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往往经历工作生产力和病假的损失，且频繁地经历显著的身心和社交功能的损害。3,4,13 头痛是一种慢性间歇性神经血管疼痛障碍，随着患病率的增加，目前影响了超过12%的丹麦人口。7 尽管头痛的确切起源尚不完全清楚，但头痛一直被归因于急性炎症和高敏感性导致的疼痛途径的病变，以及促炎性介质的增强，如肿瘤坏死因子-α，可以促进疼痛途径的敏感化。6-8 促炎症介质、血小板活化因子和血管紧张素介质等在皮炎的病程中被归因于皮肤炎症和高敏感性。2,3,8,9

**METHODS**

研究批准是由丹麦数据保护机构(Reference 2007-58-0015，内部参考号GEH-2014-018，ISuite 02736)和与一个伦理委员会没有要求的注册在丹麦研究所。所有丹麦公民有相同的平等和免费的医疗保健，以及个人水平的联系是可能在该全国性的行政医疗机构。关于疾病信息的收集是通过丹麦全国病历登记系统(Sundhedsvæsenets Klassifikations System/Health Authority Classification System [SKS])代码。详细的和准确的信息在所有药物的分发被登录到丹麦卫生产品统计数据库中。14 医药程序(包括医院为基础的药理治疗，例如生物治疗)被编码在丹麦卫生产品统计数据库中。

该研究包含所有18岁以上的丹麦公民，由1997年1月1日到2011年12月31日，并且持续到第一次头痛发作。患者被排除在研究之前，以确保有正确的风险-时间分配。对有皮炎或头痛史的患者被排除，以确定皮炎和头痛的诊断。患者的皮炎和头痛将在全国性的丹麦人口中被调查。

**Pharmacologic treatment, medical comorbidities, and socioeconomic status**

基线的共病和药理治疗状态如在表I中描述。这些定义用于描述研究期间的医疗和药理治疗状态，并且持续到研究的最后。对皮炎的治疗和头痛的治疗被定义为每种治疗方式的前3个月，分别定义为轻度、中度或重度治疗。用药包括生物药、环孢素、羟基脲、光敏剂、维甲酸或甲氨喋呤。任何超过3个月的治疗被定义为重度治疗，以符合严重疾病的标准，如果合适。皮炎的严重程度定义为每种治疗方式的前3个月，分别定义为轻度、中度或重度治疗。用药包括生物药、环孢素、羟基脲、光敏剂、维甲酸或甲氨喋呤。
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 G43 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 5,799,859 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), 1.55 (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

### 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

The number of individuals with incident psoriasis and incident migraine 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.

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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

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**Table I. Baseline characteristics of the study population**

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

COPD, Chronic obstructive pulmonary disease.

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**Fig 1.** Study flow chart.
disease.\textsuperscript{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.\textsuperscript{19,22,23} Indeed, there is significant overlap of proinflammatory mediators in psoriasis and atherosclerosis, and psoriasis is strongly associated with obesity and smoking.\textsuperscript{24,25} Moreover, data suggest that psoriasis is an independent risk factor for atrial fibrillation.\textsuperscript{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.\textsuperscript{9} Also, migraine has been associated with an unfavorable cardiovascular risk profile, and a 2-fold increased 10-year risk of coronary heart disease.\textsuperscript{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.\textsuperscript{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.\textsuperscript{26-30}

Only very few studies have to our knowledge reported on the association between psoriasis and migraine.\textsuperscript{3,13} In a study of 1685 adult Taiwanese patients with psoriasis, no significant risk of migraine was observed compared with 5055 control subjects.\textsuperscript{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.\textsuperscript{5,17} 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.\textsuperscript{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.\textsuperscript{53} 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.\textsuperscript{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.\textsuperscript{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 II. Incidence rates of migraine per 1000 person-years in the reference population, and patients with mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively

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

CI, Confidence interval.
Table III. Incidence rate ratios of migraine in patients with psoriasis or psoriatic arthritis

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th></th>
<th>Age- and sex-adjusted</th>
<th></th>
<th>Fully adjusted</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR 95% CI</td>
<td>P value</td>
<td>IRR 95% CI</td>
<td>P value</td>
<td>IRR 95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Mild psoriasis</td>
<td>1.36 1.29-1.44</td>
<td>&lt;.001</td>
<td>1.51 1.43-1.60</td>
<td>&lt;.001</td>
<td>1.37 1.30-1.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td>1.58 1.31-1.90</td>
<td>&lt;.001</td>
<td>1.80 1.49-2.16</td>
<td>&lt;.001</td>
<td>1.55 1.29-1.86</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>2.40 2.07-2.78</td>
<td>&lt;.001</td>
<td>2.39 2.06-2.77</td>
<td>&lt;.001</td>
<td>1.92 1.65-2.22</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

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.

REFERENCES


