



Bidirectional association between uveitis and psoriasis: a systematic review and meta-analysis

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Abstract

Background In recent years, the prevalence of uveitis among patients with psoriasis has shown a noticeable upward trend. Previous studies have investigated the immunological mechanisms underlying the potential connection between psoriasis and uveitis, but systematic studies exploring their bidirectional relationship is absent. This study aims to systematically evaluate the bidirectional association between psoriasis and uveitis to provide evidence.

Methods We thoroughly searched PubMed, Embase, and the Cochrane Library for relevant observational studies published from the inception of these databases up to Mar 11th, 2024. Our systematic review was based on priori protocol pre-registered in PROSPERO (No. CRD42024522464). Risk and bias assessments were analyzed using STATA 16.0.

Results We analyzed the results from 7 studies involving 81,775,820 subjects. The results showed that the incidence of uveitis was higher in patients with psoriasis compared to patients without psoriasis (OR = 1.16, 95% CI: 1.11–1.21). At the same time, patients with uveitis showed heightened susceptibility to psoriasis (OR = 1.52, 95% CI: 1.34–1.70, I²: 90.6%, P < 0.01). The subgroup analysis found that uveitis affects the severity and type of psoriasis.

Conclusions The current systematic review and meta-analysis found a bidirectional association between psoriasis and uveitis. Notably, patients with severe psoriasis and psoriasis with joint symptoms should be informed about their increased risk to developing uveitis.

Keywords Psoriasis · Uveitis · Meta-analysis · Immunology · Inflammatory disease

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Introduction

Psoriasis is a chronic erythematous scaly skin disease that is difficult to treat and prone to relapse. Psoriasis can occur at any age, and its prevalence ranges from 0.14% (95% CI 0.05–0.40%) in East Asia to 1.99% (0.64–6.60%) in Australasia [1]. Psoriasis greatly affects the quality of life of patients and brings the risk of many other diseases, such as cardiovascular disease [2], diabetes [3], stroke [4], metabolic syndrome [5], inflammatory bowel disease [6], etc., so psoriasis itself and its comorbidities should be taken seriously.

Recently, the relationship between psoriasis and eye diseases has gradually attracted the attention of doctors, including uveitis [7], dry eye [8], etc. Ocular diseases are closely linked to immune system abnormalities and inflammatory skin disorders. Dysregulation or abnormal activation of the immune system can not only lead to ocular inflammation but also trigger or exacerbate inflammatory skin conditions such as psoriasis and atopic dermatitis. In recent years, advancements in immunology and molecular biology have gradually uncovered shared pathological mechanisms among these diseases, particularly the interplay between inflammatory factors and immune cells [9, 10]. Uveitis refers to inflammation of the iris, ciliary body and choroidal tissue. It can be divided into anterior, middle, posterior and panuveitis according to the different sites of the lesions. It is a common vision-threatening and easily overlooked eye disease. If not diagnosed and treated in time, it can lead to blindness. Eye diseases are frequently linked to aberrant immune environments, particularly as the association between uveitis and rheumatic diseases, such as psoriatic arthritis, has been well-documented in prior studies [11]. This underscores the imperative for ophthalmologists to adopt a comprehensive diagnostic approach.

However, the relationship between uveitis and non-articular psoriasis has gradually been revealed. Some scholars have found that uveitis is very common in HLA-B27-positive psoriasis patients, with an incidence of uveitis between 1.5% and 2.5% [12], and can occur independently in psoriasis patients without joint symptoms. Studies have found that HLA-B27-positive psoriasis patients may have more drug resistance and are more prone to more difficult to control, recurrent uveitis [13]. In previous studies, some scholars have found changes in the bidirectional prevalence of psoriasis and uveitis [14], and some scholars have conducted a systematic analysis based on the incidence of uveitis in psoriasis patients [7, 15], but the bidirectional relationship between the two has not been systematically studied and explored.

Materials and methods

This systematic review and meta-analysis adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16] and was registered in advance on the International Prospective Register of Systematic Reviews (PROSPERO) platform (No. CRD42024522464). Prior to registration, we established the foundational information, detailed research design, methodological choices tailored to the specific research design, and conducted an initial literature review. Subsequently, we refined the pertinent information in accordance with the registration guidelines of the PROSPERO website, ensuring both the comprehensiveness and precision of the data. The website offers recommendations for revisions, and we are required to implement the necessary adjustments based on this feedback.

Literature search

We conducted a comprehensive search of PubMed, Embase, and the Cochrane Library for relevant studies spanning from the inception of these databases to March 11th, 2024. Our search strategy utilized medical subject headings (MeSH) and synonyms for psoriasis and asthma, without any restrictions on geographical location or language. Details of the search strategy are provided in Supplementary Table 1.

Inclusion criteria and literature screening

The criteria for study selection included: (1) Observational studies that reported on the prevalence or risk factors of uveitis in psoriasis patients or vice versa, encompassing cohort, case–control, or cross-sectional designs. (2) For studies involving psoriasis patients as the case or exposure group, the control group consisted of individuals without psoriasis. Additionally, we excluded duplicate publications, conference abstracts, comments, letters, or studies with irrelevant findings. Studies utilizing the same cohort or having a sample size of less than 10 were also excluded. Study selection was performed independently by two authors (DDW and RC), who screened titles and abstracts and obtained full texts of potentially eligible studies. In cases of disagreement between the two authors, a third author (NL) resolved the discrepancy.

Data extraction

Data extraction was independently conducted by two authors (YP and JM) using a predefined form based on systematic review and meta-analysis guidelines [17]. Extracted baseline

data encompassed first author, publication year, country, study design, participant demographics (age), duration of follow-up, diagnostic criteria used, sample size, adjustments made, and quality assessment. Disagreements were resolved through consensus discussion or by involving a third author (NL) for final adjudication.

Risk of bias assessment

Quality assessment of cohort and case–control studies was conducted using the Newcastle–Ottawa Scale (NOS) [18]. Scores ranging from 0 to 3, 4 to 6, and 7 to 9 indicated low, moderate, and high-quality studies, respectively. The assessment was independently performed by two authors (SRB and KLZ).

Statistical analysis

We utilized Stata 16.0 (Stata Corp, College Station, Texas) for data analysis investigating the association between psoriasis and uveitis. For case–control and cross-sectional studies, we computed odds ratios (ORs) with 95% confidence intervals (CIs), while for cohort studies, incidence rate ratios (IRRs) were calculated. Heterogeneity was assessed using I^2 statistics. A fixed-effect model was employed if $P > 0.1$ and $I^2 \leq 50\%$; otherwise, a random-effects model was used for $I^2 > 50\%$, indicating substantial heterogeneity. In cases of significant heterogeneity, sensitivity or subgroup analyses were conducted, with recalculations performed after excluding studies contributing to the heterogeneity. Funnel plots were generated to evaluate publication bias, and Begger's and Egger's tests were applied accordingly. Throughout the study, our primary focus was on assessing the influence of various factors on the meta-analysis outcomes. These factors encompass both demographic characteristics, such as age, gender, and race, as well as disease-related variables, including diagnostic criteria, disease severity, classification, and treatment modalities. We will strategically select relevant categories for more in-depth subgroup analysis, aiming to mitigate the impact of heterogeneity on our results.

Results

Study characteristics

A total of 5942 records were initially retrieved. After removing 545 duplicates, 5397 unique records remained for screening. Through title and abstract review, following our predefined inclusion and exclusion criteria, 5324 irrelevant articles were excluded. Subsequently, after full-text assessment of the remaining 73 articles, we identified 7 studies meeting our criteria for inclusion in the analysis. Figure 1

illustrates the PRISMA flow chart detailing the study selection process.

The 7 studies [19–25] conducted between 2015 and 2024, included a total of 81,775,820 subjects. All the studies were cohort studies. The main characteristics of the included studies are summarized in Table 1.

Quality assessment

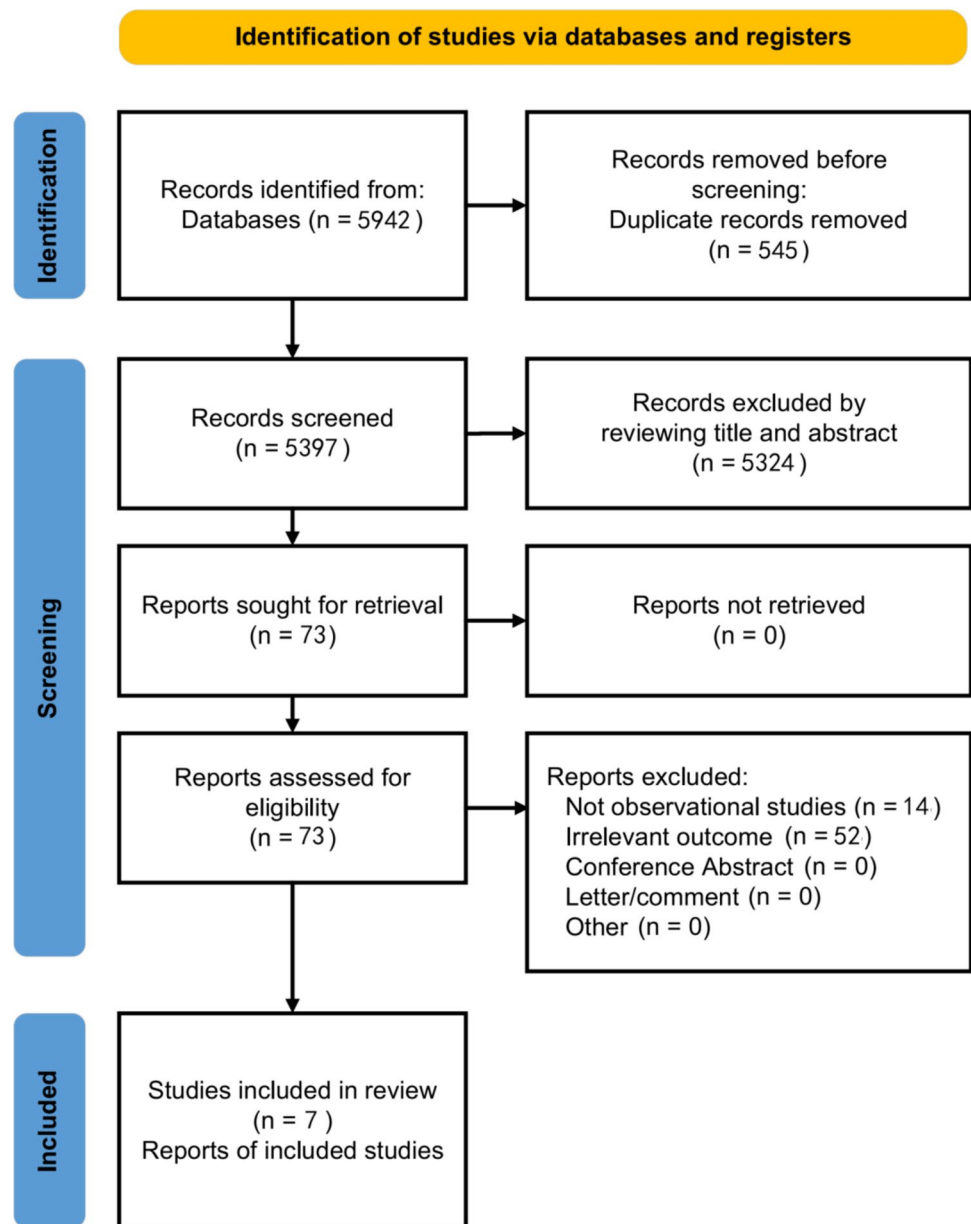
The quality assessment of cohort studies was conducted using the Newcastle–Ottawa Scale (NOS), with scores ranging from 6 to 9 points and an average score of 7.4 for studies involving patients with psoriasis and uveitis. Studies focusing on patients with both conditions had NOS scores ranging from 6 to 9 points, with an average score of 7.7 points. All studies included in this meta-analysis were rated as medium to high quality. Detailed scores can be found in Table 1.

Bidirectional association between psoriasis and uveitis

Six cohort studies [19, 21–25] were included in the analysis examining the risk of asthma among patients with psoriasis. According to the meta-analysis, uveitis was associated with an increased incidence of psoriasis (OR = 1.16, 95% CI: 1.11–1.21, Fig. 2), with low statistical heterogeneity ($I^2 = 21.4\%$, $P < 0.001$). Among these studies, two were bidirectional cohort studies [21, 25], therefore the investigation into the risk of psoriasis in patients with uveitis was based on three cohort studies [20, 21, 25]. The meta-analysis indicated that psoriasis was associated with an increased incidence of uveitis (OR = 1.52, 95% CI: 1.34–1.70, $I^2 = 90.6\%$, $P < 0.01$, Fig. 3). Given the high I^2 value ($> 50\%$), a random-effects model was employed to account for heterogeneity. Sensitivity analysis did not identify any single study significantly contributing to heterogeneity, hence no exclusions were made.

Subgroup analysis

Our findings suggest that uveitis may influence the severity and type of psoriasis. Specifically, the risk of uveitis was higher among patients with moderate to severe psoriasis (OR = 1.27, 95% CI 1.04–1.54) compared to those with mild psoriasis (OR = 1.13, 95% CI 1.04–1.23). Furthermore, different types of psoriasis also influenced the incidence of uveitis. The risk of uveitis was significantly higher in the psoriatic arthritis subgroup (OR = 2.17, 95% CI 1.64–2.69) than in the general psoriasis group (OR = 1.17, 95% CI 1.10–1.24). Detailed results are presented in Table 2.

Fig. 1 the PRISMA flow chart of study selection

Publication bias

There was no significant publication bias in the studies investigating the relationship between psoriasis and uveitis (Fig. 4). Both the funnel plot visual examination and Egger's regression test results ($P=0.096, >0.05$) revealed no substantial evidence of publication bias. However, for the studies focusing on uveitis risk in psoriasis patients, we identified publication bias ($P=0.01, <0.05$, Fig. 5). To address this, we applied the trimming and filling method, conducting three iterations that involved reanalyzing results from three articles. Following adjustments, no publication bias was evident across all eleven articles. The final trimmed and filled hazard ratio was 1.430 (95% CI: 1.299–1.575),

consistent with the initial analysis results (OR = 1.52, 95% CI: 1.34–1.70). Consequently, considering the reliability of the original findings, future studies should aim to expand the dataset to mitigate potential biases.

Discussion

Main findings

A total of 7 studies were included in this bidirectional meta-analysis, with a total number of 81,775,820 participants. The results reveal that uveitis increases the risk of psoriasis by 1.16 times, whereas psoriasis increases the risk of uveitis

Table 1 Study Characteristics

Author	Year	Country	Study Type	Age (Mean \pm SD)	Follow-up years	Diagnostic criteria	No. of participants	Adjustment	Quality assessment
Studies investigating the odds of asthma in psoriasis patients									
Egeberg	2015	Denmark	Cohort study	Mild 43.8 \pm 16.8 Severe 42.6 \pm 15.7	Starting January 1, 1997, and followed up until December 31, 2011	Psoriasis ICD-8 code 696.10 , 696.19, ICD-10 code L40	5508,878	Age, sex, socioeconomic status, and comorbidities	A
Chi	2017	Taiwan	Cohort study	Psoriasis 44.4 \pm 19.8 Control 44.4 \pm 19.8	At least 2 outpatient visits or 1 hospital admission	Psoriasis: ICD-9-CM 696 , 696.1 or 696.8	29,908	Age, sex, type II diabetes mellitus, hypertension, and hyperlipidemia	8
Brandon	2018	USA	Cohort study	0–16	NA	ICD-9-CM code	49,552	NA	7
Aletaha	2019	Austria	Cohort study	46.5 \pm 11.6	NA	ICD-9-CM code	74,343,272	NA	6
Kim	2022	Korea	Cohort study	Psoriasis 48.42 \pm 16.70 Control 48.43 \pm 16.67	60 days	ICD-10-CM	953,820	Age group, sex, and presence of diabetes, hypertension and hyperlipidemia	7
Patt	2024	Israel	Cohort study	Psoriasis 36.1 \pm 19.3 Control 36.1 \pm 19.3	NA	ICD-9 code	305,015	Age, sex, and uveitis related comorbidities	8
Studies investigating the odds of psoriasis in uveitis patients									
Egeberg	2015	Denmark	Cohort study	NA	Starting January 1, 1997, and followed up until December 31, 2011	Uveitis ICD-8 code 364, ICD-10 code H20.0-H20.9	5,508,878	Age, sex, socioeconomic status, and comorbidities	A
Aletaha	2019	Austria	Cohort study	46.5 \pm 11.6	NA	ICD-9-CM code	74,343,272	NA	6
Chen	2021	Taiwan	Cohort study	50.2 \pm 17.2	Mean follow-up years: 6.02 years	ICD-9-CM code	585,375	Age, sex, insurance cost, hypertension, diabetes, hyperlipidemia, and obesity	8

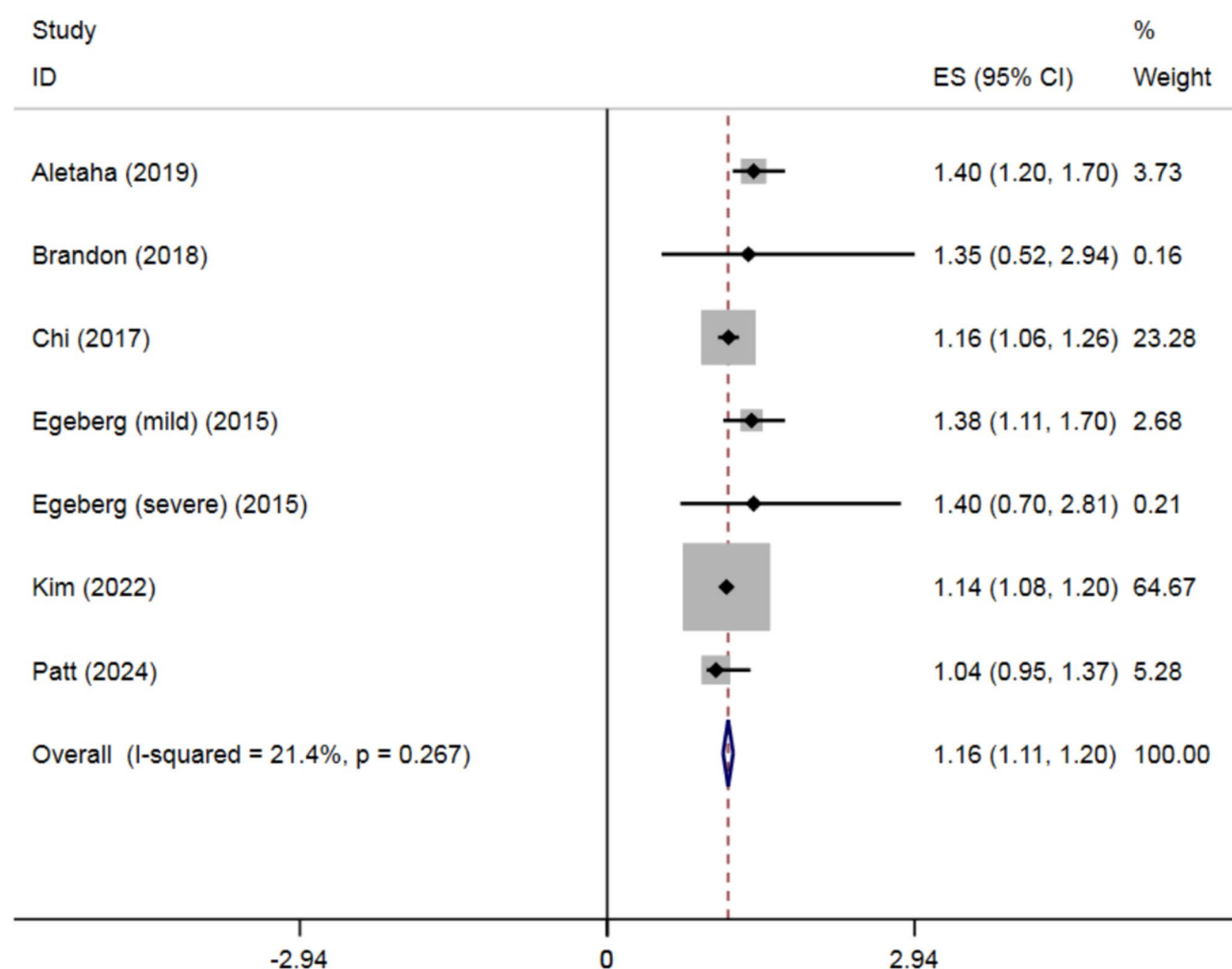


Fig. 2 Forest plot for studies of the association on psoriasis with uveitis

by 1.52 times. We also conducted a subgroup analysis of the risk of uveitis in patients with psoriasis and found that the severity of psoriasis affected the incidence of uveitis, with higher severity correlating with a higher probability of developing uveitis.

Interpretation of the main results

The association between psoriatic diseases and uveitis has garnered significant scholarly attention. Mounting evidence underscores a link between psoriasis, psoriatic arthritis, and uveitis, particularly highlighting the connection between psoriatic arthritis and uveitis [26]. Nevertheless, the relationship between psoriasis and uveitis remains contentious. Recent observations indicate uveitis occurrences in psoriatic patients without joint involvement [27], suggesting a need for broader investigation into this bidirectional link. This study aims to comprehensively explore the mutual association between psoriasis and uveitis

for the first time. HLA-B*27, a commonly implicated risk gene in psoriatic arthritis and uveitis, underscores genetic susceptibility. Immunological pathways also contribute to the pathogenesis of both conditions [28], notably the IL-23/Th17/IL-17 axis. Th17/IL-23 serves as a pivotal pathogenic factor in psoriasis, promoting keratinocyte proliferation. IL-23, produced by Th1 cells, activates dendritic cells and induces naïve CD⁺T cells to differentiate into Th17 cells, thereby exacerbating psoriasis pathogenesis. Uveitis is an intraocular disease driven by autoinflammation or autoimmune responses. The immunological mechanisms involved encompass the interplay of various immune cells and cytokines, such as the dysregulation of the Th17/Treg cell balance, the overexpression of cytokines like TNF- α and IL-6, among others. The association between uveitis and psoriasis is linked to the activation of the IL-23/IL-17 pathway, which is crucial for the expansion and pathogenicity of Th17 cells [9]. This indicates that psoriasis and uveitis share common immune mechanisms.

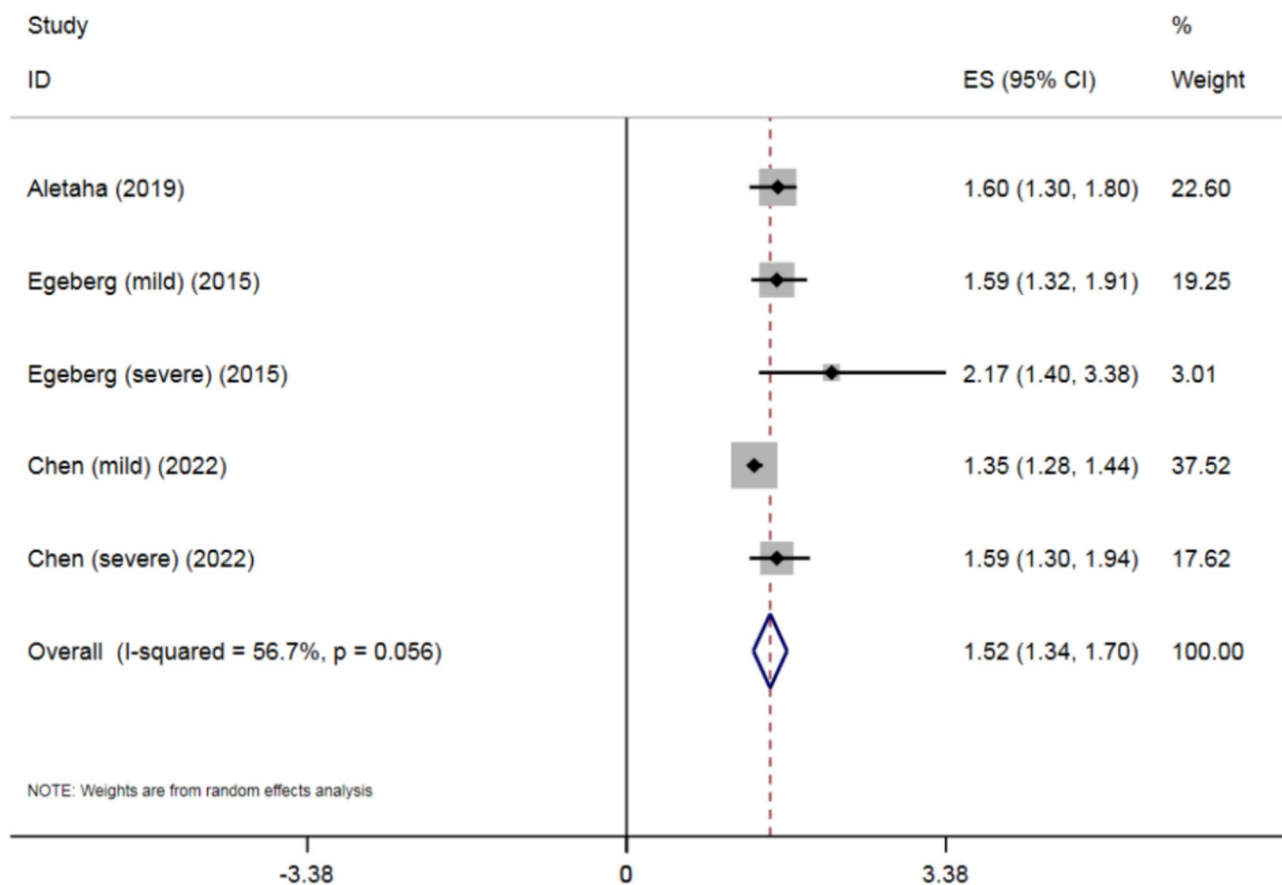


Fig. 3 Forest plot for studies of the association on uveitis with psoriasis

Table 2 Subgroup analysis

Subgroups	Included Studies	OR (95%CI)	Heterogeneity	Significance test	
			I ² (%)	Z	P-values
Severity of Psoriasis					
Mild	3 [17, 19, 20]	1.13 (1.04, 1.23)	51.2	2.89	0.004
Severe	3 [17, 19, 20]	1.27 (1.04, 1.54)	70.5	2.35	0.019
Subgroups differences	6		64.3	3.93	0.000
Type of psoriasis					
Psoriasis	6 [17, 19–23]	1.17 (1.10, 1.24)	21.4	7.11	0.000
Psoriatic arthritis	5 [17, 19–21, 23]	2.17 (1.64, 2.69)	73.1	1.76	0.079
Subgroups differences	11		81.8	7.20	0.000

We performed subgroup analyses based on varying severities and types of psoriasis, revealing that the severity of psoriasis and the presence of joint symptoms influence the incidence of uveitis. The subgroup analysis demonstrated that more severe psoriasis lesions correlate with a higher risk of uveitis. Specifically, patients with severe psoriasis (OR = 1.27, 95% CI 1.04–1.54) face a greater risk compared to those with mild psoriasis (OR = 1.13, 95% CI 1.04–1.23). Furthermore, psoriatic arthritis is associated with an increased likelihood of uveitis among psoriasis

patients (OR = 2.17, 95% CI 1.64–2.69), presenting a significant difference compared to those without psoriatic arthritis (OR = 1.17, 95% CI 1.10–1.24). These findings align with prior research on the impact of uveitis in psoriatic arthritis, noting a relative lack of exploration and attention given to uveitis in the context of psoriasis alone.

For healthcare providers, optimizing the management of patients with moderate to severe psoriasis—particularly those with psoriatic arthritis—is of paramount importance. This can be accomplished through the adoption of systematic

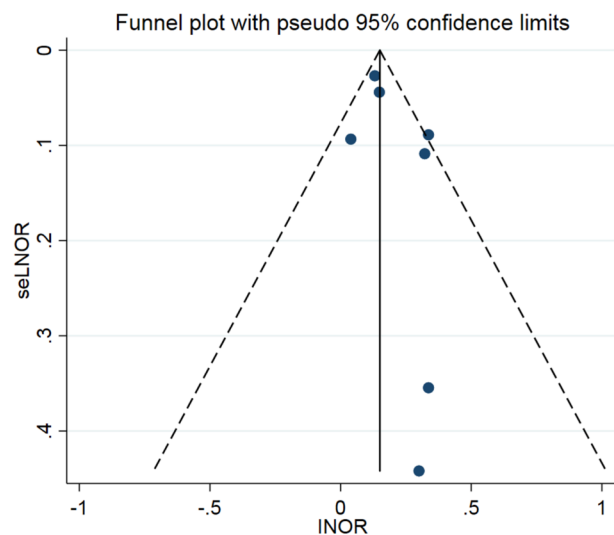


Fig. 4 Publication bias of psoriasis patients with uveitis

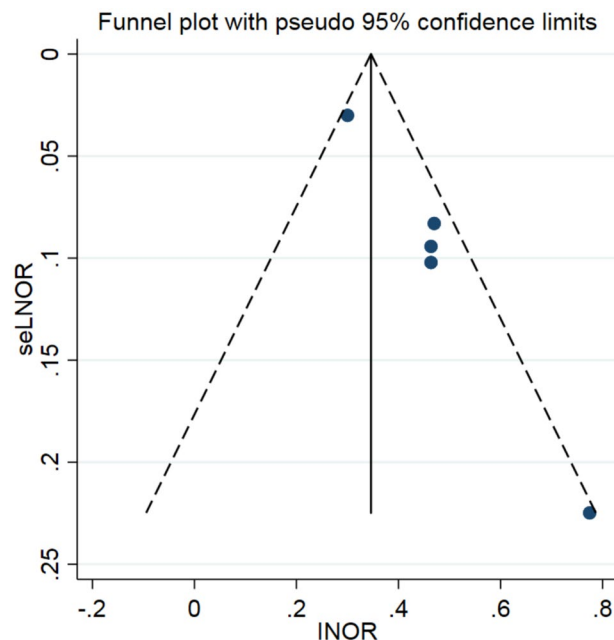


Fig. 5 Publication bias of uveitis patients with psoriasis

screening protocols and preventive interventions. In clinical practice, it is recommended that all patients with moderate to severe psoriasis undergo annual ophthalmologic evaluations to screen for uveitis [29]. For patients with psoriatic arthritis, who are at an elevated risk, the screening interval should be reduced. Effective interdisciplinary collaboration between dermatologists and ophthalmologists is essential to ensure a comprehensive approach to patient evaluation and management.

Patient education plays a vital role in this process. Patients should be informed about the potential link between psoriasis and uveitis, with an emphasis on the importance of routine eye examinations. They should also be encouraged to promptly report any ocular symptoms, such as redness, pain, or visual disturbances. For high-risk individuals, implementing structured long-term follow-up protocols is critical to facilitate ongoing monitoring and timely therapeutic interventions. Furthermore, in psoriasis patients receiving systemic therapies, including biologics, the potential effects on ocular inflammation should be thoroughly assessed, and treatment regimens should be tailored accordingly.

Implications and limitations

Previous studies have identified a bidirectional association between psoriasis and uveitis [12]. This study distinguishes itself by conducting the first systematic review and meta-analysis of observational studies to explore this bidirectional relationship, thereby enhancing the reliability of the findings. However, this study is limited by significant heterogeneity and a lack of research on psoriasis among uveitis patients. Sensitivity analysis failed to identify the source of this heterogeneity, and subgroup analyses were not performed. Expanding the literature on psoriasis incidence in uveitis patients may help mitigate such heterogeneity. Moreover, while previous research has investigated a possible link between pustular psoriasis and uveitis, the majority of current studies have primarily concentrated on case reports and the efficacy of biologic therapies [30, 31]. The scarcity of large-scale epidemiological studies may be attributed to the rarity of generalized pustular psoriasis (GPP). Further evidence is required to validate these findings and ensure their applicability to all patients with pustular psoriasis. Importantly, only one study has investigated uveitis recurrence, emphasizing the need for increased research attention in this area.

Conclusions

This study reveals a bidirectional relationship between psoriasis and uveitis, underscoring significant risks associated with each condition in relation to the other. However, research on this topic remains relatively sparse, especially concerning the prevalence of psoriasis among uveitis patients. Therefore, additional evidence is crucial to deepen our understanding of how these diseases interact. Conducting comprehensive subgroup analyses is advised to better stratify diseases, with particular attention to

specialized forms of psoriasis and recurrent episodes of both psoriasis and uveitis.

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Author contributions Conceptualization: Doudou Wu, Rui Cai, Ying Pang Data extraction: Ying Pang, Jie Ma Quality assessment: Bailin Chen, Kaili Zheng Formal analysis: Doudou Wu, Rui Cai, Siran Bao Methodology: Yiming Qi, Wenbo Jiang Original Draft: Doudou Wu Final revision: Doudou Wu, Nuo Li Funding acquisition: Nuo Li All the authors put forward their own opinions during the research and design stage, and completed the research rigorously according to the process, strictly reviewed the first draft and approved the final version after discussion, and agreed to take responsibility for the work.

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Availability of data and material No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval and consent to participate Not applicable.

Consent for publication Not applicable.

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