bodies, with high markers of inflammation. Recent research has shown a connection between RA and sleep problems, suggesting that the body's circadian rhythm and sleep patterns can affect RA.²⁸ Long-term inflammation in the body can make the signs of RA worse. Enhancing sleep and lowering inflammation can help ease RA symptoms and enhance the quality of life for patients. The bond between RA and Insomnia appears to work both ways.²⁸ Uncontrolled RA can cause physical changes that make it hard for patients to sleep, and Insomnia itself can lead to more health problems and higher levels of inflammation in people with RA.²⁸ Identifying and treating Insomnia in these patients is essential for their overall health and managing the impact of the disease. Trouble moving due to arthritis in the knees or hips can contribute to elevating Body Mass Index (BMI), a known risk factor for Insomnia. Controlling RA to reduce inflammation can help prevent Insomnia and improve sleep quality for RA patients.²⁹

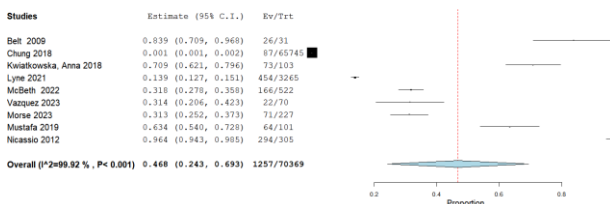


Figure 2. Frequency of insomnia in rheumatoid arthritis

Table 2. Heterogeneity Test and Publication Bias in included studies.

Test for heterogeneity	Publication bias	
Q	5372.2774	
DF	8	
Significance level	P < 0.0001	
	Egger's test	
	Intercept	24.3579
	CI (95%)	11.4065 to 37.3093
I2	99.85%	Significance level P =

Strength and Limitations

Our Systematic review and meta-analysis exhibit numerous advantages. Primarily, it embodies the best exhaustive meta-analysis to date concerning the prevalence of Insomnia within the RA population. Secondly, the meta-analysis draws upon studies characterized by a high level of methodological rigor. Thirdly, the study employs stringent selection criteria to encompass diverse populations within the RA demographic. However, the study has its limitations. Notably, significant heterogeneity was

observed across the studies during the synthesis of prevalence estimates. This heterogeneity could be elucidated through subgroup analyses or meta-regressions. Despite attempts to address heterogeneity through sensitivity analysis, which revealed minimal heterogeneity made after the Berlin questionnaire criteria, other factors might contribute to the observed heterogeneity, necessitating further investigation. While conventional statistical techniques, such as the funnel plot and the Egger regression test, are recommended for assessing publication bias, their utility in studies of proportions is limited²⁶. Furthermore, Evaluations for asymmetry in funnel plots attain their peak effectiveness in scenarios where a meta-analysis encompasses a minimum of 10 studies. Consequently, these methodological considerations should be considered and addressed in subsequent research.

4. Conclusion

A significant prevalence of Insomnia is evident in individuals diagnosed with Rheumatoid Arthritis (RA). These findings underscore the importance of maintaining a vigilant awareness among patients with RA, facilitating the identification of potential Insomniac patients. The incorporation of a straightforward screening questionnaire for Insomnia may provide supplementary advantages. Recommending a specialized sleep physician for comprehensive evaluation and management, as deemed necessary, would be an apt course of action. The treatment of concurrent Insomnia in RA patients holds promise for mitigating future co-morbidities and potentially ameliorating indicators of inflammation and pain.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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