

INVESTIGATIVE REPORT

Psoriasis and New-onset Depression: A Danish Nationwide Cohort Study

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Psoriasis is associated with an increased risk of depression, but results are inconsistent. This study examined the risk of new-onset depression in patients with psoriasis in a nationwide Danish cohort including some 5 million people in the period 2001–2011. A total of 35,001 patients with mild psoriasis and 7,510 with severe psoriasis were identified. Incidence rates per 1,000 person-years and incidence rate ratios (IRRs) were calculated. Incidence rates for depression were 20.0 (95% confidence interval 19.9–20.0), 23.9 (23.1–24.7) and 31.6 (29.5–33.8) for the reference population, mild, and severe psoriasis, respectively. Adjusted for age, sex, and inclusion year, IRRs were 1.08 (1.04–1.12) in mild and 1.36 (1.27–1.46) in severe psoriasis. After adjustment for comorbidity, the IRR was significant in only patients <50 years with severe psoriasis (IRR 1.23 (1.03–1.46)). In conclusion, the risk of new-onset depression in psoriasis is mediated primarily by comorbidities, except in younger individuals with severe psoriasis, in whom psoriasis itself may be a risk factor. *Key words: psoriasis; depression; cohort; nationwide; epidemiology; risk.*

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Psoriasis is a chronic inflammatory skin disease that affects 2–3% of the world's Caucasian population (1). The exact aetiology of psoriasis is not fully understood, but both genetic and environmental factors have been implicated in its onset and progression, which is characterized by a chronic low-grade inflammatory state driven by T-helper (Th)1 and Th17 cells (2). Research suggests that psoriasis exerts a major impact on health-related quality of life and that the condition has profound effects on a person's physical appearance (3–5). This may cause social isolation and stigmatization, which may lead to stress-related diseases, anxiety and depression (6–11). In addition, psoriasis is associated with a frequent and markedly increased rate of chronic inflammatory and metabolic comorbidities, which may also increase the risk of depression (12, 13). Depression is considered to have

a strong inflammatory component, with mechanisms involving many of the same inflammatory mediators as those implicated in psoriasis, e.g. interleukin (IL)-2, IL-6, IL-12, and tumour necrosis factor (TNF)- α (14–17).

The association between psoriasis and depression has been examined previously in various settings, ranging from small tertiary-based studies to larger population-based studies. Depending on study design, study population, sample size, and definition of depression, the reported prevalence of depression in patients with psoriasis ranges from, for example, 6–62% (11, 18–21). To the best of our knowledge, no study has previously investigated this important topic in a nationwide setting with adjustments for confounding factors. The aim of the current study was therefore to examine the association between psoriasis and new-onset depression, including the impact of the severity of psoriasis, in a nationwide population-based setting adjusted for measured confounders.

METHODS

Data sources and study population

The study was approved by the Danish Data Protection Agency. In Denmark registry studies are exempted from review by an ethics committee. The study comprised all Danish individuals aged ≥ 18 years from 2001 to 2011. The unique and lifelong personal registration number enabled us to link data at the individual level from the following prospectively recorded registries. Firstly, information on date of birth, sex, and vital status were available from the Central Population Register (22). Secondly, The National Patient Registry, which holds information on all inpatient or outpatient visits to Danish hospitals since 1978 according to the International Classification of Diseases (ICD) (prior to 1994 according to the 8th revision (ICD8) and thereafter the 10th revision (ICD10)), was used to obtain information on morbidity (23). Data on death, comorbidity, and concomitant medication were linked at the individual level and were also linked to socio-economic data. Finally, the Registry of Medicinal Product Statistics holds information on all prescription claims since 1995 and all drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification (24). Pharmacies in Denmark are required to register all dispensed prescriptions, and patients with mild psoriasis were identified by topical vitamin D (ATC: D05AX) prescription claims (at least 2) and classified as severe psoriasis by inpatient or outpatient hospital-based treatment (psoriasis diagnosed at least 3 times), as previously validated (ICD10: L40) (25, 26). We excluded patients with a history of psoriasis,

hospitalization for depression, and/or a history of antidepressant use prior to the study start.

Co-morbidities

The following co-morbidities were included in the analyses: cardiovascular diseases (ICD10: I00–I99), malignancies (CD10: C00–C96), pulmonary diseases (ICD10: J00–J99), gastrointestinal and hepatic diseases (ICD10: K00–K93), rheumatological and locomotor system diseases (ICD10: M00–M99), and neurological diseases (ICD10: G00–G29, G40–H99).

Endpoints

The primary endpoint was initiation of antidepressant medication (ATC: N06A), and we examined the incidence rates of hospitalization for depression (ICD10: F32–F33) as a secondary endpoint (27).

Statistical analysis

Patients were included on 1 January 2001 or on the subsequent day that subjects reached 18 years of age, and were censored on 31 December 2011 or during follow-up if an event or death occurred. Mortality rates per 1,000 person-years and 95% confidence intervals (CIs) were calculated and multivariable adjusted Poisson regression models were used to estimate incidence rate ratios (IRRs) and 95% CIs. Psoriasis status, age, and co-morbidities were included as time-dependent variables to ensure accurate allocation of time at risk and ensure inclusion of continuously updated information on co-morbidities in the analyses. One-year time-bands were created and age was updated at each time-band. In addition, we repeated the analyses without inclusion of rheumatological diseases in the multivariable adjusted model to address the potential impact of adjustment for concomitant psoriatic arthritis in patients with psoriasis. Model assumptions were tested and found valid unless otherwise reported. A 2-sided p -value <0.05 was considered statistically significant. Statistically significant interaction between severe psoriasis and age was demonstrated (p for interaction <0.05) and we therefore present overall and age-stratified IRRs. All analyses were performed with the use of SAS software (version 9.2, SAS Institute), and Stata software (version 11.0, StataCorp).

RESULTS

The total study population comprised 5,216,826 individuals, aged ≥ 18 years between 1 January 2001 and 31 December 2011. A total of 449,567 individuals with

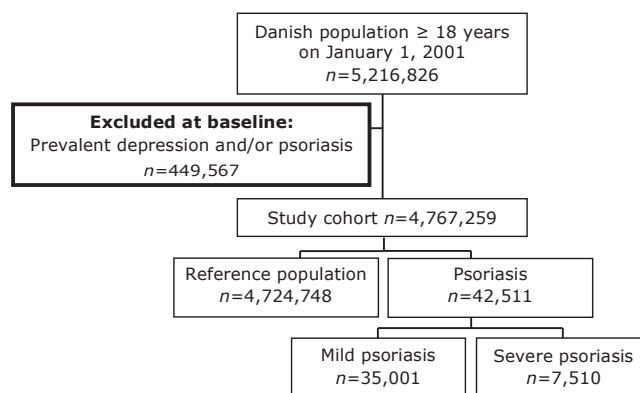


Fig. 1. Selection of the study population.

a previous history of antidepressant use or hospital admission with depression and/or psoriasis were excluded from study participation at baseline. The final cohort comprised a total of 4,767,259 persons with a maximum follow-up of 10 years. The study flow chart is shown in Fig. 1. We identified individuals with mild ($n=35,001$) and severe psoriasis ($n=7,510$) and compared them with the reference population ($n=4,724,748$). The baseline characteristics of the study population are shown in Table I.

Incidence rates per 1,000 person-years of initiation of antidepressants were 20.0 (95% CI 19.9–20.0), 23.9 (95% CI 23.1–24.7), and 31.6 (95% CI 29.5–33.8) for the reference population and patients with mild and severe psoriasis, respectively (Table II). The age-, sex-, and year of inclusion-adjusted IRRs were 1.08 (95% CI 1.04–1.12) in patients with mild psoriasis and 1.36 (95% CI 1.27–1.46) in patients with severe psoriasis. However, after adjustment for comorbidity there was no difference between the groups (IRRs 1.01 (95% CI 0.97–1.07) and 1.07 (95% CI 0.97–1.20) for mild, and severe psoriasis, respectively), albeit that an age-stratified analysis indicated a slightly higher risk in younger (<50 years) patients with severe psoriasis (RR 1.23 (95% CI 1.03–1.46)).

Similarly, there were no significant differences between the groups with regards to risk of hospitalization

Table I. Baseline characteristics of the study population

	Reference population $n=4,724,748$	Mild psoriasis $n=35,001$	Severe psoriasis $n=7510$	p -value
Age, years, mean (SD)	41.4 (19.2)	44.8 (17.2)	43.5 (15.7)	<0.001
Male, n (%)	2,389,157 (50.6)	17,417 (49.8)	3628 (48.3)	<0.001
Follow-up time, years, mean (SD)	8.3 (3.7)	4.2 (3.1)	3.7 (2.7)	
Socioeconomic status, mean (SD)	2.1 (1.4)	2.4 (1.3)	2.4 (1.3)	<0.001
Medical history, n (%)				
Cardiovascular diseases	290,824 (6.2)	2,449 (7.0)	497 (6.6)	<0.001
Pulmonary and lower respiratory diseases	144,894 (3.1)	1,044 (3.0)	273 (3.6)	0.01
Malignancies	241,598 (5.1)	1,987 (5.7)	476 (6.3)	<0.001
Gastrointestinal and hepatological diseases	401,018 (8.5)	3,366 (9.6)	900 (12.0)	<0.001
Rheumatological and locomotor system diseases	487,379 (10.3)	4,349 (12.4)	734 (9.8)	<0.001
Neurological diseases	58,126 (1.2)	469 (1.3)	86 (1.2)	0.14

SD: standard deviation.

Table II. Incidence rates with 95% confidence intervals (CIs) per 1,000 person-years and numbers of events for new-onset depression with adjustments for confounders

	Reference population	Mild psoriasis	Severe psoriasis
Events, <i>n</i>	793,291	3550	827
Incidence rate per 1,000 person-years (95% CI)	20.0 (19.9–20.0)	23.9 (23.1–24.7)	31.6 (29.5–33.8)
Age- and sex- adjusted incidence rate ratio (95% CI)	1	1.08 (1.04–1.12)	1.36 (1.27–1.46)
Age-, sex-, income-, and time-dependent co-morbidity adjusted incidence rate ratio (95% CI)	1	1.01 (0.92–1.07)	1.07 (0.97–1.20)

due to depression after adjusting for comorbidity (not shown). The additional analysis without inclusion of rheumatological diseases gave results similar to the primary analysis (not shown).

DISCUSSION

In this nationwide cohort of the Danish population with a maximum follow-up of 10 years, we examined the association and impact of psoriasis on the risk of new-onset depression. We found an increased initiation of antidepressant pharmacotherapy in patients with both mild and severe psoriasis compared with the general population. However, after adjustment for comorbidity there was no difference between the groups. Therefore, increased risk of new-onset depression seems to be primarily mediated by the presence of comorbid conditions associated with psoriasis, except in younger patients with severe psoriasis who had an increased risk of incident depression, which remained even after adjustment for comorbidities. Thus, it is tempting to speculate that, in patients with severe psoriasis, younger individuals are more psychologically affected than older individuals by the visible characteristics of psoriasis.

Evidence is emerging that, like psoriasis, depression is associated with systemic low-grade inflammation, and the systemic inflammatory profile of the 2 conditions show similar traits, e.g. with elevated plasma concentrations of IL-2, IL-6, IL-12 and TNF- α (14–17). Psoriasis is also associated with an increased risk of a range of chronic comorbidities (diabetes, metabolic syndrome, obesity and cardiovascular diseases), which may confer an increased risk of depression and mood disorders (12, 13). Although previous studies have examined the association between psoriasis and risk of depression, the hitherto reported prevalence of depression in patients with psoriasis varies greatly and no well-adjusted nationwide data have been reported previously (11, 18–20). A recent systematic review and meta-analysis examined the association between psoriasis and depression in 98 eligible studies and a total of 401,703 patients with psoriasis (20). The heterogeneity between the studies was considerable, and more than 25% of the studies in the analysis were from tertiary centres, and only 5 included more than 20,000 patients each. The majority of the studies used questionnaires to measure depressive symptoms, and only a few were population-based with

use of ICD codes for depression. The meta-analysis showed that patients with psoriasis were approximately one and a half times more likely to exhibit signs of depression compared with healthy controls, and that 25% of patients with psoriasis have symptoms of depression. Furthermore, according to this analysis, one in every 10 patients showed signs of clinical depression (20). Compared with these prior results, the current results are primarily supported by the large and unselected study population, and statistical adjustments for presence of a range of comorbidities for which data were continuously updated during follow-up.

Study strengths and limitations

The population-based setting employed here strengthens the validity of the results, and through the inclusion of the entire Danish population we avoided selection bias related to sex, age, health insurance status, and labour market participation. We used topical vitamin D derivatives (which are preferred first-line treatment for psoriasis in Denmark) for identification of patients with mild psoriasis. However, we were unable to identify patients with psoriasis who were not treated pharmacologically or who were treated with topical corticosteroids alone. This allows for potential misclassification of some patients with psoriasis as part of the general population, which may have led to underestimation of the psoriasis-related risk of depression. Likewise, the use of hospital-based treatment for identification of patients with severe psoriasis may have biased the results towards higher prevalence of comorbid conditions in these patients compared with patients with severe psoriasis who were not captured by our criteria. The use of antidepressant pharmacotherapy as a surrogate marker of depression may have misclassified subjects treated with these drugs for other reasons, e.g. anxiety disorders. However, recent evidence showed that, in Denmark, the main indication for antidepressant treatment was depression (57.1% of recorded indications) followed by anxiety disorders (9.0%) (28). Furthermore, according to our clinical experience with patients with psoriasis in Denmark, antidepressants are not routinely used for indications other than depressions (e.g. pruritus). Also, we were not able to adjust for unmeasured confounders including those of relevance to psoriasis and depression, e.g. obesity, smoking, and alcohol intake, but as the latter are more prevalent in

subjects with psoriasis, their inclusion in the analysis would probably have strengthened the overall results. Finally, the Danish population is predominantly of Caucasian descent and extrapolation of the results to other ethnicities should only be done with caution.

In conclusion, in this nationwide population-based study, psoriasis was associated with a disease severity dependent increased risk of depression, but this risk was mediated by the impact of co-morbid conditions. These novel results add to the growing body of evidence that highlights the importance of treatment of psoriasis-associated comorbidities through a multidisciplinary approach to maximize quality of life and life expectancy in these patients.

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Conflicts of interest. LS has received consultancy and/or speaker honoraria from Abbott, Pfizer, Janssen-Cilag, MSD, and Leo Pharma. LS is a member of the advisory boards of MSD, Novartis, Eli Lilly, Abbvie, Celgene, Amgen, and Janssen-Cilag. AE is currently employed by Pfizer.

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