Association between psoriasis and migraine: what should we expect from a meta-analysis?

Rui Xu
Sun Yat-sen University First Affiliated Hospital
Ying Xiong
Sun Yat-sen University Zhongshan School of Medicine
Xiaolan Wei
Fujian Medical University Affiliated First Quanzhou Hospital
Xiaobao Huang
Sun Yat-sen University First Affiliated Hospital
Yuting Chen
Sun Yat-sen University First Affiliated Hospital
Jande Han (hanjd@mail.sysu.edu.cn)
Sun Yat-sen University First Affiliated Hospital https://orcid.org/0000-0002-4465-7632

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Abstract

Background Although many studies have demonstrated the commodity of psoriasis with migraine and indicated that they may have similar susceptibility genes and pathophysiologic mechanism, the clinic association between the migraine and psoriasis remains unclear.

Methods We have already searched Pubmed, Embase, and Web of Science for case–control, cross-sectional, or cohort studies, and extract rate, odds or risk of migraine in subjects with psoriasis or without psoriasis. Using defined inclusion and exclusion criteria, finally include nine studies. Pooling of the suitable data was applied when necessary.

Results Five cross-sectional studies included 6355 psoriasis patients and 934413 controls, migraine highly occurred in psoriasis patient (pooled OR 1.64; 95% confidence interval [1.28; 2.11]). In addition, with 4375 psoriasis patients provided, the rate of migraine occurred in psoriasis patient (pooled rate 0.21; 95% confidence interval [0.13; 0.35]).

Conclusion Migraine and psoriasis present a clear co-occurrence and similar pathophysiologic mechanism, which lead to the assumption that the two diseases might be linked. Screening and selection of proper assessment of migraine among psoriasis patients are warranted and needed.

Introduction

As psoriasis is an immune-mediated, polygenic and chronic, systemic disorder, and the prevalence is around 2–3% of the population worldwide[1]. Its clinic hallmark is itching and painful erythematous scaly plaques that can occur on any part of skin. To date, psoriasis has been re-considered from a skin related disorder to a systemic disease, which cause a long-term damage to multiple tissues and organs[1–3] and impair the quality of life. In some cases, patients often experience associated neurological or psychiatric morbidity[4], such as multiple sclerosis, epilepsy, migraine, depression, anxiety and suicidal behavior and so on. Meanwhile, there are several reports present that psoriasis patients with nerve injury or denervation have presented unilateral regional improved, even total remission of their skin lesions in the affected or damaged area[5]. There is some meta-analysis of multiple sclerosis[6], stress and suicidality[7, 8] comorbided with psoriasis. It draws our attention on the neurological systems in the pathophysiology of psoriasis.

Migraine is a primary episodic neurovascular headache disorder. Although the precise pathogenesis is still unclear, migraine has been defined as a local sterile meningeal inflammation,mediated by several proinflammatory mediators which also serve an important impact on the mechanism of psoriasis[9, 10], and neuroimmune interactions allow the dynamic regulations of systemic and local inflammations through the nerve-based “inflammatory reflex”[11]. Even more, 2-fold higher risk of cardiovascular disease (CV) is associated with migraine with aura (MA) [12–14] which might have impact on the co-morbidity status in psoriasis.

Besides, using of biologic medication has represented a great advancement in the treatment of psoriasis,and with the increasing popularity of biologics[15], their side events[16] including neurological side[17] (e.g. Headache) have been a constant concern. Additionally, efalizumab was withdrawn from the market in 2009 for side-effect of progressive multifocal leukoencephalopathy[4, 16]. Earlier evaluation of neurologic complications

of biologic agents should be needed in the treatment of psoriasis. Thus, increased high-lighten on co-morbidity of migraine with psoriasis may be notified in clinic assessment.

Previous studies have showed that migraine and psoriasis may have similar predilected genes and neuro-immunologic physiology mechanisms leading to overactive immune responses[18–20]. However, the results of clinic correlation between migraine and psoriasis are controversial among some studies. so, this study conducted a meta-analysis of appropriately included and selected studies to assess the correlation of migraine with psoriasis.

Material And Methods

Literature Search strategy

We followed PRISMA guidelines[21] to evaluate the association between migraine and psoriasis until December 2019. Two researchers (Xu, Xiong) performed all procedures of the study independently and any disagrees between researchers was solved by a third and senior author. We searched Pubmed, Embase, and Web of Science for relevant studies until December 2019. The search strategy was “(psoriasis OR psoriatic) AND (migraine OR migraines OR migrainosus OR headache OR headaches)” with language limitation on English, we also included relevant studies found in conference presentations.

Study Selection: inclusion and exclusion criteria

The inclusion studies as follows: (i) observational studies including case-control, cross-sectional, and cohort studies; (ii) the exposure group consisted of patient diagnosed with psoriasis, the control group comprised of non-psoriasis participant; (iii) the outcome was either the standardized incidence ratio (SIR’S), odds ratio (OR’s),relative risk (RR’s) or hazard ratio (HR’s) of migraine in subjects with psoriasis. We excluded cases series without observational studies.

Two authors (Xu, Xiong) independently scanned the titles and abstract of studies and determined whether they suitable for our inclusion criteria. The third and Senior investigator would solve the differing decisions between the two authors by discussion. two investigator would independently assess the quality and bias of included studies by using Newcastle-Ottawa quality assessment scale (NOS)[22].

Data Extraction

Extracte the following data were from the included studies by applying a standard data collection checklist: last name of the first author, publication year, country, study method, study subjects, diagnosed criteria and results. We subdivided the included studies into two types: (i) cross-sectional studies and (ii) cohort studies. Two authors (Xu, Xiong) independently assess the quality and bias of included studies by applying NOS. A study could be rated as low quality (NOS≦3), moderate quality ((NOS score between 4 and 6) and high quality (NOS score ≧7) based on its effects on validity in each parts accordingly (NOS: selection of study groups, comparability, and exposure/outcome assessment) [22].

Analysis

Review Manager 5.3 software from Cochrane Collaboration and R package meta x64 3.6.2 were used for conducting the meta-analysis. We present the odds ratios (OR) for cross-sectional studies, separate pooling the overall prevalence rate was calculated for single rate meta-analysis. The heterogeneity was evaluated by using the I^2 statistic. An I^2 value of ≥ 50% represents substantial heterogeneity[23], we apply a random-effects model meta-analysis because under the consideration of clinical heterogeneity.

Results

Characteristics of Selected Studies

As illustrated in **Fig. 1**, our search protocol identified 1004 articles after removing duplicated articles and screening the records. Eventually, with exclusion of the articles related with drug side-effects, we assessed 9 full-text publications, which were identified as eligible as they examined co-occurrence of migraine and psoriasis. **Table 1** present the characteristics of the included studies and the results or interpretations by authors, including 7 cross-sectional[24-30], and 2 cohort studies[31, 32]. Studies were conducted in Italy, Danish, Brazil, British, Denmark, European Union, United States, Taiwan, and Korea. Precisely, 7 studies[24-27, 29-31] reported an increase risk of migraine in patient with psoriasis, while 1 study[30] found no significant association between the disorder and 1 report [28] only compared the rate between psoriasis and psoriatic arthritis groups.

The quality and evaluation of bias for included cross-sectional studies, and cohort studies is illustrated in **Fig. 2a, b**, respectively. Use the Newcastle Ottawa Scale (NOS) to check the quality and study bias of the included studies. 9 studies included in this article: high quality for 3 studies (NOS score≧7), moderate quality for 4 studies (NOS score between 4 and 6) and low-quality studies for 2 studies (NOS score≦3).

Correlation of Psoriasis and Migraine

1) Pooled OR of Migraine in Patients with Psoriasis in Cross-Sectional Studies

Among the cross-sectional studies, two studies were not suitable for this model of meta-analysis process, including Capo, A et al. [24] and Narayanan, S et al.[28], which didn't contain or use the controlled group without the psoriasis. Finally, five cross-sectional studies[21, 25-27, 29, 30] included, with 6355 psoriasis patients and 934413 controls provided data of this outcome. As shown in **Fig. 3**, we found heterogeneity (I^2 = 83%). migraine highly occurred in psoriasis patient (pooled OR 1.64; 95% confidence interval (CI) [1.28; 2.11]).

2) Pooled single rate of Migraine in Patients with Psoriasis in Cross-Sectional Studies

Among the cross-sectional studies, one studies were not suitable for this meta-analysis process. Galili, E et al.[26] study population was among the adolescents. Finally, six cross-sectional studies included, with 4375 psoriasis patients provided data of this outcome. As shown in **Fig. 4**, we found heterogeneity (I^2 = 98%). The rate of migraine occurred in psoriasis patient (pooled rate 0.21; 95% confidence interval [0.13; 0.35]).

3) Risk of Migraine in Patients with psoriasis in Cohort Studies

Although, two cohort studies used different methodologic model to analyze their data and adjusted by different subgroup factors, their results presented a result of an increase new-onset risk of migraine in psoriasis. In details, Egeberg, Alexander et al.[31] found that severity score of psoriasis is a 'dependent increased risk of migraine with psoriasis, and an increased risk of migraine in psoriatic arthritis, the fully adjusted IRRs of migraine were 1.37 (95%CI 1.29-1.45),1.55(95% CI 1.27-1.85), and 1.92(95% CI 1.65-2.23) for mild, severe psoriasis and psoriatic arthritis, respectively'. Min C. et al.[32] found that migraine associated with psoriasis patient than in control group (adjusted hazard ratio (HR)=1.16,95% CI 1.04-1.31 P<.05). In the stratification evaluation of the age subgroup, migraine occurred more frequently in the group of middle-aged males (adjusted HR=1.62 95% CI=1.22-2.13, P=.001).

Discussion

This systematic review and meta-analysis demonstrated that there is a significant correlation between migraine and psoriasis with overall OR 1.64 (95% CI 1.28; 2.11). Besides, in our results presented that the rate of migraine occurred in psoriasis patient (pooled rate 0.21; 95% CI 0.13; 0.35), is higher than the prevalence rate 14.4% of the general adult population[9, 24]. The included two large cohort studies[31, 32] also strengthened the evidence for the causal association. The studies' heterogeneity was presented in this meta-analysis, which might originate from the difference in selection criteria, population demography and population sizes.

Although the underlying fundamental causes for this observed association remained unclear, the aspects of pathophysiology, molecule, and therapy need to be taken into consideration as explanatory factors.

The Clinic Characteristic Phenotype

In precisely, according to an analysis from the 2016 Global Burden of disease study, the prevalence of migraine worldwide is around 14.4% overall, 18.9% in women, and 9.8% in men[33]. In our results showed that the pooled rate 21% is higher than 14.4%. Meanwhile, after integration of the differences in sex and age stratification of included studies, studies showed large discrepancies. One cohort study[31] reported psoriasis was related with increased risk of migraine in both sex; While, another study demonstrate it was higher in male patients and in the age 45 to 49 group[32]. It might attribute to the lack of relevant evaluations to confirm the results, and different methods to adjust the socioeconomic and lifestyle factors. Thus, additional larger randomized control studies are necessary to evaluate whether the sex or age could be a single increased risk of migraine in psoriasis.

The correlation between the clinic classification or the severity of migraine and psoriasis was also involved in some studies. Capo, A 2018[24] demonstrated that the classification of migraine with aura (MA) was more prevalent in psoriasis compared with non-psoriatic migraine population (62.5% vs 16%-20%)[24], Furthermore the mean number of crises is much higher than general data found in MA patients without psoriasis[24]. MA has been an established independent risk factor for CV less than 45 years old[33, 34] and the number of MA crises is a sign of CV disease severity[24, 35]. CV also is the highest caused death rate among the commodity with psoriasis, which indicating that MA might be an adjunctive risk factor in psoriasis for CV event. While, it might suggest that there would be a shared pathophysiologic pathway located further upstream or downstream in migraine and psoriasis, further detailed studies are necessary to confirm the new assessment sides of migraine as an essential comorbidity of psoriasis disorder and their possibilities in development of CV events.

The Pathophysiologic Mechanism

More and more studies suggest that migraine is not only a neurologic disorder[36], and psoriasis have already been redefined as from a skin disease to a chronic, immune-mediated systemic disorder[1]. In clinical aspects, psoriatic lesions could occur on the skin with bilateral symmetrical distribution, which indicate that the nervous system involvement in this pathological development, and the psychosocial stress exacerbate symptoms and correlated commodity in psoriasis patients[37–40], furthermore, psoriatic lesions don't occur on the sites where there is injury to the nervous system in a that region, the reason might be the fewer neural related molecule to adjust the immune cells and to maintain the hyper-proliferation of keratinocyte[40, 41].

In molecular aspect, there is evidence to support the participant of neurotransmitter, the interaction between neuropeptides and immune response in psoriatic skin[42], and the nervous system take significant part in the development of the inflammatory reaction via the synthesis of neuropeptides and neurotransmitter, and these molecules' correspondent receptors are also presented in the innate and adaptive immune cells, which build up the correlation between the neurological and immunological systems[43]. While, the inflammatory etiology of migraine pain involves many aspects[44], and increasing evidence suggest a type of sterile inflammatory in the intracranial meninges trigger the trigeminal meningeal nociceptors being activated[45]. The sterile inflammatory is defined as the interaction of neuropeptides (such as substance p (SP), calcitonin gene related peptide (CGRP)) from the trigeminal innervation[42, 45]. Indeed, the correlation between pain and inflammation and increased dysfunction of the neuroimmune system which appear to be shared in the pathophysiologic mechanism of psoriasis and migraine.

Significant correlation and overlap of the proinflammatory of mediators in neurovascular mechanism and neuroinflammatory mechanism plays a vital role in psoriasis and migraine[42, 43, 45]. Further specific studies are warranted and needed to determine a clear correlation between these two diseases.

Treatment Or Sides-effect

Along with sharing the potential similar pathophysiologic pathway or inflammatory mediator, the treatment targets might have similarities or overlapping parts between psoriasis and migraine.

Biologic medication has represented a great advancement in psoriasis and migraine[1, 15, 44]. Firstly, as for various chronic pain therapy, biologic therapies-monoclonal antibodies (mAbs) increasingly applied in it[46], anti-CGRP mAbs are an innovative therapeutic class for migraine[47]. In the skin, the ability of neuropeptides (SP, CGRP, vasoactive intestinal peptide (VIP), protein gene product 9.5 (PGP9.5), nerve growth factor (NGF)) to initiate and maintain inflammation in psoriasis[39, 47]. Meanwhile, some biologics or drugs that regulate neuropeptides improve the skin symptom of psoriasis, such as capsaicin (analgesic), and Peptide T (VIP analogue)[38, 48, 49]. It suggests the possibility of innovative migraine therapies to relieve the symptoms of psoriasis or psoriatic arthritis (painful knee).

Secondly, Tumor necrosis factor alpha (TNF-α) inhibitors are widely and safely applied in psoriasis and psoriatic arthritis which have gotten great advancement. While, the expression of TNF-α and TNF-α-Induced inflammatory molecules, has been detected at a various levels in peripheral and central mechanism during the transmission of pain in both human and mice studies[44, 46]. Currently some available biologic drug that target TNF-α could inhibit pain related signaling pathway in arthritis and improve the symptoms in psoriatic arthritis[50], which suggesting the possible target for anti-inflammatory biologic therapy in migraine headache. But the specific efficiency of TNF-α inhibitors that could alleviate pain would be complicated, it also included the aspect caused

by specific pain/stimulus pathways[46]. As refer to the specific aspect of pain, TNF-α inhibitors should be re-evaluated in certain condition; and it would help us complement the recommendations in the future.

In addition, headache is commonly reported as a side-effect symptom of certain systemic anti-psoriatic therapies including the biologic medicine[17, 51]. Multiple neurological side-effects [17] (e.g. Headache, Demyelinating disorder, Leukoencephalopathy) have been a constant concern. The evaluation of neurologic complications of biologic agents could be needed before or after the treatment of psoriasis.

Limitations

There were some limitations of this analysis should be carefully considered. First, included studies is small number which was more susceptible to high heterogeneity in terms of selection criteria, diagnose criteria, population demography, socioeconomic status, and population sizes. Second, this study was limited to studies published in English language only, so publication bias cannot be excluded.

Conclusion

The prevalence of migraine might be higher among the patient with psoriasis, which lead to assumption that migraine might be an adjunctive risk factor in psoriasis patients for cardiovascular event. Due to the clinic correlation between these two disorders, similar pathophysiologic overlap of neuroimmune system might be shared in them. However, the clear correlation between them haven't yet been identified, thus, the detailed sub-categorization of patient studies, large clinical cohort studies and randomized clinical trials are necessary to confirm further correlation of these two disease and the possibility and efficacy of using migraine medications (anti-CGRP) in psoriasis.

Clinical Implication

1.The prevalence of migraine might be higher among the patient with psoriasis.

2.Migraine might be an adjunctive risk factor in psoriasis patients for cardiovascular event.

3.Migraine and psoriasis might share a similar pathophysiologic overlap of neuroimmune system.

4.There could be a possibility and efficacy of using migraine medications (anti-CGRP) in psoriasis patients with migraine, to assess the clinic response of the skin lesions and pain.

List Of Abbreviations

CV: cardiovascular disease; M: migraine; MA: migraine with aura; Ps: psoriasis; PsO: psoriasis only; PsA: psoriatic arthritis; SP: substance p; CGRP: calcitonin gene related peptide; mAbs: monoclonal antibodies; VIP: vasoactive intestinal peptide; PGP9.5: protein gene product 9.5; NGF: nerve growth factor; TNF-α: Tumor necrosis factor alpha; OR: odds ratios; SIR'S: standardized incidence ratio, RR: relative risk; HR: hazard ratio; CI: confidence interval; HR: hazard ratio; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; NOS: Newcastle-Ottawa quality assessment scale.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for Publication: Not applicable

Availability of supporting data: The datasets generated or analyzed during this study are included in this review.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: RX, YX, XLW, XBH, YTC and JDH were major contributors in conceiving and writing the manuscript. RX and JDH conceived the study plan, RX, and YX did the literature search, data collection and analysis, wrote and edited the manuscript, and did primary figure development, RX, XLW, XBH and YTC assisted data collection and analysis, wrote and edited the manuscript. and JDH oversaw data planning. All authors read and approved the final manuscript

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Tables

Table 1. Characteristics of included studies

Author	Year	Country	Study methods	Study subjects	Age (years-old)	Diagnosed criteria	Results
Capo et al. [24]	2018	Italy	Cross-section	68 consecutive psoriatic subjects (32 (with M) / 68 (Ps))	18 ~ 65	ICHD 3 (beta version 2013)	47.05% incidence of M in the investigated Ps
				20 (with MA) / 32 (Ps with M)	18 ~ 65	Specialist evaluation	62.5% with MA compared with 17.02% of the examined M (P < 0.0001)
Egeberg et al. [31]	2015	Danish	Cohort study (follow-up of 15 years)	Final cohort comprised a total of 5,379,859 individuals,	≧ 18	ICD-8 346 and ICD-10 G43	Adjusted incidence rate ratios for M were 1.37 (95% confidence interval 1.30–1.45), 1.55 (95% confidence interval 1.29–1.86), and 1.92 (95% confidence interval 1.65–2.22) for mild, severe Ps, and PsA, respectively
Fujii et al [25].	2011	Brazil	Cross-section	Of the 12,000 respondents, 205 diagnosed with psoriasis(82 (with M) / 205 (Ps))	≧ 18	Not mentioned	Higher percentage of co-morbidities was found among patients diagnosed Ps
Galili et al. [26]	2018	Britain	Cross-section	3112 out of 887 765 adolescents diagnosed of psoriasis (185 (with M) / 3112 (Ps))	16 ~ 18	ICD-10 criteria.	Overall chronic headaches were identified in 5.9% of the adolescents with psoriasis compared with 3.4% of control (adjusted OR 1.45, 95% CI 1.24– 1.70)

M migriane, Ps psoriasis, MA migraine with auro, PsO psoriasis only, PsA psoriatic arthritis,CI confidence interval, HR hazard ratio, OR odds ratio

Author	Year	Country	Study methods	Study subjects	Age (years-old)	Diagnosed criteria	Results
Le et al. [27]	2010	Denmark	Cross-section	Of all the subjects who returned the questionnaire, 31856 had answered both migraine questions (398 (with M) / 1276 (Ps))	28 ~ 79	Based on questionaires	All subgroups showed essentially identical results (OR 1.4)
				148 (with MA) / 398 (Ps with M)	28 ~ 79	Based on questionaires	All subgroups showed essentially identical results (OR 1.4)
Min et al. [32]	2019	Korea	Cohort study (follow-up of 11 years)	11071 patients with incident psoriasis	≧ 20	ICD-10 of G43	The rate of migraine was higher in Ps (3.3%, 369/ 11,071) than in control participants (2.9%, 1265/44,284). The adjusted HR of Ps for M was 1.16 (95% CI = 1.04– 1.31, P = .011)
Narayanan et al. [28]	2014	European Union	Cross-section	1064 eligible Psoriasis patients (185 (with M) / 926 (PsO))	mean 48	Not mentioned	Burden of comorbidities among Ps is high, and significantly more so among subset of PsA
Steuer et al. [29].	2014	USA	Cross-section	Based on 2003–2004 National Health and Nutrition Examination Survey (24 (with M) / 77 (Ps))	mean 40	Based on questionaires	Ps was significantly associated with a history of M in themultivariable model (OR 3.97 [95% CI, 1.76–8.95]; P < 0.003)

M migriane, Ps psoriasis, MA migraine with auro, PsO psoriasis only, PsA psoriatic arthritis,CI confidence interval, HR hazard ratio, OR odds ratio

Author	Year	Country	Study methods	Study subjects	Age (years-old)	Diagnosed criteria	Results
Yang et al. [30]	2014	Taiwan	Cross-section	Based on Taiwan's National Health Insurance (NHI) programme (32 (with M) / 1685 (Ps))	mean 48.6	ICD-9-CM	P = 0.409 (statistically insignificant)

M migriane, Ps psoriasis, MA migraine with auro, PsO psoriasis only, PsA psoriatic arthritis,CI confidence interval, HR hazard ratio, OR odds ratio

Figures

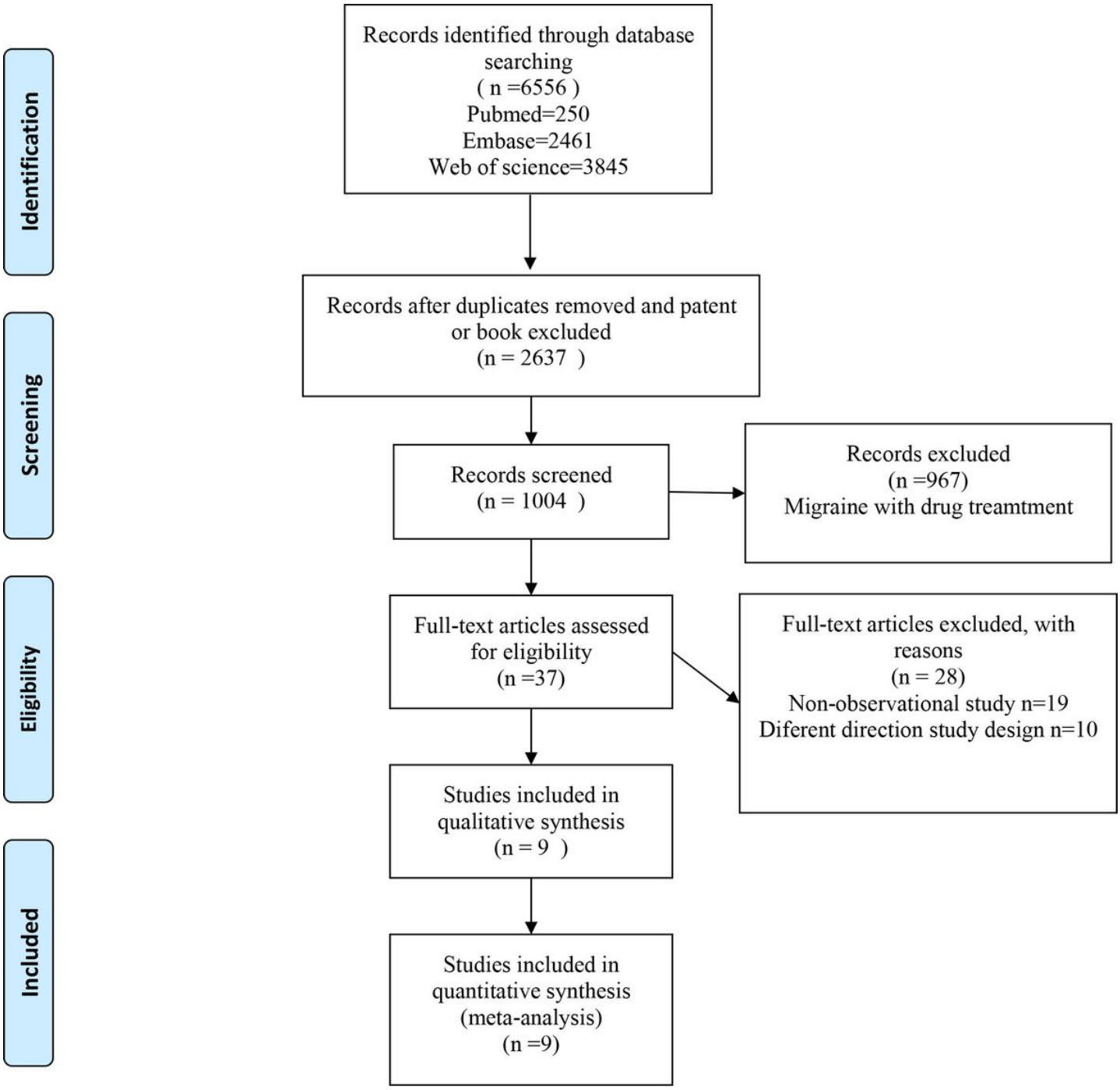

Figure 1

Prisma study flow chart

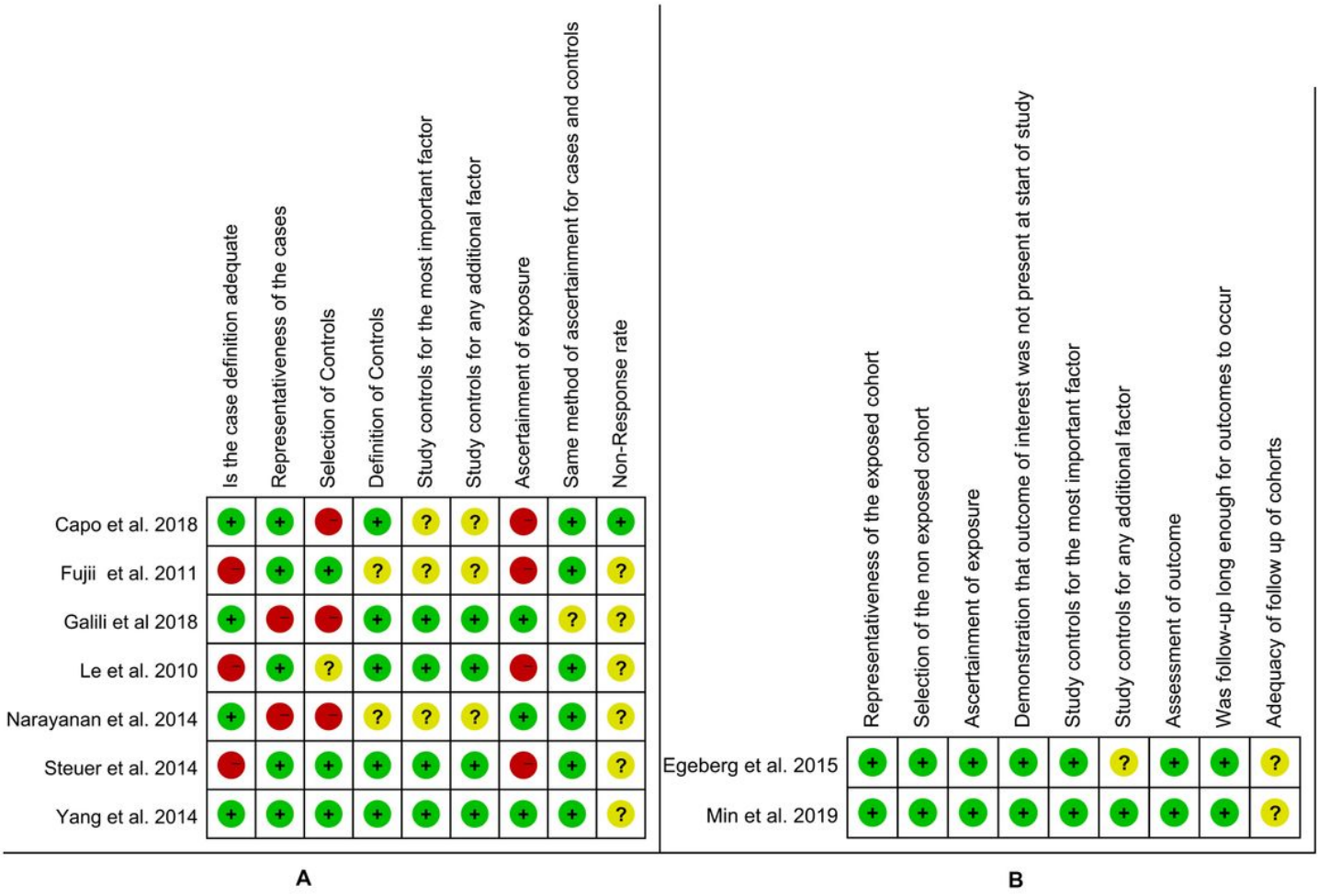

Figure 3

A. Risk of bias of included cross sectional studies, B. Risk of bias of included cohort studies

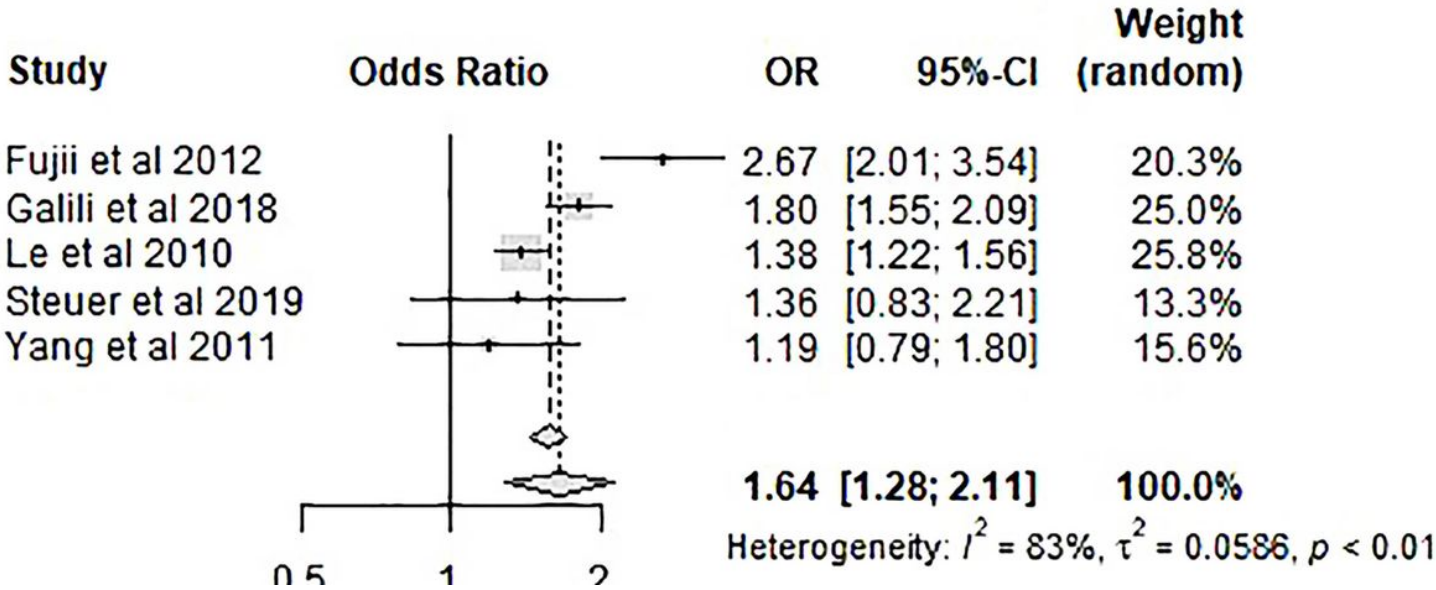

Figure 5

Odds Ratio of migraine in patients with psoriasis in cross sectional studies

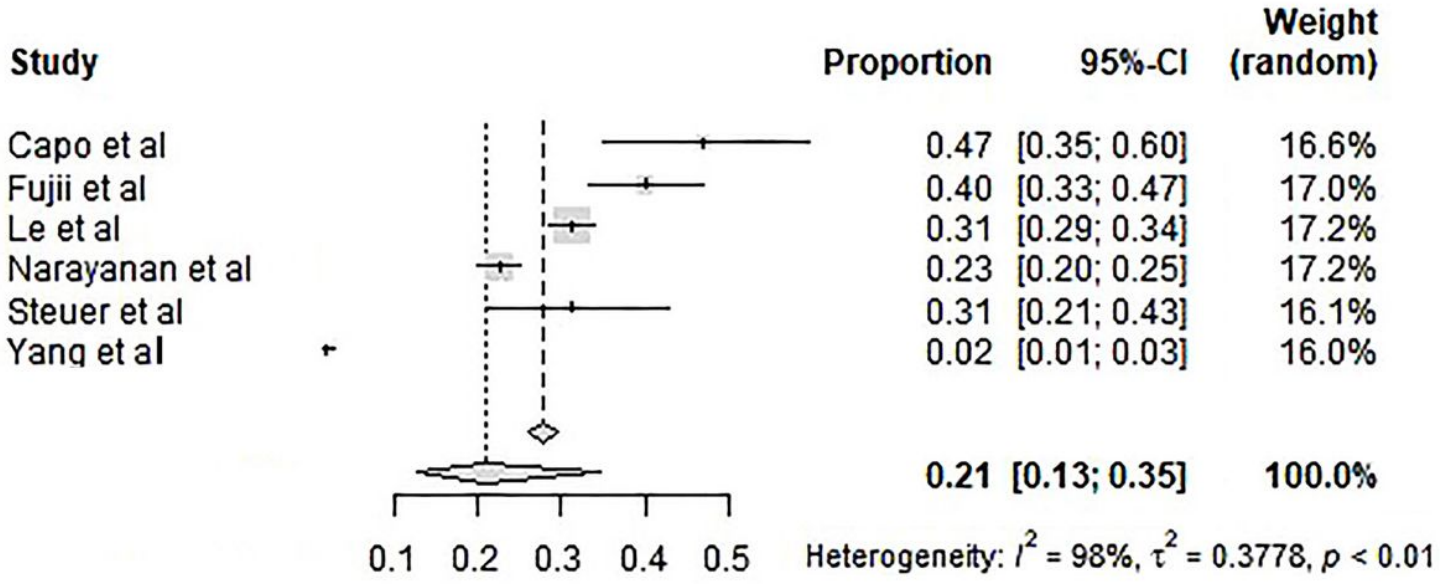

Figure 7

The pooled rate of migraine among patients with psoriasis