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CLINICAL REPORT

Impact of Depression on Risk of Myocardial Infarction, Stroke and Cardiovascular Death in Patients with Psoriasis: A Danish Nationwide Study

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Psoriasis is associated with depression, myocardial infarction (MI) and stroke. Patients with depression have increased cardiovascular risk. However, the link between psoriasis, depression and cardiovascular disease is unclear. This link was investigated in a nationwide Danish cohort of patients with psoriasis (n = 29,406). Incidence rates were calculated, and incidence rate ratios (IRRs) adjusted for age, gender, socio-economic status, medication and comorbidity were estimated by Poisson regression models. Risk of MI (IRR 1.57, 95% confidence interval (95% CI) 1.07–2.29), stroke (IRR 1.95, 95% CI 1.43–2.66), and cardiovascular death (IRR 2.24, 95% CI 1.53–3.26) were increased significantly during acute depression, and risk of stroke (IRR 1.51, 95% CI 1.19–1.90) was increased significantly in chronic depression. During remission from depression, only the risk of stroke was increased. In conclusion, in patients with psoriasis, depression is associated with increased risk of MI, stroke and cardiovascular death, especially during acute depression. ***Key words: psoriasis; depression; myocardial infarction; stroke; cardiovascular death; epidemiology.***

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Psoriasis is a chronic immune-mediated inflammatory disease, with an estimated prevalence of 2–3% in Europeans (1). In recent years, there has been increasing focus on the systemic nature of psoriasis, with a markedly increased rate of comorbidities, in particular in patients with more severe disease (2, 3). For example, significant association between psoriasis and ischaemic heart disease has been firmly established (4–6). While depression also carries an inflammatory component, the reported prevalence of depression in patients with psoriasis varies widely (e.g. from 6% to 62%) depending on differences in study design, sample population, diagnostic depression criteria, etc. (7–11). Also, a recent meta-analysis found that patients with psoriasis were at least 1.5 times more likely to have clinical depression, and had a 4 times higher use of antidepressants compared with the general population. Patients with depression may carry an increased risk of cardiovascular disease (CVD), but large-scale epidemiological data on the influence of depression on the risk of CVD in patients with psoriasis are lacking (12, 13). The present study therefore investigated the impact of depression on the risk of myocardial infarction (MI), stroke, and cardiovascular death in patients with psoriasis in a case-control study.

MATERIALS AND METHODS (for detailed description see Appendix S1[1])

Data sources and study population

The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (14). Approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736), and approval from an ethics committee is not required for register studies in Denmark. The unique personal identification number assigned to each citizen at birth or immigration allows for unambiguous linkage across administrative registries in Denmark (15, 16).

Cases were defined as all Danish patients with psoriasis and subsequent depression aged ≥ 18 years starting from 1 January 1997 and followed until 31 December 2011, emigration, death or a diagnosis of MI or stroke, respectively. Ascertainment of the stages of depression (acute, chronic, and remission from depression, respectively) was done through diagnoses of depression, and use of antidepressants, respectively (Fig. S1[1]) (17). Baseline (index date) for cases was the first occurrence of depression, and each case was matched (according to age, sex and calendar time) with up to 4 controls from the population of patients with psoriasis without depression. Baseline pharmacological treatment was defined up to 6 months, and baseline comorbidity was described up to 5 years prior to study inclusion, respectively. We calculated an index of socioeconomic status between 0 and 4 based on the average gross annual income (standardized by age) during a 5-year period before study inclusion. Information on medication and comorbidity was continually updated during the follow-up. The primary endpoints were a diagnosis of MI, ischaemic stroke, and cardiovascular death, respectively, with a secondary composite endpoint of MI, stroke, and cardiovascular death (18, 19).

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Statistical analysis

Baseline characteristics were presented as frequencies with percentages for categorical variables and means with standard deviations for continuous variables. Incidence rates were summarized per 1,000 patient-years at risk. Incidence rate ratios (IRRs) were estimated by multivariable Poisson regression models, with patients with incident depression as cases, stratified by stages of depression (acute/chronic/remission), and patients who never experienced depression as the reference population. Two-tailed *p*-values less than 0.05 were considered statistically significant and the results were reported with 95% confidence intervals (95% CIs) where applicable.

RESULTS

From 1 January 1997 to 31 December 2011 the total study population was comprised of 5,536,422 individuals, aged ≥18 years. The study flow chart is shown in Fig. S2[1]. After exclusion of individuals with a history of depression, MI, stroke, or antidepressant use prior to inclusion, the final study cohort comprised 29,406 patients with psoriasis, including 6,244 (21.2%) patients with incident depression, and 23,162 matched controls (psoriasis patients without depression), with a maximum follow-up of 15 years. The baseline characteristics of the study population are shown in Table SI[1]. Use of medications and the percentage of comorbidities were marginally higher at baseline in patients with depression. During the study, 901 (3.06%) patients initiated treatment with biological therapy, of whom 262 (4.20%) were among cases (the incident depression group) and 639 (2.76%) were among controls (the reference population), respectively, and treatment with methotrexate was initiated in 919 (14.72%) cases, and 2,844 (12.28%) controls. There was a slight predominance of female patients with depression, and the index of socio-economic status was somewhat lower (1.7 vs. 2.0) in patients with depression.

Table I. *Risk of myocardial infarction, stroke, and cardiovascular death in patients with psoriasis with or without depression*

	Person-years	Events *n*	IR	Adjusted IRR[a]	95% CI	*p*-value
Myocardial infarction						
Acute depression	4,634.2	30	6.47	1.57	1.07–2.29	<0.05
Chronic depression	10,544.2	51	4.84	0.94	0.68–1.28	0.675
Remission	13,097.0	48	3.66	1.12	0.81–1.55	0.493
Never depression (ref.)	129,442.3	387	2.99	1.00		
Stroke						
Acute depression	4,613.1	44	9.54	1.95	1.43–2.66	<0.001
Chronic depression	10,516.4	84	7.99	1.51	1.19–1.90	<0.05
Remission	13,064.6	60	4.60	1.37	1.05–1.80	<0.05
Never depression (ref.)	129,413.9	472	3.65	1.00		
Cardiovascular death						
Acute depression	4,659.9	90	19.31	2.24	1.53–3.26	<0.001
Chronic depression	10,672.9	171	16.02	1.33	0.97–1.84	0.080
Remission	13,240.6	53	4.00	1.02	0.62–1.68	0.942
Never depression (ref.)	130,314.8	659	5.06	1.00		
Composite endpoint[b]						
Acute depression	4,590.0	130	28.32	2.02	1.68–2.42	<0.001
Chronic depression	10,398.0	236	22.70	1.49	1.29–1.72	<0.001
Remission	12,927.7	137	10.60	1.19	1.00–1.42	0.055
Never depression (ref.)	128,588.1	1,234	9.60	1.00		

[a]Adjusted for age, sex, socio-economic status, medication, and comorbidity. [b]myocardial infarction, stroke, and cardiovascular death combined.
IR: incidence rate per 1000 person-years; IRR: incidence rate ratio.

Risk of myocardial infarction in patients with psoriasis with or without depression

The incidence rates of MI per 1,000 person-years were 2.99 (95% CI 2.71–3.30) for the reference population, and 6.47 (95% CI 4.52–9.26), 4.84 (95% CI 3.68–6.36), and 3.66 (95% CI 2.76–4.86) for acute depression, chronic depression, and remission, respectively, in the depression population. The Poisson regression analyses, adjusted for age and sex, showed increased risk of MI in psoriasis patients with acute depression (IRR 1.78, 95% CI 1.23–2.59) and remission (IRR 1.42, 95% CI 1.05–1.92), respectively, and a non-significant increase in chronic depression (IRR 1.31, 95% CI 0.98–1.75), compared with the reference population. In the fully adjusted model, the risk of MI was only significantly increased in patients with acute depression (Table I, Fig. 1).

Risk of stroke in patients with psoriasis with or without depression

In patients with depression and psoriasis, the incidence rates of stroke per 1,000 person-years were 3.65 (95% CI 3.33–3.99) for the reference population, and 9.54 (95% CI 7.10–12.82), 7.99 (95% CI 6.45–9.89), and 4.60 (95% CI 3.57–5.91), and IRRs adjusted for age and sex were 2.07 (95% CI 1.52–2.82), 1.68 (95% CI 1.33–2.15), and 1.49 (95% CI 1.14–1.95) for acute depression, chronic depression, and remission, respectively, in the depression population. For all 3 groups, the results remained statistically significant in the fully adjusted model (Table I).

Risk of cardiovascular death in patients with psoriasis with or without depression

In analyses where we specifically estimated the risk of cardiovascular death, the incidence rates per 1,000 person-years were 5.06 (95% CI 4.69–5.46) in the reference population, and 19.31 (95% CI 15.71–23.75), 16.02 (95% CI 13.79–18.61), and 4.00 (95% CI 3.06–5.24) for acute depression, chronic depression, and remission, respectively, in the depression population. The age- and sex-adjusted IRRs were significantly increased for acute depression (IRR 2.67, 95% CI 2.14–3.31), and chronic depression (IRR 2.17, 95% CI 1.83–2.57), but not for remission (IRR 1.02, 95% CI 0.77–1.35). The results remained similar in the fully adjusted models (Table I), except for chronic depression ($p = 0.080$).

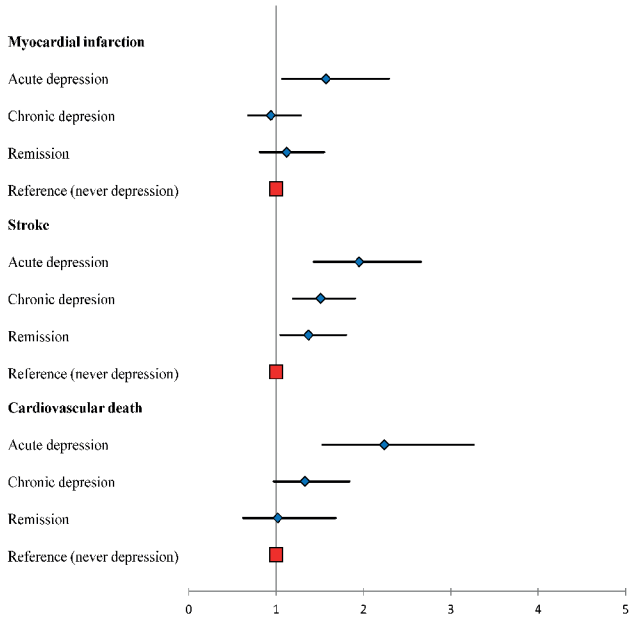

Fig. 1. Forest plot of adjusted incidence rate ratios for myocardial infarction, stroke, and cardiovascular death in patients with psoriasis with or without depression.

Secondary composite endpoint and sensitivity analyses

Compared with the reference population, the secondary composite endpoint (MI, stroke, and cardiovascular death) yielded incidence rates per 1,000 person-years of 9.60 (95% CI 9.08–10.15), 28.32 (95% CI 23.85–33.63), 22.70 (95% CI 19.98–25.79), and 10.60 (95% CI 8.96–12.53), for the reference population, acute depression, chronic depression, and remission, respectively, and the age- and sex-adjusted risk was significantly increased in acute (IRR 2.26, 95% CI 1.89–2.71) and chronic (IRR 1.77, 95% CI 1.54–2.04) depression, and remission (IRR 1.35, 95% CI 1.13–1.61). Results remained consistent in the fully adjusted models, except for remission, where the increase in IRR was only of borderline significance ($p = 0.055$). In sensitivity analyses with altered duration of acute depression from 180 to 240 days, there were no significant changes in any of the reported results (data not shown).

DISCUSSION

In the present study, we used the nationwide Danish registries to examine the impact of depression on the risk of MI, stroke, and cardiovascular death in patients with psoriasis. After adjustment for confounding factors (Table SI[1]) we found a significant increase in IRRs for all endpoints in patients with acute depression compared with the reference population, and an increased risk of stroke, and a composite of MI, stroke, and cardiovascular death, respectively, in patients with chronic depression. During remission from depression, only the risk of stroke was increased, compared with patients who never experienced depression. The findings remained consistent in sensitivity analyses.

Psoriasis is one of the most common immune-mediated inflammatory diseases (20, 21). While the vast impact of psoriasis on quality of life has been proposed to be a mechanism for development of depression, inflammatory cytokine production may be a contributory factor (22, 23). Indeed, many of the pro-inflammatory mediators that probably contribute to the pathogenesis of psoriasis, such as interleukin (IL)-2, IL-6, IL-12, and tumour necrosis factor (TNF)-α have also been found in increased circulating levels in patients with depression (24–27). In patients with depression who are resistant to treatment with selective serotonin reuptake inhibitors (SSRIs), levels of TNF-α have been found to be dramatically elevated, and studies of patients with psoriasis have shown reduction in depressive symptoms following anti-TNF-α- or anti-IL12/23 treatment (28–31). Moreover, the imbalance between pro- and anti-inflammatory cytokines in depression may be decreased using antidepressants and a recent report found that SSRI use in patients with psoriasis was associated with decreased need for systemic psoriasis treatment (32–35).

In our analyses, both hospital diagnoses and antidepressant medication were used for identification of patients with depression. Notably, a recent meta-analysis concluded that there was no evidence of an association between use of SSRIs or tricyclic antidepressants and risk of coronary heart disease including MI (36). Previously, it has been suggested that dermatologists believe that psychiatric disorders are substantially less frequent than they actually are in many skin conditions (37). Moreover, depressive symptoms can influence psoriasis and CVD risk factor management, e.g. patients with concurrent psoriasis and depression may be less likely to adhere to antipsoriatic treatment and use healthcare resources (38). Consequently, depression is likely to be underdiagnosed and may contribute considerably to undertreatment of psoriasis, and underdiagnosis and undertreatment of CVD risk factors in patients with psoriasis, respectively (39–41).

It is generally accepted that patients with depression have an increased risk of stroke and, in addition to the contribution of inflammation, activation of the sympathetic nervous system, increased platelet activation, and other factors, such as increased smoking, physical inactivity, obesity, comorbidities, non-compliance with therapy, and unhealthy diet, respectively, in patients with depression may be among mechanisms underlying the association between depression and stroke (42, 43). The reduction in depressive symptoms by treatment with anti-TNF-α- or anti-IL12/23 treatment in patients with psoriasis is also suggestive of shared immune-inflammatory mechanisms between these 2 diseases and it possible that such mechanisms may also be relevant to CVD (28–31).

Study strengths and limitations

Use of nationwide databases allows analysis of large numbers of patients, while reducing selection bias due to, e.g. gender, age or socioeconomic status. Due to complete prospective registration of respective codes, the registries ensure that recall bias and bias caused by non-response are minimal. The study was strengthened by the time-dependent assessment of depression stage (acute, chronic, remission), and although this definition was arbitrary, as was the assumption that acute depression leaves patients at risk for 180 days, increasing the duration of acute depression to 240 days had no significant bearing on the results. While we demonstrated an increased risk of MI, stroke, and cardiovascular death in patients with psoriasis during active stages of depression, the observational design of our study does not permit us to establish any causal link. Whether the observed effect is due to a higher inflammatory load caused by depression, or the findings are mainly due to poor treatment adherence, unmeasured confounders (e.g. lifestyle factors), and other mechanisms requires further examination. Information on important risk factors for CVD, such as body-mass index, smoking status, blood pressure and lipid levels were not available, albeit that we attempted to adjust for these confounders by using surrogates, e.g. a diagnosis of chronic obstructive pulmonary disease, and use of antihypertensive and lipid-lowering drugs, for smoking, blood pressure and lipid levels, respectively.

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