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

**CURRENT STATUS:** POSTED

| Author                  | Institution                                         |
|-------------------------|------------------------------------------------------|
| 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               | Sun Yat-sen University First Affiliated Hospital     |

Corresponding Author
hanjd@mail.sysu.edu.cn
ORCID: https://orcid.org/0000-0002-4465-7632

**DOI:**
10.21203/rs.3.rs-23751/v1

**SUBJECT AREAS**
Neurology

**KEYWORDS**
migraine, psoriasis, psoriatic arthritis, systematic review, meta-analysis
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 study was 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 moleculer 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,
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

Funding: Project supported by the National Science Foundation for Young Scientists of China (Grant No.81903231).

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.

Acknowledgements: Thank all the participants for their support of this research.

References
1. Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, Mehta NN, Finlay AY (2016) Gottlieb AB: Psoriasis. Nat Rev Dis Primers 2:16082
2. Boehncke WH (2015) Etiology and Pathogenesis of Psoriasis. Rheum Dis Clin North Am 41(4):665–675
3. Boehncke WH, Schon MP (2015) Psoriasis. Lancet 386(9997):983–994
4. Amanat M, Salehi M, Rezaei N (2018) Neurological and psychiatric disorders in psoriasis. Rev Neurosci 29(7):805–813
5. Zhu TH, Nakamura M, Farahnik B, Abrouk M, Lee K, Singh R, Gevorgyan A, Koo J, Bhutani T (2016) The Role of the Nervous System in the Pathophysiology of Psoriasis: A Review of Cases of Psoriasis Remission or Improvement Following Denervation Injury. Am J Clin Dermatol 17(3):257–263
6. Liu CY, Tung TH, Lee CY, Chang KH, Wang SH, Chi CC (2019) Association of Multiple Sclerosis with Psoriasis: A Systematic Review and Meta-Analysis of Observational Studies. Am J Clin Dermatol 20(2):201–208
7. Hall JM, Cruser D, Podawiltz A, Mummert DI, Jones H, Mummert ME (2012) Psychological Stress and the Cutaneous Immune Response: Roles of the HPA Axis and the Sympathetic Nervous System in Atopic Dermatitis and Psoriasis. Dermatol Res Pract 2012:403908
8. Chi CC, Chen TH, Wang SH, Tung TH (2017) Risk of Suicidality in People with Psoriasis: A Systematic Review and Meta-Analysis of Cohort Studies. Am J Clin
9. Silberstein SD (2004) Migraine. Discov Med 4(23):270-276

10. Yilmaz IA, Ozge A, Erdal ME, Edgunlu TG, Cakmak SE, Yalin OO (2010) Cytokine polymorphism in patients with migraine: some suggestive clues of migraine and inflammation. Pain Med 11(4):492-497

11. Terrando N, Pavlov VA (2018) Editorial: Neuro-Immune Interactions in Inflammation and Autoimmunity. Front Immunol 9:772

12. Etminan M, Takkouche B, Isorna FC, Samii A (2005) Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ 330(7482):63

13. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T (2009) Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 339:b3914

14. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S (2010) Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med 123(7):612-624

15. von Csiky-Sessoms S, Lebwohl M (2019) What's New in Psoriasis. Dermatol Clin 37(2):129-136

16. Patel SV, Khan DA (2017) Adverse Reactions to Biologic Therapy. Immunol Allergy Clin North Am 37(2):397-412

17. Lin EJ, Reddy S, Shah VV, Wu JJ (2018) A review of neurologic complications of biologic therapy in plaque psoriasis. Cutis 101(1):57-60

18. Gibson RA, Xu CF, White NJ, McCarthy L, Hewett D, Purvis I, Roses A (2000) Identifying susceptibility genes for psoriasis and migraine by SNP LD mapping. Am J Hum Genet 67(4):34-34

19. Guo R, Li FF, Chen ML, Ya MZ, He HL, Li D (2015) The role of CGRP and CALCA T-692C
single-nucleotide polymorphism in psoriasis vulgaris. Pharmazie 70(2):88–93

20. Santos-Lasaosa S, Belvis R, Cuadrado ML, Diaz-Insa S, Gago-Veiga A, Guerrero-Peral AL, Huerta M, Irimia P, Lainez JM, Latorre G et al: Calcitonin gene-related peptide in migraine: from pathophysiology to treatment. Neurologia 2019

21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62(10):1006–1012

22. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560

24. Capo A, Affaitati G, Giamberardino MA, Amerio P (2018) Psoriasis and migraine. J Eur Acad Dermatol Venereol 32(1):57–61

25. Fujii RK, Mould JF, Tang B, Brandt H, Pomerantz D, Chapnick J, Sternbach N, Manfrin DF (2012) Burden of disease in patients with diagnosed psoriasis in Brazil: Results from 2011 National Health and Wellness Survey (NHWS). Value in Health 15(4):A107

26. Galili E, Barzilai A, Shreberk-Hassidim R, Merdler I, Caspi T, Astman N (2018) Neuropsychiatric comorbidity among adolescents with psoriasis. Br J Dermatol 178(4):910–916

27. Le H, Tfelt-Hansen P, Russell MB, Skytthe A, Kyvik KO, Olesen J (2010) Comorbidity of migraine with somatic diseases in a large population based study. Journal of Headache Pain 11:S7

28. Narayanan S, Franceschetti A (2014) Prevalence of comorbidites among patients with psoriasis (PSO) with and without psoriatic arthritis (PSA) in european union (EU).
29. Steuer AB, Cohen JM, Wong PW, Ho RS: Psoriasis and the Risk of Migraines in the United States. *Journal of the American Academy of Dermatology* 2019

30. Yang YW, Keller JJ, Lin HC (2011) Medical comorbidity associated with psoriasis in adults: a population-based study. *Br J Dermatol* 165(5):1037–1043

31. Egeberg A, Mallbris L, Gislason GH, Skov L, Hansen PR (2015) Increased risk of migraine in patients with psoriasis: A Danish nationwide cohort study. *J Am Acad Dermatol* 73(5):829–835

32. Min C, Lim H, Lim JS, Sim S, Choi HG (2019) Increased risk of migraine in patients with psoriasis: A longitudinal follow up study using a national sample cohort. *Medicine* 98(17):e15370

33. Burch RC, Buse DC, Lipton RB (2019) Migraine: Epidemiology, Burden, and Comorbidity. *Neurol Clin* 37(4):631–649

34. Sacco S, Kurth T (2014) Migraine and the risk for stroke and cardiovascular disease. *Curr Cardiol Rep* 16(9):524

35. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE (2006) Migraine and risk of cardiovascular disease in women. *JAMA* 296(3):283–291

36. Chen D, Willis-Parker M, Lundberg GP: Migraine headache: Is it only a neurological disorder? Links between migraine and cardiovascular disorders. *Trends Cardiovasc Med* 2019

37. Farber EM, Nickoloff BJ, Recht B, Fraki JE (1986) Stress, symmetry, and psoriasis: possible role of neuropeptides. *J Am Acad Dermatol* 14(2 Pt 1):305–311

38. Farber EM, Cohen EN, Trozak DJ, Wilkinson DI (1991) Peptide T improves psoriasis when infused into lesions in nanogram amounts. *J Am Acad Dermatol* 25(4):658–664

39. Chapman BP, Moynihan J (2009) The brain-skin connection: role of psychosocial
factors and neuropeptides in psoriasis. Expert Rev Clin Immunol 5(6):623–627

40. Piccolo V, Russo T, Ruocco E, Baroni A (2014) Selective localization or sparing of skin disorders in neurologically injured areas: an underestimated connubium. Indian J Dermatol 59(6):612–613

41. Ravikumar B, Sinhasan (2014) Psoriasis sparing the polio-affected limb: is it merely the koebner phenomenon? Indian J Dermatol 59(5):505–506

42. Sandoval-Talamantes AK, Gomez-Gonzalez BA, Uriarte-Mayorga DF, Martinez-Guzman MA, Wheber-Hidalgo KA, Alvarado-Navarro A (2020) Neurotransmitters, neuropeptides and their receptors interact with immune response in healthy and psoriatic skin. Neuropeptides 79:102004

43. Saraceno R, Kleyn CE, Terenghi G, Griffiths CE (2006) The role of neuropeptides in psoriasis. Br J Dermatol 155(5):876–882

44. Goadsby PJ, Holland PR (2019) An Update: Pathophysiology of Migraine. Neurol Clin 37(4):651–671

45. Ramachandran R (2018) Neurogenic inflammation and its role in migraine. Semin Immunopathol 40(3):301–314

46. Yeh JF, Akinci A, Al Shaker M, Chang MH, Danilov A, Guileen R, Johnson K, Kim YC, El-Shafei A, Skljarevski V et al (2017) Monoclonal antibodies for chronic pain: a practical review of mechanisms and clinical applications. Mol Pain 13:1744806917740233

47. Levin M, Silberstein SD, Gilbert R, Lucas S, Munsie L, Garrelts A, Kennedy K, Everman N, Pearlman E (2018) Basic Considerations for the Use of Monoclonal Antibodies in Migraine. Headache 58(10):1689-1696

48. Bernstein JE, Parish LC, Rapaport M, Rosenbaum MM, Roenigk HH Jr (1986) Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. J Am Acad
49. Marcusson JA, Talme T, Wetterberg L, Johansson O (1991) Peptide T a new treatment for psoriasis? A study of nine patients. Acta Derm Venereol 71(6):479-483

50. Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, FitzGerald O, Winthrop K, van der Heijde D, Emery P, Smolen JS, Marzo-Ortega H (2012) A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis 71(3):319-326

51. Liu M, Huang YY, Hsu S, Kass JS (2016) Neurological and Neuropsychiatric Adverse Effects of Dermatologic Medications. CNS Drugs 30(12):1149-1168

Tables

Table 1. Characteristics of included studies

| Author          | Year | Country   | Study methods     | Study subjects                                      | Age (years-old) | Diagnosed criteria | Results                                                                 |
|-----------------|------|-----------|-------------------|-----------------------------------------------------|-----------------|---------------------|------------------------------------------------------------------------|
| Capo et al.     | 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)                        |                 | Specialist evaluation | 62.5% with MA compared with 17.02% of the examined M (P < 0.0001)       |
| Egeberg et al.  | 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     | 2011 | Brazil    | Cross-section     | Of the 12,000 respondents Ps                        | ≥ 18            | Not mentioned       | Higher percentage of co-morbidities                                   |
| Authors          | Year | Country | Study Design | Sample Size | Age | ICD-10 Criteria | Morbidities Among Patients Diagnosed with Ps | Overall Chronic Headaches Were Identified in | (OR) 95% CI, P Value |
|------------------|------|---------|--------------|-------------|-----|----------------|--------------------------------------------|-----------------------------------------------|---------------------|
| Galili et al. [26] | 2018 | Britain | Cross-sectional | 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) |
| Le et al. [27] | 2010 | Denmark | Cross-sectional | Of all the subjects who returned the questionnaire, 31856 had answered both migraine questions (398 (with M) / 1276 (Ps)) | 28 ~ 79 | Based on questionnaires | 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-sectional | 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-sectional | Based on 2003-2004 National Health and Nutrition Examination Survey (24 (with M) / 77 (Ps)) | mean 40 | Based on questionnaires | Ps was significantly associated with a history of M in the multivariable model (OR 3.97 95% CI 1.65 ~ 9.48, P = .002) |
| 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 migrane, 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
Records identified through database searching
(n = 6556)
Pubmed = 250
Embase = 2461
Web of science = 3845

Records after duplicates removed and patent or book excluded
(n = 2637)

Records screened
(n = 1004)

Full-text articles assessed for eligibility
(n = 37)

Studies included in qualitative synthesis
(n = 9)

Studies included in quantitative synthesis
(meta-analysis)
(n = 9)

Records excluded
(n = 967)
Migraine with drug treatment

Full-text articles excluded, with reasons
(n = 28)
Non-observational study n = 19
Different direction study design n = 10

Figure 1
Prisma study flow chart
|                  | Is the case definition adequate | Representativeness of the cases | Selection of Controls | Definition of Controls | Study controls for the most important factor | Study controls for any additional factor | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-Response rate |
|------------------|---------------------------------|--------------------------------|-----------------------|-----------------------|---------------------------------------------|----------------------------------------|----------------------------|--------------------------------------------------|------------------|
| Capo et al. 2018 | ✅                              | ✅                             | ✅                    | ✅                    | ✅                                          | ✅                                      | ✅                          | ✅                                               | ✅                |
| Fujii et al. 2011| ✅                              | ✅                             | ✅                    | ✅                    | ✅                                          | ✅                                      | ✅                          | ✅                                               | ✅                |
| Galli et al. 2018| ✅                              | ✅                             | ✅                    | ✅                    | ✅                                          | ✅                                      | ✅                          | ✅                                               | ✅                |
| Le et al. 2010   | ✅                              | ✅                             | ✅                    | ✅                    | ✅                                          | ✅                                      | ✅                          | ✅                                               | ✅                |
| Narayan et al. 2014| ✅                            | ✅                             | ✅                    | ✅                    | ✅                                          | ✅                                      | ✅                          | ✅                                               | ✅                |
| Steuer et al. 2014| ✅                             | ✅                             | ✅                    | ✅                    | ✅                                          | ✅                                      | ✅                          | ✅                                               | ✅                |
| Yang et al. 2014 | ✅                              | ✅                             | ✅                    | ✅                    | ✅                                          | ✅                                      | ✅                          | ✅                                               | ✅                |

**Figure 2**

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

**Figure 3**

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

| Study                | Odds Ratio | 95% CI       | Weight (random) |
|----------------------|------------|--------------|-----------------|
| Fujii et al 2012     | 2.67       | [2.01; 3.54] | 20.3%           |
| Galili et al 2018    | 1.80       | [1.55; 2.09] | 25.0%           |
| Le et al 2010        | 1.38       | [1.22; 1.56] | 25.8%           |
| Steuer et al 2019    | 1.36       | [0.83; 2.21] | 13.3%           |
| Yang et al 2011      | 1.19       | [0.79; 1.80] | 15.6%           |

Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.0586$, $p < 0.01$

The pooled rate of migraine among patients with psoriasis

| Study                | Proportion | 95% CI       | Weight (random) |
|----------------------|------------|--------------|-----------------|
| Capo et al           | 0.47       | [0.35; 0.60] | 16.6%           |
| Fujii et al          | 0.40       | [0.33; 0.47] | 17.0%           |
| Le et al             | 0.31       | [0.29; 0.34] | 17.2%           |
| Narayanan et al      | 0.23       | [0.20; 0.25] | 17.2%           |
| Steuer et al         | 0.31       | [0.21; 0.43] | 16.1%           |
| Yang et al           | 0.02       | [0.01; 0.03] | 16.0%           |

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.3778$, $p < 0.01$
The pooled rate of migraine among patients with psoriasis