Appendix S1

MATERIALS AND METHODS

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. Denmark has a long tradition of register-based epidemiological research, linking individual data across national registries using the unique personal identification number, which is assigned to each citizen at birth or immigration (15). All citizens have free, equal and universal healthcare access in Denmark. Data on morbidity were retrieved from the Danish National Patient Register, in which hospital admissions, procedures and diagnoses have been recorded since 1978 using International Classification of Diseases (ICD) codes (ICD-8 until 1994, and ICD-10 hereafter). Hospital procedures (including hospital-based pharmacological treatment, e.g. with biological therapy) are coded in the Danish National Patient Register as treatment procedure (SKS) codes. Data (e.g. date of dispensing, dosage, formulation and quantity) on all pharmacy-dispensed medications are accurately registered according to the international Anatomical Therapeutical Chemical (ATC) classification in the Danish Registry of Medicinal Products Statistics since 1994 (16). Within 14 days of death, all deaths and causes of deaths are registered in the National Causes of Death Registry using ICD-10 codes.

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. Patients with prevalent depression and/or a history of MI or stroke at baseline were excluded. We identified patients by their first in- or outpatient consultation for psoriasis (ICD-10 L40) or psoriatic arthritis (M070-M073), or when they dispensed their second prescription of topical vitamin D derivates (ATC D05AX), which is the preferred first-line treatment for psoriasis in Denmark.

Patients with depression were identified by their first in- or outpatient consultation for depression (F32-33), or when they claimed their first prescription of antidepressant medication (ATC N06A), whichever came first (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. The index date of the control subjects were defined as the date of first occurrence of depression for the corresponding case. Acute depression was defined as a 180-day period from the day of initiation of antidepressant therapy, and/or hospitalization for depression, following 180 days free of prescription of antidepressants or hospitalizations due to depression. We further defined periods of chronic depression, as those that succeeded acute episodes if additional hospitalizations or antidepressant prescriptions had taken place within the 180 days from an episode of acute depression. Remission from depression (henceforth named "remission") periods started 180 days after last hospitalization or prescription of antidepressants, and ended at the time of reinitiating of antidepressant therapy or hospitalization (Fig. S1[1]). We calculated an index of socioeconomic status between 0 and 4, based on the mean gross annual income (standardized by age) during a 5-year period before study inclusion.

Pharmacological treatment and medical comorbidities

Baseline treatment up to 6 months before study inclusion was defined for the following drugs: azathioprine, biological drugs (adalimumab, efalizumab, etanercept, infliximab, and ustekinumab), cyclosporine, methotrexate, loop diuretics, platelet inhibitors, statins, systemic glucocorticoids, and vitamin K antagonists, respectively. Treatment was identified by prescriptions dispensed from pharmacies in the Registry of Medicinal Product Statistics, and treatment for psoriasis administered at the hospital was identified by hospital treatment procedure (SKS) codes. Baseline comorbidity for the following diagnoses was described by ICD codes up to 5 years prior to study inclusion: cardiac dysrhythmia, diabetes, chronic obstructive pulmonary disease, renal disease, hypertension, venous thromboembolic disease, and heart failure, respectively. Hypertension was defined by either a hospital diagnosis, or if a patient within 90 days received treatment with at least 2 of the following classes of antihypertensive drugs: α-adrenergic blockers, non-loop diuretics, vasodilators, β-blockers, calcium-channel blockers, and renin-angiotensin system inhibitors. Diabetes was defined by either a hospital diagnosis, or use of glucose-lowering drugs. Information on medications, comorbidity, and hospital treatment procedures was continually updated during the follow-up period by use of the respective ICD, ATC and SKS codes, as appropriate (STable).

Outcomes

The primary endpoints were a diagnosis of MI (I21–I22), ischaemic stroke (I63–I64), and cardiovascular death (I00–I99), respectively, and a secondary composite endpoint of MI,

STable. *Overview of ICD, ATC, and SKS codes*

Comorbidity	ICD-10/ICD-8
Cardiac dysrhythmia	I44–I49 and 427.3–427.6, 427.9
Diabetes	E10–E14 and 250
Chronic obstructive pulmonary disease	J42, J44 and 490–492
Heart failure	I42, I43, I50 and 110, 517
Hypertension	I10–I15 and 400–404
Renal disease	N03, N04, N17–N19, R34, I12, I13 and 582–588
Venous thromboembolic disease	I26, I80, I82, and 415, 453 excluding I80.8, I80.0 and I82.0
Pharmacological treatment	ATC/SKS
Azathioprine	L04AX01, BWHB83
Biological drugs (adalimumab, efalizumab, etanercept, infliximab, ustekinumab)	L04AB01, L04AB02, L04AB04, L04AC05, L04AA21, BOHJ18A1-BOHJ18A3, BOHJ18B3
Cyclosporine	L04AD01, BOHJ20
Glucose-lowering drugs	A10
Hypertension (α-adrenergic blockers, non-loop diuretics, vasodilators, β-blockers, calcium-channel blockers, and renin-angiotensin system inhibitors)	C02A, C02B, C02C, C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, C02DB, C02DD, C02DG, C07, C07F, C08, C09BB, C09DB, C09
Methotrexate	L03BA01, L04AX03, BWHA115
Loop diuretics	C03C
Platelet inhibitors	B01AC
Statins	C10A
Systemic glucocorticoids	H02AB
Vitamin K antagonists	B01AA

ATC: Anatomical Therapeutical Chemical; ICD: International Classification of Diseases; SKS: hospital procedure codes.

stroke, and cardiovascular death. The identification of MI and stroke has previously been validated in the National Patient Registry (18, 19).

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. The models were adjusted for potential confounding factors such as sex and socio-economic status, and we included age, use of medication, comorbidities, and depression status as time-dependent variables. We adjusted for severity of psoriasis by use of systemic anti-psoriatic therapy. Patients lost to follow-up due to emigration, or due to missing information, were censored at time of emigration, or excluded, respectively. For sensitivity analyses, we changed the duration of acute depression to 240 days to assess the potential impact of our definition on the estimated cardiovascular risk. Two-tailed *p*-values less than 0.05 were considered statistically significant and results were reported with 95% confidence intervals (CIs) where applicable. Model assumptions, including the linearity of continuous variables and absence of interactions, were tested and found to be valid unless otherwise specified. All statistical analyses were performed with the STATA software version 11.0 (StataCorp, College Station, TX, USA) and SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC, USA).