

## Original Article

# Burden of rheumatic diseases among people with diabetes: A systematic review and meta-analysis

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## Abstract

Diabetes mellitus type 2 (DM2) is a prevalent metabolic condition affecting over 500 million people globally and associated with serious comorbidities, including various rheumatologic conditions. Some studies have reported a significant association between rheumatological conditions and DM2. However, the global burden of rheumatological conditions among people with DM2 remains unknown. The aim of this study was to assess the cumulative prevalence of rheumatological conditions in DM2 patients. An extensive electronic search was conducted utilizing multiple databases of studies published until January 2024. The quality of the studies included in the review was evaluated using a modified version of the Newcastle-Ottawa Scale (NOS). The overall quality of the studies included was rated as moderate. The review included a total of 13 studies, with 830,649 DM2 patients reported to have rheumatological conditions. Eleven studies were used to determine the individual results of rheumatoid arthritis (RA), gout, and osteoarthritis (OA). The pooled prevalence of OA was 26% (95%CI: 19–32%) and the prediction interval ranged from 6% to 51%. The pooled prevalence of gout disease was 1% (95%CI: 0.0–5.0%), and the prediction interval ranged from 0% to 99%. For RA, the combined prevalence was 0.3% (95%CI: 0.2–0.5%) and the prediction interval ranged from 0% to 5%. In conclusion, this review suggests a considerable prevalence of OA among DM2 patients, while the prevalence of RA and gout was minimal. Early diagnosis and management of certain rheumatologic conditions in individuals with DM2 may help improve health outcomes and prevent premature mortality. Further research is warranted to explore and understand the mechanisms underlying the association between DM2 and rheumatological conditions.

**Keywords:** Osteoarthritis, rheumatoid arthritis, diabetes, gout, comorbidity



## Introduction

Diabetes mellitus (DM) is one of the most prevalent chronic metabolic conditions globally. The International Diabetes Federation (IDF) reported that more than 500 million people worldwide have diabetes, and it is anticipated that this number will cross 700 million individuals by 2045 [1]. Type 2 diabetes mellitus (DM2) is the most common type of diabetes and is associated with serious comorbidities, including cardiovascular disease, kidney disease, neuropathy, retinopathy, and various rheumatologic conditions [2]. Similarly, the prevalence of another chronic disease, rheumatoid arthritis (RA), was projected to increase by 80% by 2050, rising from 17.6 million in 2020 to 31.7 million [3,4]. RA is a chronic autoimmune inflammatory disease characterized by pain, swelling, and stiffness, primarily in the hands and feet, which can lead to long-term disability and premature mortality without timely and adequate treatment [3,5].

Recent evidence suggested that individuals with DM2 may have a higher risk of developing rheumatological conditions, including osteoarthritis (OA), RA, psoriatic arthritis, and degenerative joint diseases such as gout [3,5]. Factors like aging, obesity, and other metabolic factors contribute to this increased risk [6]. The association between OA and DM2 involves complex mechanisms, as both conditions are associated with low-grade chronic inflammation. Elevated blood glucose levels in DM2 lead to the formation of advanced glycation end (AGE) products that accumulate in joint tissues and contribute to the development of OA [7]. Additionally, DM2 increases oxidative stress, affects insulin resistance, and alters hormonal factors, all of which can impact joint health [7]. Shared genetic factors may also play a role [8,9]. Despite these prepositions, the exact mechanisms and the global burden of the comorbidity of DM2 and rheumatological conditions are not yet fully understood [10-12]. Thus, the aim of this study was to assess the cumulative prevalence of rheumatological conditions in individuals with DM2.

## Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this systematic review and meta-analysis. The review protocol was documented in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023465027). The review included only original research studies that reported the incidence or prevalence of rheumatologic diseases (e.g., gout, OA, RA, and osteoporosis) among people living with DM2. To ensure robustness, studies reporting pre-existing and risk factors for rheumatological diseases, abstracts, and unpublished reports were excluded (**Table 1**).

**Table 1. Inclusion and exclusion criteria**

Overview of studies	Inclusion	Exclusion
Participants	Patients diagnosed with diabetes mellitus	Patients with pre-existing rheumatological diseases
Intervention	Usual care	
Outcome	The number of rheumatological events that occurred in diabetic patients (gout, osteoarthritis, rheumatoid arthritis, knee arthritis, psoriatic arthritis, osteoporosis)	If events are not reported
Study designs	Observational studies	Clinical trials, letter to the editor, commentaries, qualitative studies, abstract only, case series, case reports, reviews, discussion papers, animal studies
	Geography: Global level	
	Date of search: January 1, 2024	
	Published articles and preprints data	Unavailable full-text articles
	No language restriction	

## Search strategy and screening process

Comprehensive literature searches were conducted on January 1, 2024, in several databases, including PubMed, Scopus, Web of Science, and Embase, to find relevant studies. The search approach was developed using various keywords related to rheumatologic conditions and DM, as

detailed in **Tables 2** and **3**. The keywords were ("arthritis" OR "joint pain" OR "osteoarthritis" OR "psoriatic arthritis" OR "gout" OR "Rheumat\*") OR 'Ankylosing spondylitis' OR "rheumatoid arthritis" OR rheumatoid arthritis [Medical Subject Headings=MeSH]) AND ('DM2' OR "type-2 diabetes mellitus" OR diabetes mellitus [MeSH]). The search was not restricted by language, publication date, or research setting. This approach allowed us to include a diverse array of studies in various contexts.

**Table 2. Key components of the research question and search terms**

Components	Search terms	MeSH terms	Text words
Population /problem	("T2DM" OR "diabetes mellitus" OR "glycemia" OR "glycemic")	Diabetes mellitus [MeSH]	T2DM, diabetes mellitus, glycemia, glycemic, hypoglycemia, hyperglycemia
Outcome	("arthritis" OR "joint pain" OR "osteoarthritis" OR "psoriatic arthritis" OR "gout" OR "rheumat*") OR "ankylosing spondylitis" OR "rheumatoid arthritis")	Rheumatoid arthritis [MeSH] Arthritis [MeSH]	Arthritis, osteoarthritis, joint pain, psoriatic arthritis, gout, ankylosing spondylitis, rheumatoid arthritis

MeSH: medical subject headings

**Table 3. The adjusted search terms as per searched electronic databases**

Database	Term	Search query	Results
PubMed	#1	("arthritis"[Title/Abstract] OR "osteoarthritis"[Title/Abstract] OR "psoriatic arthritis"[Title/Abstract] OR "gout"[Title/Abstract] OR "rheumat*"[Title/Abstract] OR "ankylosing spondylitis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms])	268,708
	#2	("T2DM"[Title/Abstract] OR "diabetes mellitus"[Title/Abstract]) OR "diabetes mellitus"[MeSH Terms])	128,390
	#3	#1 AND #2	1,241
Scopus	#1	TITLE-ABS-KEY(("arthritis" OR "joint pain" OR "osteoarthritis" OR "psoriatic arthritis" OR "gout" OR "rheumat*" OR "ankylosing spondylitis"))	343485
	#2	TITLE-ABS-KEY(("T2DM" OR "diabetes mellitus" OR "glycemia" OR "glycemic"))	943,763
	#3	#1 AND #2	593
Embase	#1	'arthritis': ti,ab,kw OR 'joint pain':ti,ab,kw OR 'osteoarthritis':ti,ab,kw OR 'psoriatic arthritis':ti,ab,kw OR 'gout':ti,ab,kw OR 'rheumat*':ti,ab,kw OR 'ankylosing spondylitis':ti,ab,kw OR 'rheumatoid arthritis':ti,ab,kw	580,222
	#2	't2dm': ti,ab,kw OR 'diabetes mellitus': ti,ab,kw	121,765
	#3	#1 AND #2	851
Web of Science	#1	TS= ("arthritis" OR "joint pain" OR "osteoarthritis" OR "psoriatic arthritis" OR "gout" OR "rheumat*" OR "ankylosing spondylitis" OR "rheumatoid arthritis")	468,954
	#2	TS= ("T2DM" OR "diabetes mellitus")	91,993
	#3	#1 AND #2	1,033

MeSH: medical subject headings

The results of the search conducted across all the databases were imported into nested knowledge (a platform for conducting systematic reviews and meta-analyses). Duplicate studies were excluded. The remaining studies underwent a two-step selection process that involved two authors. In the primary screening phase, authors evaluated the titles and abstracts of the studies to identify the relevant articles. Studies that were considered eligible for further consideration underwent a full-text screening during the secondary screening phase. To maintain precision and prevent potential bias in the selection process, any conflicts or disagreements between authors regarding the inclusion of studies were discussed and resolved with the help of the study team.

### Data extraction and quality assessment

Data extraction from the included studies was carried out by two authors according to rigorous methodological standards. Data from the included studies included variables such as the country of study, publication year, author names, mean age of the participants, male percentage, number

of patients with DM2, number of rheumatologic disease cases (e.g., gout, osteoarthritis, rheumatoid arthritis, and osteoporosis) and the treatment of patients living with DM2.

To determine robustness and minimize potential bias in the studies included in this review, a detailed quality assessment was conducted by utilizing the modified version of the Newcastle-Ottawa scale (0–6) [13]. Our assessment included four factors: representativeness, population, definition of DM2, and confirmation of rheumatological diagnosis. Each study received scores based on these criteria, with higher scores representing better quality and a lower risk of bias. Studies scoring 0–2 points were classified as low quality, 3–4 points as moderate quality, and 5–6 points as high quality.

### Data analysis

Statistical analyses were performed utilizing R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). The selected studies provided data as a dichotomous variable, indicating whether individuals with DM2 had rheumatological diseases. Subsequently, the prevalence for specific outcomes was calculated individually for osteoarthritis, rheumatoid arthritis, and gout in people living with DM2. The results of the meta-analysis were constructed using forest plots and a random-effects model. In each study, the rectangular box represented the calculated estimate (prevalence of rheumatological diseases). In the forest plot, the horizontal line represented the 95% confidence interval (CI), while the diamond shape represented the pooled prevalence of rheumatologic conditions. Furthermore, the prediction intervals were incorporated to estimate the range of results that might be found in future studies. The heterogeneity of the studies was evaluated using the I squared ( $I^2$ ) statistic and its associated  $p$ -value. Heterogeneity levels were classified as high ( $I^2 > 50\%$ ), moderate ( $I^2 = 26–50\%$ ), and low ( $I^2 < 25\%$ ). Additionally, a funnel plot was employed to visually inspect possible publication bias and assess the associated risk.

## Results

### Literature search

The systematic review search and study selection procedures are depicted in **Figure 1**. A total of 3,287 studies were identified from the initial database search and three from additional sources, of which 1,162 duplicate studies were removed, resulting in 2,128 studies available for primary screening based on their titles and abstracts. Subsequently, 70 studies were deemed eligible for full-text screening, of which 13 studies met the predetermined inclusion criteria. Furthermore, by a citation search, we found three additional studies, but none of them met the inclusion criteria.

A final pool of 13 studies was included in the review, of which 11 were included in the meta-analysis. These studies consisted of 830,649 people living with DM2 and demonstrated a moderate overall quality. One study achieved a score of 6, four studies scored 5, five studies scored 4, two studies scored 3, and one study scored 2 (**Table 4**). The included studies were conducted in ten countries, with most participants from Canada [14], involving 295,907 participants and the fewest were from Egypt [10], with only 44 participants.

The characteristics of these studies varied, including retrospective, cross-sectional, population-based cohort, and prospective observational designs. The studies focused on the prevalence of gout, osteoarthritis, rheumatoid arthritis, and osteoporosis among DM2 patients, with treatment regimens including glucagon-like peptide-1 (GLP1) and sodium-glucose co-transporter-2 (SGLT2) inhibitors, metformin, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and statins. The characteristics of the studies included are presented in **Table 5**. A notable publication bias was observed among the included studies by visual inspection of the funnel plot illustrated in the **Underlying data** as an appendix.

### Prevalence of rheumatological diseases

The findings from eight studies, which included 234,589 participants, indicated that the pooled prevalence rate of OA among individuals with DM2 was 26% (95%CI: 19.8–32.8%;  $I^2$ : 100%;  $p < 0.01$ ), and the prediction intervals ranged from 6.9% to 51.8% as depicted in **Figure 2A**. Three studies involving 300,109 participants determined the prevalence of RA among patients with

DM2. The result identified a pooled prevalence of 0.3% (95%CI: 0.2–0.5%; I<sup>2</sup>: 97%;  $p < 0.01$ ), and the prediction intervals ranged from 0% to 5.1%, as illustrated in **Figure 2B**.

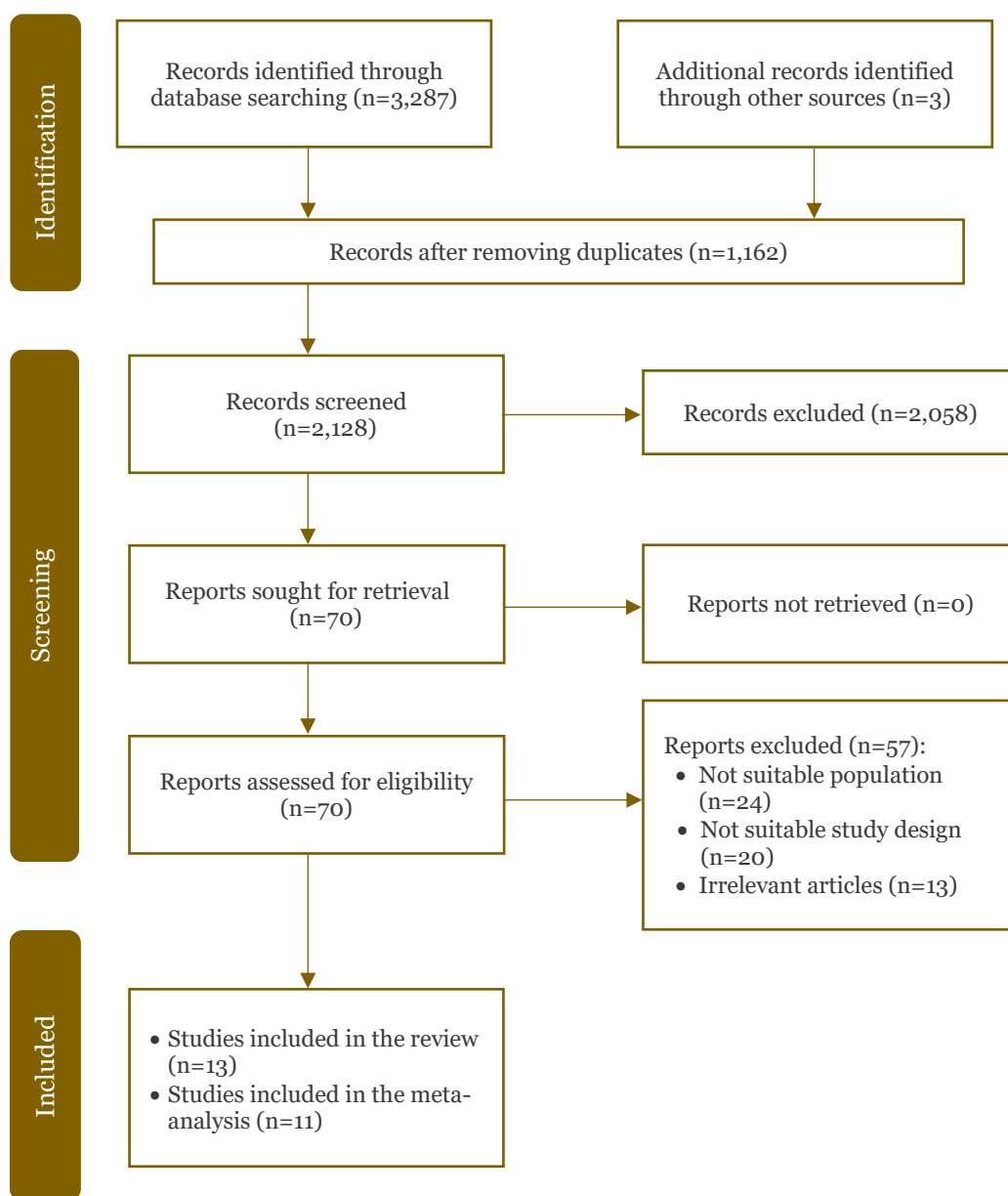


Figure 1. PRISMA flow diagram illustrating the process of conducting literature search and selection process.

Table 4. Quality assessment using a modified Newcastle-Ottawa scale

Study	Represent ativeness	Sample size 500	T2DM definition	Ascertainment of rheumatological disease	Total
Adrosy <i>et al.</i> , 2017 [10]	1	0	1	1	3
Fatemi <i>et al.</i> , 2015 [15]	1	0	1	0	2
Fralick <i>et al.</i> , 2020 [14]	1	1	2	1	5
Handa <i>et al.</i> , 2023 [16]	2	0	1	1	4
Huang <i>et al.</i> , 2021 [17]	1	1	1	1	4
Kim <i>et al.</i> , 2015 [18]	2	1	1	0	4
Nielen <i>et al.</i> , 2019 [12]	1	1	2	1	5
Nieves-Plaza <i>et al.</i> , 2013 [19]	2	1	2	1	6
Mathew <i>et al.</i> , 2011 [20]	2	1	1	1	5
Subramanian <i>et al.</i> , 2023 [21]	1	1	1	1	4
Tentolouris <i>et al.</i> , 2018 [11]	2	1	1	1	5
Zemedikun <i>et al.</i> , 2021 [22]	1	1	2	0	4
Zhu <i>et al.</i> , 2022 [23]	1	1	1	0	3

Table 5. Characteristics of studies included for review

Study, year	Country	Study design	Age (mean)	Male (%)	Total population	Outcomes				Treatment
						Gout	Osteoarthritis	Rheumatoid arthritis	Osteoporosis	
Adrosy <i>et al.</i> , 2017 [10]	Egypt	Retrospective study	50	NA	44	NA	NA	NA	13	NA
Fatemi <i>et al.</i> , 2015 [15]	Iran	Cross-sectional study	56.6	39.7	88	NA	65	NA	NA	NA
Fralick <i>et al.</i> , 2020 [14]	Canada	Population-based cohort study	54.3	49.9	295,907	1,472	NA	NA	NA	GLP1 and SGLT2 inhibitor
Handa <i>et al.</i> , 2023 [16]	Japan	Prospective observational	NA	NA	101	NA	17	NA	NA	NA
Huang <i>et al.</i> , 2021 [17]	Taiwan	Retrospective cohort study	56.75	47.89	48,904	2,755	4,105	NA	NA	Metformin and AGIs
Kim <i>et al.</i> , 2015 [18]	USA	Population-based cohort	55.5	NA	73,928	NA	NA	179	NA	Dipeptidyl peptidase-4 inhibitors
Nielen <i>et al.</i> , 2019 [12]	Netherland	Population-based cohort study	58.3	54.9	141,476	NA	11,975	NA	NA	NIADs
Nieves-Plaza <i>et al.</i> , 2013 [19]	USA	Cross-sectional study	53.3	46	100	NA	49	NA	NA	NA
Mathew <i>et al.</i> , 2011 [20]	India	Cross-sectional study	56.5	52.2	310	NA	NA	NA	75	NA
Subramanian <i>et al.</i> , 2023 [21]	UK	Retrospective open cohort study	61.84	55.9	43,043	85	9,334	NA	1,693	SGLT2 inhibitors and DPP-4 inhibitors
Tentolouris <i>et al.</i> , 2018 [11]	Greece	Prospective cohort	66.5	55.8	1,630	NA	NA	4	NA	NA
Zemedikun <i>et al.</i> , 2021 [22]	UK	Population-based retrospective open cohort study	63.1	55.92	224,551	NA	NA	971	NA	Metformin and statins
Zhu <i>et al.</i> , 2022 [23]	China	Cross-sectional study	64.43	57.5	567	NA	181	NA	NA	NA

AGIs: alpha-glucosidase inhibitors; DPP-4: dipeptidyl peptidase-4; GLP1: glucagon-like peptide-1; NA: not available; NIADs: non-insulin anti-diabetics; SGLT2: sodium-glucose cotransporter 2

Regarding gout, three studies with a total of 387,854 participants showed that the prevalence of gout among DM2 patients was 1% (95%CI: 0–5%;  $I^2$ : 100%;  $p < 0.01$ ), and the prediction intervals ranged from 0% to 99% (Figure 2C). Finally, as it relates to osteoporosis, only two studies were found to be relevant. One study reported a notably high prevalence, with 13 osteoporosis events out of 44 DM2 patients (29.5%) [10]. In contrast, another large cohort study reported 1,693 osteoporosis cases among 43,043 people living with DM2, resulting in a comparatively low prevalence of 3.9% [21].

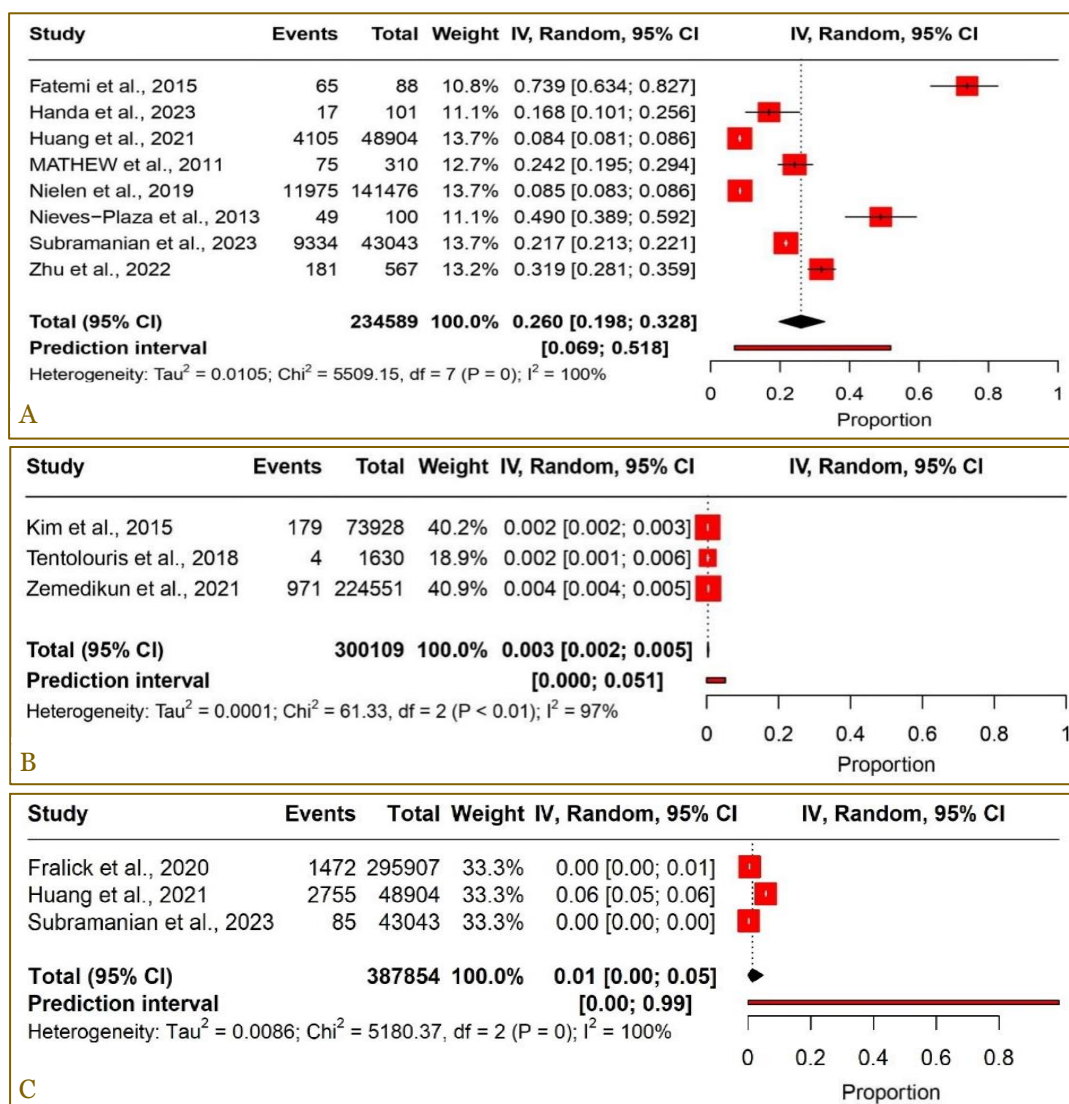


Figure 2. Forest plot illustrating the overall prevalence of osteoarthritis (A), rheumatoid osteoarthritis (B), and gout in patients with type 2 diabetes (C).

## Discussion

The novel aspect of this review is its comprehensive assessment of all major rheumatologic conditions among people living with DM2, particularly OA, RA, gout, and osteoporosis. This review found that the prevalence rate of OA was 26% among people living with DM2, suggesting a potential shared underlying pathophysiological mechanism between the two diseases. OA is associated with DM2 and may be attributed to systemic inflammation, altered biomechanics, or end products of glycation that affect joint tissues [24].

The prevalence of RA was 0.3%, which may seem relatively low. However, considering the serious implications of comorbid DM2 and RA, even this small percentage has significant clinical relevance. Both conditions have inflammation as a central component, and RA might exacerbate DM2 or vice versa [25]. The management of one condition can affect the other. For example, corticosteroid treatment in RA can affect glucose metabolism [25]. The prevalence of gout was 1%

among people living with DM2, emphasizing the importance of understanding the metabolic intricacies of hyperuricemia (high uric acid levels) and insulin resistance. Furthermore, few epidemiological studies have shown that diabetes can induce osteoporosis, also known as diabetes-induced osteoporosis, which involves both the usual effects of osteoporosis and an increased risk of fractures due to diabetes [26-28].

In exploring the prevalence of osteoporosis in patients with DM2, this review found limited data, with only two available studies. These studies showed contrasting results, with one smaller study reported a prevalence of 29.5%, indicating a significant burden of comorbidity of DM2 and osteoporosis [10]. In contrast, the second study, which involved a larger cohort, reported a much lower prevalence of 3.9% [21]. High heterogeneity was found in all the studies reporting on osteoarthritis and gout among people with DM2, raising concerns about the variability in study populations and methodologies. Factors that contribute to this heterogeneity could include differences in the study populations or different study methodologies. Some studies on the risk of RA in DM2 patients on various antidiabetic medications found a significant association between the use of medication and the reduction of gout and the rate of RA [29-31].

Some studies have explored factors that influence the risk of rheumatological conditions in people with DM2 [11,14,19,22,23]. A study conducted by Fralick *et al.* in Canada focused on newly diagnosed individuals with gout and excluded those with a history of gout. Among nearly 300,000 adults diagnosed with DM2, the study revealed a lower incidence of gout among those prescribed sodium-glucose cotransporter-2 (SGLT2) inhibitors compared to individuals prescribed glucagon-like peptide-1 (GLP1) agonists or dipeptidyl peptidase-4 (DPP4) inhibitors [14]. Zemedikun *et al.* conducted a retrospective cohort study to assess the impact of metformin and DPP4 inhibitors on the risk of developing RA. The findings suggested a potential association between statin use and a reduced risk of RA [22]. In another cross-sectional study by Zhu *et al.*, a positive correlation was identified between DM2 and OA when adjusted for age, sex, and race [23]. Surprisingly, Tentolouris *et al.* conducted a robust decade-long prospective study where the authors found a decrease in the prevalence of RA among people living with DM2. This study supports the hypothesis that immunosuppression in individuals with long-standing DM2 may play a role in the decreased prevalence of RA among those with DM2 [11]. Furthermore, the study demonstrated that the prevalence of RA is lower and tends to occur at an older age in individuals with preexisting DM2 than in those without the condition [11]. Nieves-Plaza *et al.* conducted a population-based study to assess the link between OA and diabetes among Hispanics. The researchers found that individuals with DM2 were at a higher risk of developing OA in the hands or knees compared to individuals without DM2. Within the DM2 cohort, women manifested OA in the hands or knees. The study also found that the administration of insulin was inversely associated with the onset of OA, suggesting a protective relationship between insulin usage and the development of OA [19]. Studies by Abourazzak *et al.* and Mathew *et al.* found that people with DM2 often have problems like carpal tunnel syndrome [20,32]. Sözen *et al.* found that muscle and joint problems occur more often in people with DM2, and these can make treating diabetes more complicated, and the comorbidities also reduce the quality of life [33]. These studies also suggest that DM2 could increase the risk for additional musculoskeletal disorders that need further exploration [20,32,33].

The strength of this review lies in its comprehensive assessment of the prevalence of rheumatological conditions in individuals with DM2, providing valuable insights into the global burden of these comorbidities by following a rigorous methodological approach. This meta-analysis uniquely highlighted the significant prevalence of OA among DM2 patients and underscored the importance of early diagnosis and management of rheumatological conditions to improve health outcomes. However, the potential limitations of our review were related to the exclusive consideration of published papers, which may lead to publication bias and the omission of unpublished studies and grey literature. Furthermore, studies with pre-existing rheumatological diseases were excluded, which might have provided additional relevant data about the relationship between DM2 and rheumatological conditions. These exclusions limit the generalizability and comprehensiveness of the review's findings. Additionally, the moderate quality of the included studies and the high heterogeneity, likely due to variations in their



methodology, are notable limitations. The limited population in a few of the included studies also posed challenges in addressing heterogeneity.

Future research should include long-term prospective studies with larger sample sizes and analyses of different patient groups, such as those varying in age, gender, ethnicity, and duration of DM2. These studies should investigate the development of rheumatological conditions and aim to improve care for patients with DM2 and these comorbidities. Despite these limitations, this is the first meta-analysis related to this topic, and the findings highlight the importance of early identification and treatment of various rheumatological conditions in people living with DM2. Healthcare providers should consider a comprehensive approach to address both DM2 and its related conditions. Exploring how DM2 can suppress the immune system could also lead to newer treatment options [34].

## Conclusion

This study revealed a considerable prevalence of OA among patients with DM2. The incidence of RA and gout was observed to be minimal. These findings emphasized the need for personalized treatment approaches for rheumatological diseases in individuals with DM2. Additional research is needed to further explore and understand the link between DM2 and rheumatological diseases, ultimately leading to better prevention, early diagnosis, and management for individuals affected by both conditions.

## Ethics approval

Not required.

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None to declare.

## Competing interests

All the authors declare that there are no conflicts of interest.

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## Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request. The supplementary data can be found at <https://figshare.com/ndownloader/files/49067875>.

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