Increased risk of migraine in patients with psoriasis: A Danish nationwide cohort study

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Background: Psoriasis and migraine are common conditions with potential overlap of pathophysiological mechanisms. Both these diseases have been associated with increased cardiovascular risk but little is known about their interplay.

Objective: We sought to investigate the link between psoriasis, and the risk of new-onset migraine, in a nationwide cohort of the Danish population.

Methods: Data on all Danish citizens aged 18 years or older from January 1, 1997, to December 31, 2011, were linked at individual-level in nationwide registers. Incidence rates per 1000 person-years were calculated and crude and adjusted incidence rate ratios were estimated by Poisson regression models.

Results: The study comprised a total of 5,379,859 individuals, including 53,006 and 6831 patients with mild and severe psoriasis, respectively, and 6243 patients with psoriatic arthritis. Fully adjusted incidence rate ratios for migraine 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 psoriasis, severe psoriasis, and psoriatic arthritis, respectively. Stratification for sex revealed increased risk of migraine in both male and female patients.

Limitations: We were unable to distinguish between subtypes of migraine, eg, migraine with and without aura.

Conclusions: Psoriasis was associated with a disease severity-dependent increased risk of migraine independent of measured confounders. Further studies are warranted to determine the effects of antipsoriatic treatment on this association, and whether migraine modifies the psoriasis-associated risk of cardiovascular disease. (J Am Acad Dermatol 2015;73:829-35.)

Key words: epidemiology; headache; inflammation; migraine; psoriasis.

Psoriasis is a common T-helper-1 and -17 cell-mediated chronic inflammatory disease, affecting more than 2% to 3% of Europeans and up to 9% of individuals in some Nordic countries.[1] Increasing evidence suggest that psoriasis is associated with a variety of medical comorbidities, including ischemic heart disease, stroke, hypertension, dyslipidemia, type 2 diabetes mellitus, and obesity.[2,3] In addition to the direct medical costs as a result of treatment of the disease, patients with

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psoriasis often experience loss of work productivity and sick days, and frequently experience significant impairment of their physical, psychological, and social functioning.[3,4] Migraine is a chronic intermittent neurovascular pain disorder with increasing prevalence, currently affecting more than 12% of the Danish population.[5] Although the exact origin is not fully understood, migraine has been attributed to episodes of local sterile meningeal inflammation and hypersensitization of pain pathways, and proinflammatory mediators that contribute to the pathogenesis of psoriasis, such as tumor necrosis factor-alfa, can promote migraine, eg, by sensitization of meningeal nociceptors and peripheral nerve endings through activation of p38 mitogen-activated protein kinases, and increased dural mechanosensitivity.[6-8]

CAPSULE SUMMARY

- Psoriasis and migraine are each associated with cardiovascular disease.
- Psoriasis may be an independent risk factor for migraine.
- Increased focus on symptoms of migraine in patients with psoriasis may be warranted.

An association between migraine and cardiovascular disease has been established, and migraine with aura is associated with a 2-fold increased risk of ischemic stroke.[9] Indeed, like psoriasis and other inflammatory conditions, migraine appears to be associated with systemic endothelial dysfunction.[4,10-12] To our knowledge, only very few studies have described the association between psoriasis and migraine, and results are inconsistent.[3,13] We therefore investigated impact of psoriasis and psoriatic arthritis on the risk of new-onset migraine in a nationwide cohort of the Danish population.

METHODS

Study approval was obtained from the Danish Data Protection Agency (reference 2007-58-0015, internal reference GEH-2014-018, I-Suite 02736), and approval from an ethics committee is not required for register studies in Denmark. All Danish citizens have free, equal, and universal health care access, and individual-level linkage is possible among the nationwide administrative registries. Information on morbidity was obtained from the Danish National Patient Register, in which information on hospital admissions, procedures and diagnosis has been recorded since 1978. Data are recorded using *International Classification of Diseases, Revision 8* (*ICD-8*) codes from 1978 to 1994 and *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) codes from 1994 to present (*International Classification of Diseases, Ninth Revision* was never used in Denmark).[14] Hospital procedures (including hospital-based pharmacologic treatment, eg, with biological therapy) are coded in the Danish National Patient Register as treatment procedure (Sundhedsvæsenets Klassifikations System/Health Authority Classification System [SKS]) codes. Detailed and accurate information on all drugs dispensed from pharmacies are recorded in the Danish Registry of Medicinal Products Statistics according the international Anatomical Therapeutical Chemical (ATC) classification.[15]

The cohort comprised all Danish citizens aged 18 years or older from January 1, 1997, to December 31, 2011, and followed up until migration, death from any cause, or the occurrence of migraine, whichever came first. Patients with a history of psoriasis or migraine were excluded before study inclusion to accurately determine the temporal relationship between onset of psoriasis and risk of migraine, and ensure correct risk-time allocation. Patients with psoriasis were identified when they dispensed their second prescription of topical vitamin-D derivatives (ATC D05AX), which is the favored first-line treatment for psoriasis in Denmark, or by their first inpatient or outpatient consultation for psoriasis (*ICD-8* 696.10, 696.19, and *ICD-10* L40) or psoriatic arthritis (*ICD-8* 696.09 and *ICD-10* M070-M073), respectively. Patients were classified as having mild disease from onset of psoriasis and until they fulfilled the criteria for severe disease, if appropriate. Severe psoriasis was defined as receiving systemic treatment consistent with severe disease, ie, treatment with biological drugs, cyclosporine, hydroxyurea, psoralens, retinoids, or methotrexate, respectively. The primary end point was the first dispensed prescription of antimigraine drugs (ATC N02C) recorded in the Danish Registry of Medicinal Products Statistics.

Pharmacologic treatment, medical comorbidities, and socioeconomic status

Baseline comorbidity and pharmacologic treatment as described in Table I were defined up to 5 years, and 6 months before study inclusion, respectively, by use of ATC and *ICD* codes. Hypertension was defined by an algorithm, as previously described and validated with a positive predictive value of greater than 80%.[16] Diabetes was defined by either a hospital diagnosis or use of

Abbreviations used:

ATC:	Anatomical Therapeutical Chemical
CI:	confidence interval
ICD-8:	*International Classification of Diseases, Revision 8*
ICD-10:	*International Statistical Classification of Diseases, 10th Revision*
IRR:	incidence rate ratio

glucose-lowering drugs. Information on medications, comorbidity, and hospital treatment procedures was continually updated during the follow-up period. We calculated an age-standardized index of socioeconomic status between 0 and 4 based on the average gross annual income during a 5-year period before study inclusion. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were used for conduct and reporting of this study.[17]

Statistical analysis

We described baseline characteristics with means and SD for continuous variables, and frequencies and percentages for categorical variables. To ensure accurate registration of time at risk, psoriasis status and severity were included as time-dependent variables so that patients with psoriasis contributed risk time in the reference group until they fulfilled the psoriasis criteria, and were only at risk in the mild psoriasis group until they (if appropriate) were classified with severe psoriasis. SAS statistical software (Version 9.4, SAS Institute Inc, Cary, NC) and STATA software (Version 11.0, StataCorp, College Station, TX) were used to summarize incidence rates per 1000 person-years, and Poisson regression was performed to obtain incidence rate ratios (IRRs) for the risk of incident migraine. IRRs for migraine were calculated as crude, age adjusted, and fully adjusted (in which age, socioeconomic status, concomitant medication, and comorbidities were considered), respectively. To confirm the findings of our primary analyses, we performed a sensitivity analysis using a hospital diagnosis of migraine (*ICD-8* 346 and *ICD-10* G43) as the end point. Because psoriasis and migraine are associated with ischemic stroke, and migraine in patients with psoriasis may be caused, in part, by the occurrence of subclinical stroke, we performed sensitivity analyses with exclusion of patients with a history of ischemic stroke before or during the study period.[9,18,19] All statistical tests were conducted using a level of significance of .05, and results reported with 95% confidence intervals (CIs), where applicable.

RESULTS

From the initial cohort of individuals aged 18 years or older from January 1, 1997, to December 31, 2011 (n = 5,536,422), we excluded 94,420 and 22,073 individuals with prevalent migraine and psoriasis, respectively, and 512 individuals with a history of both migraine and psoriasis before study inclusion. Also, 39,558 individuals with incomplete information on migration were excluded. The final cohort comprised a total of 5,379,859 individuals, and during the maximum follow-up of 15 years we identified a total of 66,080 patients with incident psoriasis and 220,970 patients with incident migraine (Fig 1). Of patients with psoriasis, 53,006 and 6831 were classified as having mild and severe psoriasis, respectively, and 6243 patients had psoriatic arthritis. The mean age was 40.7, 44.5, 43.0, and 40.2 years among the reference population, and subjects with mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively (Table I). The sex distribution was similar, except for patients with psoriatic arthritis, where a greater proportion of patients were women (55%). Patients with migraine were predominantly female (79.6%) with a mean age of 37.7 years.

Incidence rates per 1000 person-years of migraine were 3.86, 5.25, 6.41, and 9.27 for the reference population, and subjects with mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively (Table II). Fully adjusted IRRs for migraine were 1.37 (95% CI 1.30-1.45), 1.55 (95% CI 1.29-1.86), and 1.92 (95% CI 1.65-2.22) for these respective groups (Table III). Stratified by sex, the risk of migraine was significantly increased in women with mild psoriasis (IRR 1.35, 95% CI 1.26-1.44), severe psoriasis (IRR 1.54, 95% CI 1.25-1.90), and psoriatic arthritis (IRR 1.95, 95% CI 1.66-2.29), respectively. Similarly, there was a significantly increased risk of migraine in men with mild psoriasis (IRR 1.47, 95% CI 1.30-1.66), severe psoriasis (IRR 1.55, 95% CI 1.04-2.31), and psoriatic arthritis (IRR 1.80, 95% CI 1.25-2.59), respectively. In subanalyses of patients with severe skin psoriasis and concurrent psoriatic arthritis, the incidence rate of migraine was 9.94 (95% CI 8.04-12.28), and the fully adjusted IRR was 2.01 (95% CI 1.63-2.49). In sensitivity analyses with exclusion of patients with ischemic stroke (n = 211,148), the fully adjusted IRRs of migraine were 1.37 (95% CI 1.29-1.45), 1.53 (95% CI 1.27-1.85), and 1.92 (95% CI 1.65-2.23) for mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively. We confirmed the findings of our primary analyses by using a

Table I. Baseline characteristics of the study population

	Reference population (n = 5,313,779)	Mild psoriasis (n = 53,006)	Severe psoriasis (n = 6831)	Psoriatic arthritis (n = 6243)
Age, mean (SD), y	40.7 (19.8)	44.5 (16.8)	43.0 (15.7)	40.2 (13.9)
Women, n (%)	2,665,936 (50.2)	26,800 (50.6)	3323 (48.7)	3456 (55.4)
Men, n (%)	2,647,843 (49.8)	26,206 (49.4)	3508 (51.4)	2787 (44.6)
Socioeconomic index, mean (SD)	1.8 (1.5)	2.3 (1.4)	2.3 (1.3)	2.4 (1.3)
Comorbidity, n (%)				
Cardiac dysrhythmia	38,045 (0.7)	338 (0.7)	39 (0.6)	27 (0.5)
COPD	21,341 (0.4)	181 (0.4)	20 (0.3)	14 (0.2)
Diabetes	82,107 (1.6)	982 (1.9)	104 (1.5)	70 (1.1)
Heart failure	24,355 (0.5)	169 (0.3)	10 (0.2)	10 (0.2)
Hypertension	175,311 (3.3)	2316 (4.4)	228 (3.3)	213 (3.4)
Inflammatory bowel disease	10,802 (0.2)	144 (0.3)	27 (0.4)	19 (0.3)
Renal disease	4447 (0.1)	31 (0.1)	4 (0.1)	5 (0.1)
Venous thromboembolism	12,842 (0.2)	157 (0.3)	29 (0.4)	27 (0.4)
Medication, n (%)				
Antidepressants	144,875 (2.7)	1920 (3.6)	207 (3.0)	184 (3.0)
Cholesterol-lowering drugs	28,412 (0.5)	496 (0.9)	46 (0.7)	43 (0.7)
Loop diuretics	130,694 (2.5)	1116 (2.1)	103 (1.5)	103 (1.7)
Vitamin-K antagonists/platelet inhibitors	21,471 (0.4)	230 (1.1)	24 (0.4)	17 (0.3)

COPD, Chronic obstructive pulmonary disease.

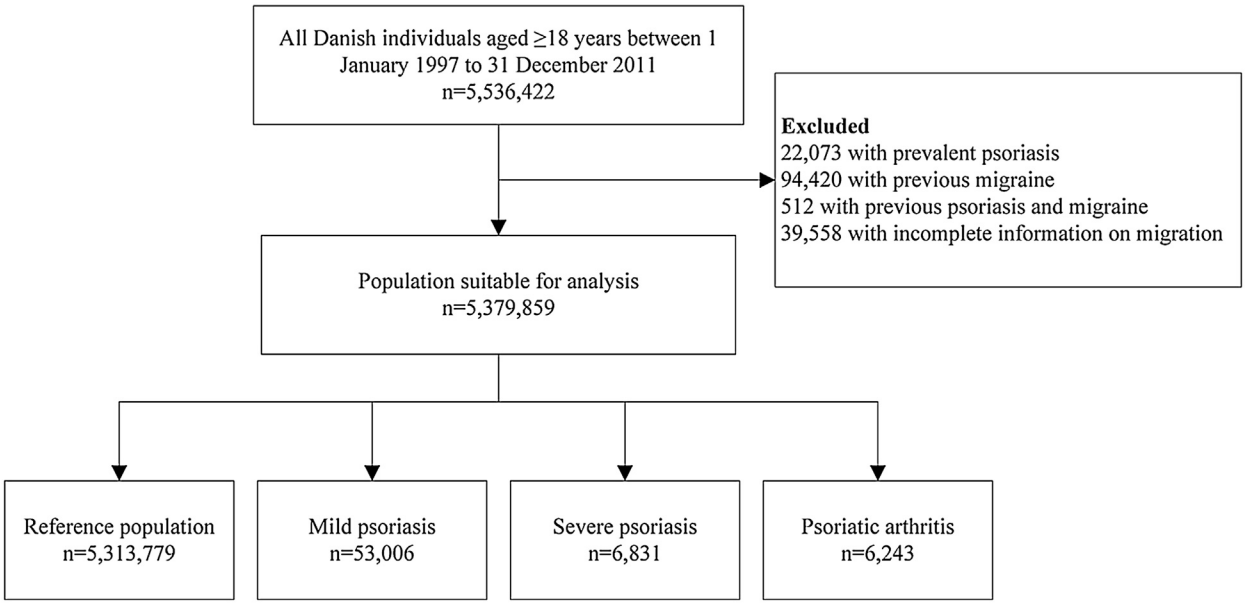

Fig 1. Study flow chart.

hospital diagnosis of migraine, which yielded fully adjusted IRRs of 1.18 (95% CI 1.01-1.37), 1.81 (95% CI 1.20-2.72), and 1.51 (95% CI 1.02-2.24), respectively.

DISCUSSION

In this nationwide cohort study with a maximum follow-up of 15 years, we found an increased risk of new-onset migraine in patients with psoriatic arthritis, and a disease severity-dependent increased risk of migraine in patients with psoriasis of the skin only. The increased risk remained consistent in fully adjusted models and in sensitivity analyses with exclusion of patients with ischemic stroke.

Psoriasis is one of the most common chronic inflammatory diseases and has a strong negative impact on quality of life.[20,21] In addition to an increased risk of myocardial infarction in subjects with psoriasis, several large-scale studies have confirmed a psoriasis-associated increased risk of ischemic stroke, in particular in patients with severe

Table II. Incidence rates of migraine per 1000 person-years in the reference population, and patients with mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively

	Reference population	Mild psoriasis	Severe psoriasis	Psoriatic arthritis
No. of events	219,471	1193	128	178
Person-years	56,864,057	227,408.4	19,960.5	19,206.9
Incidence rate	3.86	5.25	6.41	9.27
95% CI	3.84-3.88	4.96-5.55	5.39-7.63	8.00-10.73

CI, Confidence interval.

disease.[19,22,23] Previously, this risk has mainly been attributed to the role of systemic low-grade inflammation in both atherothrombosis and psoriasis, and shared underlying risk factors such as exercise, obesity, and smoking.[19,22,23] Indeed, there is significant overlap of proinflammatory mediators in psoriasis and atherosclerosis, and psoriasis is strongly associated with obesity and smoking.[24,25] Moreover, data suggest that psoriasis is an independent risk factor for atrial fibrillation.[19] However, little attention has been given to the potential association between psoriasis and migraine, albeit that migraine (especially with aura) is an established risk factor for ischemic stroke.[9] Also, migraine has been associated with an unfavorable cardiovascular risk profile, and a 2-fold increased 10-year risk of coronary heart disease.[26] In our study, however, the psoriasis severity-dependent increased risk of migraine was independent of measured cardiovascular risk factors, eg, diabetes, hypertension, hyperlipidemia, and socioeconomic status, suggesting that shared pathogenic pathways may be located further upstream or downstream. In this regard, a role for inflammation in both conditions is suggested by the current observation of a psoriasis severity dose-response relationship with the risk of migraine. Indeed, recent research has focused on the link between pain and inflammation, and increased tumor necrosis factor-alfa levels, activation of mitogen-activated protein kinases, and endothelial dysfunction are among inflammatory mechanisms that appear to be shared by psoriasis and migraine.[6-12,27] Along this line, tumor necrosis factor-alfa inhibition may inhibit pain signaling in experimental arthritis and ameliorate endothelial dysfunction in those with psoriasis and psoriatic arthritis, suggesting the potential for targeted anti-inflammatory pharmacologic therapy in the treatment of migraine.[28-30]

Only very few studies have to our knowledge reported on the association between psoriasis and migraine.[3,13] In a study of 1685 adult Taiwanese patients with psoriasis, no significant risk of migraine was observed compared with 5055 control subjects.[3] On the other hand, in a survey of 46,418 twins in Denmark the occurrence of psoriasis was significantly increased in patients with migraine, albeit that the difference was not significant when analyses were limited to only 1 twin.[3,13] Interestingly, an increased prevalence of migraine has also been reported in other chronic autoimmune diseases, eg, systemic lupus erythematosus and multiple sclerosis, and the notion that shared inflammatory pathways contribute to this association clearly merits further study.[31,32]

Several limitations and strengths apply to the interpretation of present results. Because of the observational nature of our study we cannot determine causality. Whether the observed effect is caused, in part, by systemic low-grade inflammation caused by psoriasis, or the findings are mainly a result of shared lifestyle factors and other mechanisms requires further examination. Also, it is likely that some patients received prescription for antimigraine drugs for conditions other than migraine, eg, nonspecific chronic headache; although in a very recent Danish study only 5.1% of people with chronic headache (including medication-overuse headache) had claimed prescriptions for antimigraine drugs.[33] Moreover, we were unable to distinguish between subtypes of migraine, eg, migraine with and without aura. In addition, headache (but not migraine) is a commonly reported side effect of certain systemic antipsoriatic therapies.[34,35] However, the association between psoriasis and migraine observed in our study is supported by the fact that even patients with mild disease, ie, individuals who received no systemic treatment for psoriasis, demonstrated significantly increased risk of migraine. Finally, the Danish population is predominantly of Caucasian descent, and extrapolation of results to patients with other ethnicities should be carried out with caution, as prevalence of migraine may differ between Caucasians and non-Caucasians.[36] Important strengths of the study include the high accuracy of the nationwide registries and the available information on household income, which minimized bias as a result of sex, age, concurrent medication, and socioeconomic status. Also, the statistical adjustments for presence of a range of comorbidities for which data were continuously updated during follow-up, the length and accuracy of follow-up, the dose-response relationship between psoriasis severity and risk of migraine, the results of the sensitivity analysis with exclusion of subjects with ischemic stroke, and the large number of individuals, respectively, add credibility to our findings.

Table III. Incidence rate ratios of migraine in patients with psoriasis or psoriatic arthritis

	Crude			Age- and sex-adjusted			Fully adjusted		
	IRR	95% CI	*P* value	IRR	95% CI	*P* value	IRR	95% CI	*P* value
Mild psoriasis	1.36	1.29-1.44	<.001	1.51	1.43-1.60	<.001	1.37	1.30-1.45	<.001
Severe psoriasis	1.58	1.31-1.90	<.001	1.80	1.49-2.16	<.001	1.55	1.29-1.86	<.001
Psoriatic arthritis	2.40	2.07-2.78	<.001	2.39	2.06-2.77	<.001	1.92	1.65-2.22	<.001

CI, Confidence interval; *IRR*, incidence rate ratio.

In conclusion, we found a disease severity-dependent increased risk of migraine in patients with psoriasis, and an increased risk of migraine in patients with psoriatic arthritis. Further studies are warranted to determine the effects of antipsoriatic treatment on this association, and whether migraine modifies the psoriasis-associated risk of cardiovascular disease.

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