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INVESTIGATIVE REPORT

Psoriasis May Not Be an Independent Predictor for the Use of Cardiovascular and Anti-diabetic Drugs: A 5-year Prevalence Study

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Most studies investigating the association between psoriasis and cardiovascular disease have shown a significant relationship. This comparison study investigated the association between psoriasis and prevalent use of cardiovascular drugs. Drug exposure data for 1998 to 2006 were extracted from the Dutch PHARMO-Record Linkage System database. Psoriasis patients were selected using an algorithm of hospitalization and drug dispensing records specific for psoriasis and matched with controls for gender, age and time-period. From the records of 2.5 million Dutch residents, 9,804 (0.4%) psoriasis patients and 15,288 (0.6%) controls were selected. Psoriasis patients used significantly more anti-hypertensives, anti-coagulant and anti-platelet agents, digoxin, nitrates, lipid-lowering and anti-diabetic drugs than the reference population during a 5-year period observation. In a multiple linear regression model adjusting for the number of unique drugs used, psoriasis was no longer significantly associated with any of these drug classes. Psoriasis patients used more cardiovascular-related drugs, but surveillance bias appears to affect this association considerably. ***Key words: psoriasis; cardiovascular drugs; cardiovascular diseases; diabetes mellitus; surveillance bias; hypertension.***

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Psoriasis is becoming associated more and more with increased cardiovascular morbidity and mortality, and consequently there is a trend to "upgrade" psoriasis from a cutaneous to a systemic disease. Although the first studies suggesting an association between psoriasis and cardiovascular disease (CVD) date from 1973, recently multiple observational studies have tested the hypothesis that psoriasis is a systemic disease that is not restricted to the skin (1–5). The findings of most, but not all, studies demonstrate an increased risk of CVD, especially in patients with severe psoriasis. A Finnish and US cohort study suggested that the increased mortality rate in psoriasis patients was not due to excess CVD mortality but to liver disease and/or alcohol psychosis (6, 7). A Swedish population-based cohort study demonstrated an increased risk of CVD *mortality* only among patients who had been hospitalized for psoriasis, but not among outpatients (8). Studies that analysed the UK General Practitioner Research Database (GPRD) observed an increased risk of myocardial infarction, especially in younger psoriasis patients, and an almost two-fold higher mortality rate in patients who used systemic psoriasis therapies, but not in milder cases compared with controls (9, 10). Interestingly, a recent study using the same database showed no difference in the likelihood of having used anti-hypertensive, lipid-lowering and anti-diabetic drugs between psoriasis patients and their matched controls (11). The observed differences between the observational studies may be related to different study designs, selection procedures, outcomes, follow-up times and available information on confounders (12).

It has been argued that low-grade chronic inflammation with elevated levels of tumour necrosis factor (TNF)-alpha is the common pathway of psoriasis, CVD and metabolic syndrome (9). However, the explanation of the association between psoriasis, metabolic syndrome and CVD is likely to be more complex and multifactorial (Fig. 1) (13, 14). Most studies show that more severely affected psoriasis patients, often defined as those who have been hospitalized or have used systemic therapies, are at an increased risk of CVD (mortality). This may be due to a higher inflammatory status, but equally may be due to more impaired health-related quality of life (HRQoL) and depression, therapy-induced toxicity, and/or increased likelihood of being diagnosed with CVD (i.e. detection bias). This might be important because more than one-third of individuals with hypertension are undiagnosed (15–17).

The objective of this study is to investigate the association between psoriasis and prevalent use of drugs for CVD and diabetes in a large sample of the general population.

MATERIALS AND METHODS

Data source

This study was conducted with data from the PHARMO Record Linkage System (PHARMO RLS), which consists of several linked databases, including drug dispensing, hospital and clinical

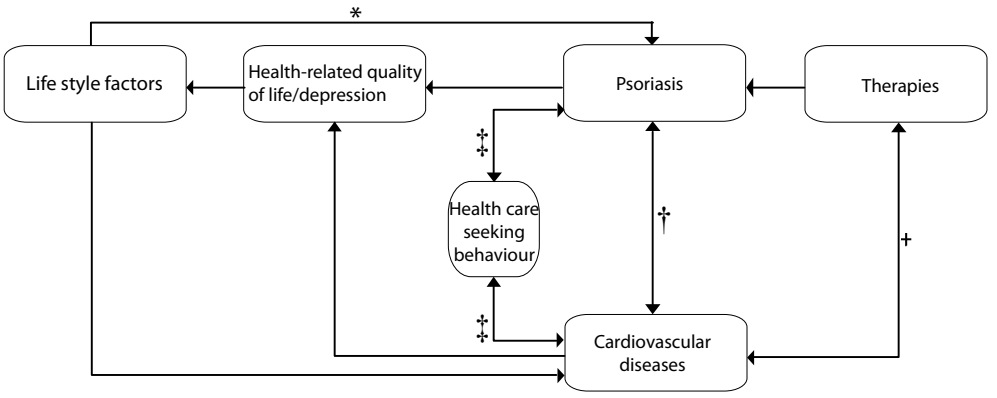

Fig. 1. Schematic example of the complex relationship between psoriasis and cardiovascular diseases (CVD). *A few observational studies suggested that several lifestyle factors contribute to the development of psoriasis (32, 33). +Several systemic psoriasis therapies may have cardiovascular side-effects (e.g. ciclosporin and hypertension), but these therapies may also alter the inflammatory status of a patient and thus affect CVD (4). Also, a history of CVD affects treatment options and may therefore have an indirect effect on psoriasis severity. ‡Once a patient seeks care for a medical problem (e.g. psoriasis) they are likely to be diagnosed with other diseases (e.g. hypertension) as well and to seek care for other complaints more easily than patients who have not visited a physician. †Another hypothesis is that psoriasis may result in an innate increased risk of CVD by the inflammatory process and there may even be a comparable genetic pathogenesis (4).

laboratory records from more than 2.5 million individuals who were ever living in defined areas in the Netherlands (18–20). The drug dispensing histories contain data on the dispensed drug, type of prescriber, dispensing date, amount dispensed, prescribed dose regimens, and the legend duration of use (prescription length). All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification (21). The hospital records include detailed information concerning primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (22). In a subset of the PHARMO RLS, medical records from the general practitioner (GP) were available, including among others diagnoses coded according to the International Classification for Primary Care (ICPC) (23).

Study design

This was a comparative prevalence study in which prevalent psoriasis patients were compared with a reference population with regard to outcomes in terms of specific drug prescriptions during a period of 5 years.

Study population

Patients with psoriasis were identified from the PHARMO database using an algorithm based on recorded hospitalizations and drug dispensing records. This algorithm comprised five steps (hospitalizations for psoriasis, psoralen-ultraviolet A (PUVA) treatment, topical treatments, systemic treatments, and exclusions). For each patient, the likelihood of psoriasis was classified as possible, probable or definite at the first four algorithm steps, based on the specificity for the diagnosis psoriasis. Only those classified as definite psoriasis during at least one of these four steps were eligible for inclusion. Details of the algorithm: patients with a hospital discharge diagnosis of psoriasis and/or psoriatic arthritis (ICD 696.1 and 696.0, respectively) were classified as definite psoriasis (step 1), patients who received psoralen prescriptions (for PUVA therapy) were classified as definite psoriasis (step 2), patients who received calcipotriol, calcitriol or ditranol, fumaric acid or efalizumab were classified as definite psoriasis (step 3 and 4); and patients who did not fill any of the above-mentioned prescriptions but who received prescriptions for topical corticosteroids or coal tar (step 3), systemic glucocorticosteroids (although not considered standard therapy according the Dutch psoriasis guidelines), retinoids, immunosuppressants (methotrexate or cyclosporine), adalimumab, etanercept and/or infliximab (step 4) were classified as possible or probable psoriasis (24). UVB therapy was not assessed in this study because it does not require a pharmacy prescription nor hospitalizations. In the fifth step of the algorithm, all psoriasis patients classified as definite psoriasis based on steps 1–4, who were also hospitalized in the period 1998 to 2006 for skin conditions other than psoriasis were excluded. Other criteria were: presence in the database during 1998 to 2006 for at least 6 months before first mention in the algorithm, age at start of follow-up (i.e. index date) ≥ 18 years and an available follow-up duration of at least 5 years. Diseases that could affect the development of psoriasis, the psoriasis severity, and/or the use of the studied drugs were excluded based on the corresponding ICD-codes (i.e. human immunodeficiency virus, immune disorders, inflammatory bowel diseases, hepatitis B and C, multiple sclerosis, rheumatoid arthritis and status after organ transplant). Reference subjects were eligible for inclusion if they were not classified as either definite, probable or possible psoriasis using the same algorithm applied to all individuals in the database (to avoid false-negative cases), if they could be matched for age and gender to a patient classified as definite psoriasis, and if they were present in the database during 1998 to 2006 for at least 6 months before the index date of the patient they were eligible to be matched to, and had at least 5 years of follow-up. Furthermore, subjects from the reference population were excluded if they were hospitalized for other dermatological diseases as defined in step 5 of the algorithm, or if they had one of the diseases or conditions listed above.

Matching

Psoriasis patients were matched in a 1:2 ratio for gender, age (in years) and similar time and duration of eligibility in PHARMO RLS to controls from the reference population. No psoriasis patient was sampled as a reference subject; however, subjects from the reference population could be matched to more than one psoriasis patient.

Classification of severity of psoriasis

Each included patient with psoriasis was classified into either mild or moderate/severe disease. Mild psoriasis was defined as

prior use of topical therapies only and patients with moderate to severe psoriasis had at least a prior dispensing of psoralen, a systemic anti-psoriatic drug and/or a recorded hospitalization for psoriasis (including psoriatic arthritis).

Validation of the algorithm to identify patients with psoriasis

For a subset of 1,211 patients with definite psoriasis and 2,227 matched controls, electronic medical records were available from their GP. Among the definite psoriasis patients, 1,174 (94%) were classified as such based on prescriptions of topical treatments (algorithm step 3). The GPs' records were searched for the ICPC code S91 ("psoriasis") in the medical Journal field, Diagnosis list, Problem list, and Referral field. Among the 1,211 patients classified as definite psoriasis, 664 (54.8%) had a recorded ICPC code S91 ("psoriasis"), whereas among the 2,227 matched controls, 12 subjects (0.5%) had a recorded ICPC code S91 ("psoriasis") in these fields. This yields a total of 676 (19.7%) diagnostic codes S91 ("psoriasis") recorded by the GPs out of 3,438 subjects in the sample (patients and controls). Considering the GPs' record of the coded diagnosis S91 ("psoriasis") as a surrogate gold standard, the sensitivity of the algorithm was calculated as 98.2% (664/676), specificity 80.2% (2,215/2,762), positive predictive value as 54.8% (664/1,211) and negative predictive value as 99.5% (2,215/2,227). However, the data of the GPs remain a surrogate gold standard, since some psoriasis patients regularly visit their medical specialist, but are rarely seen by their GP.

Follow-up period

All subjects were in the database for at least 6 months before the index date and were subsequently followed up for 5 years. A schematic example of a case with 6 months of history and a 5-year follow-up period is shown in Fig. 2. The index date, which reflects the first available date of a prescription or hospitalization associated with psoriasis, was included to ensure that there was at least one period of disease activity. A 5-year period was chosen to ensure sufficient follow-up to develop the co-morbidities of interest.

Study outcome: cardiovascular or anti-diabetic drug prescriptions

The presence of CVD or diabetes mellitus was determined by examining the prescriptions for the associated drugs in all subjects during the 5 years after the index date. The studied drugs were anti-hypertensive medication, including beta-blockers, calcium channel blockers, ACE-inhibitors, angiotensin-II receptor antagonists, diuretics (ATC codes: C07,C08, C09 and C03), vitamin K antagonists/oral anti-coagulants and platelet aggregation inhibitors excluding heparin (ATC codes: B01AA and B01AC), digoxin (C01AA05), nitrates (C01DA), lipid-lowering drugs including statins and fibrates (C10AA and C10AB) and anti-diabetic drugs including oral anti-diabetics and insulin (A10B and A10A).

Potential confounders

The association between psoriasis, CVD and metabolic syndrome is affected by multiple confounders, such as HRQoL, lifestyle factors, prior psoriasis therapies used and degree of healthcare utilization (Fig. 1). In an attempt to adjust for healthcare- and pharmacy-seeking behaviour, the total number of unique prescriptions (i.e. number of different ATC codes on ATC-3 level) recorded in the database during the 6 months prior to the index date was calculated for each eligible individual. This timeframe was chosen to obtain a reliable representation of the different drugs used, since it comprises twice the maximum prescription period of 90 days. Two different multivariate logistic regression models were applied. Topical drugs and pain medication were excluded from the total number of unique ATC codes in both multivariate analyses, because these drugs are likely to be associated with psoriasis, resulting in an unbalanced correction.

The final, a previously selected multivariate model, additionally excluded the specific drug class studied in each analysis (e.g. dependent outcome) from the total unique ATC codes. Lipid-lowering, anti-diabetic drugs and anti-depressants can be considered as proxies for increased abdominal obesity and body mass index (BMI), diabetes and depression, respectively. Therefore, the included ATC codes in this model allowed partial adjustment for BMI, diabetes and depression. However, to investigate whether including all other cardiovascular drugs in this model may have led to over-adjustment, a second analysis was conducted in which all prior CVD and metabolic drug prescriptions were excluded. No information was available on HRQoL or lifestyle factors, such as physical exercise, diet, smoking and alcohol consumption.

Statistical analysis

Continuous variables are presented as mean values with standard deviations or median values and interquartile range and were tested for statistical significant differences using the Student's *t*-test or the Mann-Whitney *U* test as appropriate. The proportion of psoriasis patients and controls using cardiovascular and anti-diabetic drugs were compared using a χ^2 test. The χ^2 test for linear trend was used to test for significant differences between controls, and patients with mild, and moderate to severe psoriasis. For each drug class separately, a logistic regression model was used to calculate (un)adjusted

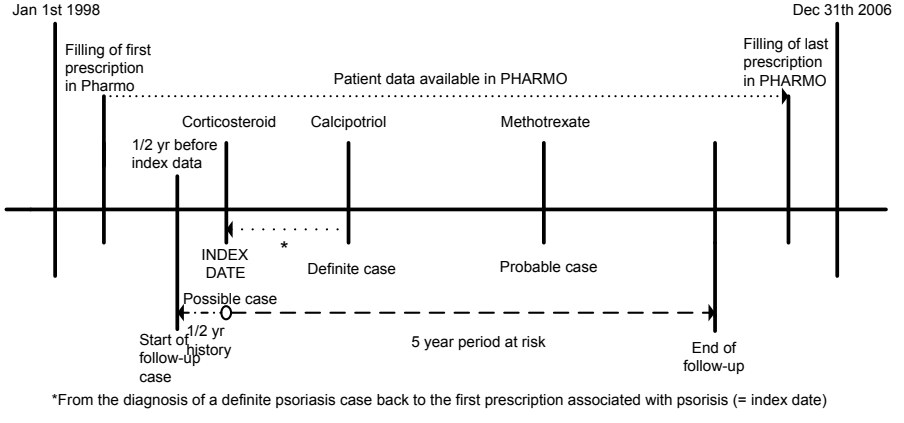

Fig. 2. Schematic example of a psoriasis patient with 6 months of history and a 5-year follow-up period as registered in PHARMO Record Linkage System.

odds ratios (OR) and 95% confidence intervals (CI) for the association between psoriasis and the studied drug class (i.e. dependent variable). Because case and controls were matched for gender, age and index date, healthcare consumption (total unique ATC codes) was the only variable adjusted for in the multivariate model. All statistical tests were two-sided with a p-value < 0.05 considered statistically significant. Analyses were performed using SPSS 15.0 (SPSS Inc. Chicago, IL, USA). The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used to ensure the reporting of this observational study (12).

RESULTS

Study population

Our algorithm identified 9,804 eligible people with a definite diagnosis of psoriasis, who were treated with specific anti-psoriatic drugs or were hospitalized for their psoriasis, as well as 15,288 matched subjects for the reference population. The 5-year prevalence of (definite) psoriasis in the study population was estimated to be 0.4%.

In both populations, 47% were male and the mean age was 49 years (Table I). Compared with the reference population, psoriasis patients were significantly more likely to have used a higher number of unique drugs in the 180 days prior to the index date ($p < 0.001$, Table I). Ninety percent of the 9,804 psoriasis patients were classified as having mild psoriasis (i.e. use of topical therapies only during 5 years of observation) and 10% had used systemic psoriasis therapies and were considered to have moderate to severe psoriasis. During the 5-year period, 5% of the psoriasis patients filled a prescription for acitretin, 3.1% for psoralen, 2.6% for ciclosporin and less than 1% for methotrexate or a biologic (Table I). Of the patients with mild and moderate to severe psoriasis, 10% and 20%, respectively, had used systemic glucocorticosteroids (e.g. prednisone or dexamethasone) during the follow-up period.

Table I. *Baseline characteristics of the study population at index date*[a]

Variable	Psoriasis patients	Reference population
Total no. (%)	9,804 (39.1)	15,288 (60.9)
Gender, *n* (%)		
Male	4,607 (47.0)	7,130 (46.6)
Female	5,197 (53.0)	8,158 (53.4)
Age (years), mean (SD)	49.0 (15.1)	48.7 (14.7)
Median (IQR)	49.0 (37.0;60.0)	49.0 (37.0;60.0)
Total person-years of follow-up, *n*	49,020	76,440
Healthcare consumption, median (IQR)[b]	2 (1;4)	1 (0;3)
Healthcare consumption corrected, median (IQR)[c]	2 (1;3)[d]	1 (0;2)[d]
Psoriasis severity, *n* (%)[e]		
Mild	8,835 (90.1)	0 (0.0)
Moderate to severe	969 (9.9)	0 (0.0)
Therapies ever used in 5-year follow-up, *n* (%)		0 (0.0)
Topical anti-psoriatic therapies	9,744 (99.4)	
PUVA therapy	303 (3.1)	
Methotrexate	65 (0.7)	
Cyclosporine	251 (2.6)	
Acitretin	490 (5.0)	
Biologics[f]	14 (0.1)	

[a]The earliest available date an anti-psoriatic drug was prescribed or a hospitalization for psoriasis occurred in patients with psoriasis, and for controls a prescription or medical diagnosis within 30 days of this date.
[b]Unique number of drugs on Anatomical Therapeutic Chemical (ATC)-3 level in 180 days before index date minus all topical therapies.
[c]Unique number of drugs on ATC-3 level in 180 days before index date minus all topical therapies and pain medication.
[d]Mann-Whitney U test, $p < 0.001$ for psoriasis patients vs. the reference population.
[e]Mild psoriasis was defined as prior use of topical therapies only and moderate to severe psoriasis as ever use of systemic drugs including PUVA and/or hospitalization for psoriasis.
[f]Adalimumab ($n = 1$), efalizumab ($n = 2$), etanercept ($n = 11$).
SD: standard deviation; IQR: interquartile range (25th and 75th percentile shown); PUVA: psoralen plus ultraviolet-A.

Use of cardiovascular drugs and anti-diabetics

Descriptive and univariate analyses. Table II presents the 5-year prevalence of all cardiovascular and anti-diabetic drugs among the psoriasis patients and matched reference population provided with a χ^2 test and a trend test to determine the presence of a significant linear trend across psoriasis severity (i.e. no, mild, and moderate to severe psoriasis). In addition, all cardiovascular and anti-diabetic drugs were significantly more frequently prescribed among patients with psoriasis than among the age and sex-matched reference population, a significant linear trend was observed for psoriasis severity. For all study drugs, the absolute difference in prevalent use observed between psoriasis patients and controls and between psoriasis severity categories was less than 5%. The largest difference in proportion of users between controls and psoriasis patients was noted for the anti-hypertensive drugs (30.2% vs. 34.8%, $p < 0.001$), especially for diuretics and calcium channel blockers. Except for beta-blockers, nitrates, platelet aggregation inhibitors and statins, the proportion of patients increased significantly with disease severity (e.g. 21.7% of patients with mild vs. 18.6% of those with moderate to severe psoriasis used beta-blockers, $p = 0.026$). Compared with controls, a significantly larger proportion of psoriasis patients used anti-coagulants or platelet aggregation inhibitors (15.8% vs. 18.8%, $p < 0.001$), lipid-lowering drugs (13.5% vs. 15.5%, $p < 0.001$) and anti-diabetic drugs (6.1% vs. 7.2%, $p = 0.001$). The prevalence of using these drug classes increased significantly with psoriasis severity. Univariate logistic regression analyses showed that psoriasis patients had approximately 20% higher odds of using drugs for hypertension, hyperlipidaemia and diabetes compared with people without psoriasis (Table III). Compared with the matched references,

Table II. *Five-year prevalence of cardiovascular and anti-diabetic drugs in patients with psoriasis and the matched reference population*

	Reference population[a] (n = 15,288) n (%)	All psoriasis patients (n = 9,804) n (%)	All psoriasis patients vs. reference population, p-value	Patients with mild psoriasis[b] (n = 8,835) n (%)	Patients with moderate to severe psoriasis[c] (n = 969) n (%)	p-value for trend[d]
Anti-hypertensive drugs total	4,619 (30.2)	3,413 (34.8)	<0.001	3,079 (34.9)	334 (34.5)	<0.001
Beta-blocker	3,031 (19.8)	2,094 (21.4)	0.003	1,914 (21.7)	180 (18.6)	0.042
ACE-inhibitor or ATII-antagonist	2,189 (14.3)	1,709 (17.4)	<0.001	1,172 (16.1)	537 (21.2)	<0.001
Ca-antagonist	1,244 (8.1)	1,095 (11.2)	<0.001	968 (11.0)	127 (13.1)	<0.001
Diuretics	1,896 (12.4)	1,639 (16.7)	<0.001	1,461 (16.5)	178 (18.4)	<0.001
Anti-coagulants/anti-platelet agents total	2,421 (15.8)	1,848 (18.8)	<0.001	1,670 (18.9)	178 (18.4)	<0.001
Oral anti-coagulants	717 (4.7)	538 (5.5)	<0.005	484 (5.5)	54 (5.6)	0.007
Platelet aggregation inhibitors	1,960 (12.8)	1,534 (15.6)	<0.001	1,396 (15.8)	138 (14.2)	<0.001
Digoxin	199 (1.3)	177 (1.8)	0.001	157 (1.8)	20 (2.1)	0.001
Nitrates	1,090 (7.1)	933 (9.5)	<0.001	845 (9.6)	88 (9.1)	<0.001
Lipid-lowering drugs total	2,062 (13.5)	1,521 (15.5)	<0.001	1,379 (15.6)	142 (14.7)	<0.001
Statins	2,002 (13.1)	1,481 (15.1)	<0.001	1,344 (15.2)	137 (14.1)	<0.001
Fibrates	97 (0.6)	89 (0.9)	0.014	75 (0.8)	14 (1.4)	0.003
Anti-diabetic drugs total	939 (6.1)	706 (7.2)	0.001	620 (7.0)	86 (8.9)	<0.001
Oral anti-diabetic drugs	798 (5.2)	601 (6.1)	0.002	527 (6.0)	74 (7.6)	<0.001
Insulin	314 (2.1)	263 (2.7)	0.001	232 (2.6)	31 (3.2)	0.001

[a]Controls matched for age, gender and index date without a possible, probable or definite psoriasis diagnosis.
[b]Mild psoriasis is defined as patients with no more than prescriptions for topical anti-psoriatic therapies.
[c]Moderate to severe psoriasis is defined as patients who used systemic anti-psoriatic drugs including psoralens and/or were hospitalized for psoriasis.
[d]χ^2 trend test for linear trend between controls, and patients with mild and moderate to severe psoriasis.
ATII-antagonist: angiotensin-II receptor inhibitor; Ca-antagonist: calcium channel blocker.

psoriasis patients had almost 40% higher odds of having used calcium channel blockers (adjusted OR = 1.42; 95% CI 1.30–1.55).

Multivariate analyses

After adjusting for the variable that comprised both a proxy for healthcare consumption (i.e. unique number of ATC codes in 6 months prior to index date) and also partially adjusted for BMI, diabetes and depression, none of the associations between psoriasis and the studied drugs remained significant (Table III), except for calcium channel blockers and diuretics (adjusted OR = 1.10; 95% CI 1.01–1.21 and adjusted OR = 1.13; 95% CI 1.04–1.21, respectively). Stratifying for psoriasis severity showed that the observed difference for

Table III. *Prevalence odds ratios of prescriptions of cardiovascular drugs and anti-diabetics in patients with psoriasis vs. controls and in patients with mild as well as moderate to severe psoriasis patients vs. controls*

	All psoriasis patients (n = 9804) vs. controls			Mild psoriasis (n = 969) vs. controls[d]	Moderate to severe psoriasis (n = 8835) vs. controls[e]
Study outcome: drug dispensing	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Adjusted OR excluding all prior CVD drugs[c] (95% CI)	Adjusted OR[b] (95% CI)	Adjusted OR[b] (95% CI)
Anti-hypertensive drugs	**1.23 (1.17–1.30)**	1.02 (0.96–1.07)	**1.09 (1.03–1.16)**	1.03 (0.97–1.09)	0.92 (0.76–1.10)
Beta-blocker	**1.10 (1.03–1.17)**	0.95 (0.89–1.01)	1.02 (0.96–1.09)	0.97 (0.91–1.04)	**0.76 (0.61–0.95)**
ACE-inhibitor or ATII-antagonist	**1.26 (1.18–1.35)**	1.05 (0.98–1.13)	**1.14 (1.06–1.22)**	1.07 (0.99–1.15)	0.87 (0.69–1.11)
Ca-antagonist	**1.42 (1.30–1.55)**	**1.10 (1.01–1.21)**	**1.21 (1.11–1.32)**	1.08 (0.99–1.19)	1.30 (0.97–1.74)
Diuretics	**1.13 (1.04–1.21)**	**1.13 (1.04–1.21)**	**1.18 (1.09–1.27)**	**1.12 (1.04–1.21)**	1.16 (0.91–1.48)
Anti-coagulants/ Anti-platelet agents	**1.23 (1.16–1.32)**	0.96 (0.90–1.03)	**1.10 (1.03–1.18)**	0.97 (0.90–1.04)	0.92 (0.73–1.17)
Digoxin	**1.39 (1.14–1.71)**	0.99 (0.80–1.23)	1.09 (0.88–1.35)	0.95 (0.76–1.19)	1.67 (0.78–3.57)
Nitrates	**1.37 (1.25–1.50)**	0.99 (0.90–1.10)	**1.20 (1.09–1.32)**	1.02 (0.92–1.13)	0.79 (0.57–1.09)
Lipid-lowering drugs	**1.18 (1.10–1.27)**	0.96 (0.89–1.03)	**1.11 (1.03–1.19)**	0.97 (0.89–1.04)	0.88 (0.69–1.13)
Anti-diabetic drugs	**1.19 (1.07–1.31)**	0.98 (0.88–1.08)	1.07 (0.96–1.19)	0.97 (0.87–1.08)	1.02 (0.74–1.42)

Statistically significant odds ratios with a p-value < 0.05 are shown in bold.
[a]Controls were matched for gender, age, and index date.
[b]Adjusted for health consumption by using the total number of unique drug prescriptions in 180 days before the index date minus all topical drugs, pain medication and the drug that is being examined.
[c]Adjusted for health consumption by using the total number of unique drug prescriptions in 180 days before the index date minus all topical drugs, pain medication and all cardiovascular disease (CVD) and metabolic syndrome associated drugs.
[d]Mild psoriasis is defined as patients with no more than prescriptions for topical anti-psoriatic therapies.
[e]Moderate to severe psoriasis is defined as patients who used, systemic anti-psoriatic drugs including psoralens and/or were hospitalized for psoriasis.
ATII-antagonist: angiotensin-II receptor inhibitor; Ca-antagonist: calcium channel blocker; CI: confidence interval; OR: odds ratio.

diuretics remained significant for mild psoriasis, but was non-significant for the calcium channel blockers in both categories of psoriasis severity. The likelihood of receiving beta-blockers was significantly lower in patients with moderate to severe psoriasis compared with controls (adjusted OR = 0.76, 95% CI 0.61–0.95). The additional multivariate analysis, which excluded all CVD and metabolic drugs from the unique number of prior prescriptions lowered the ORs less strongly. According to these adjustments, patients with psoriasis had a 1.1–1.2 greater odds of using anti-hypertensives, anti-coagulants and anti-platelet agents, nitrates and lipid-lowering drugs.

DISCUSSION

In this large Dutch population-based study, patients with psoriasis had higher prescription rates for all drugs associated with the metabolic syndrome (with an absolute maximum difference of 5%) compared with the reference population, but they were also more likely to have used other prescription drugs. After entering a variable that assessed the number of unique drugs used in the multivariate models, in order to reduce the effect of other co-morbidities and detection bias, none of the associations between psoriasis and drug use remained significant, except that more severely affected psoriasis patients used less beta-blockers. This is probably because patients with moderate to severe psoriasis are more likely to have received specialized care from dermatologists who are attentive of the possible negative effect of beta-blockers on psoriasis, especially in patients with extensive and/or therapy resistant psoriasis (25). Nevertheless, one-fifth of the psoriasis patients received a beta-blocker as an anti-hypertensive therapy.

The study's findings may suggest that not the inflammatory process, but increased healthcare utilization (i.e. surveillance bias) may be an important factor for the higher use of cardiovascular and anti-diabetic drugs in psoriasis patients. Many diseases remain subclinical and unrecognized until a patient for some other reason (e.g. the treatment of psoriasis) seeks medical attention. For example, 30–60% of the people with hypertension and 45% of those with dyslipidaemia are undiagnosed and myocardial infarctions remain clinically unrecognized in a large proportion (21–68%) of elderly patients (15–17). The consistent finding that psoriasis patients who have been hospitalized and not those who are only treated in outpatient settings are at significantly higher risk of several co-morbidities may confirm the importance of surveillance bias. Altogether, additional healthcare consumption may have a substantial effect on the detection of co-morbidities (including CVD and metabolic syndrome) and the frequency of drug utilization in psoriasis patients.

It can be argued that by adding the number of unique drugs taken (including lipid-lowering, anti-diabetic and anti-depressant drugs) to the multivariate analysis, the results suffered from over-adjustment. Patients were followed from their index date, which is the first available prescription or hospitalization for psoriasis and may therefore have already had psoriasis in the 6 months prior to inclusion, which could also have affected their use of CVD and metabolic drugs. Although prescriptions of the studied drug class (as well as painkillers and topical drugs) were excluded from this variable to minimize possible over-adjustment, there may have been associations between the other prior cardiovascular drugs and the outcome variable. Excluding all cardiovascular drugs from this variable resulted in less comprehensive reductions in the crude ORs than in the initial multivariate analyses (Table III), suggesting that over-adjustment may have occurred in the initial analyses. However, only the initial analyses allowed for partial adjustment for important cardiovascular risk factors, such as diabetes and obesity. The Pearson's correlations coefficients were comparable for the different CVD and metabolic drugs in the psoriasis population and reference population, separately (range 0.09–0.54 and 0.08–0.52, respectively). This assured equal effects of adjustments in both populations. Adding the initial proxy for healthcare consumption improved the fit of the model (Nagelkerke R-squared statistics increased considerably) and the likelihood ratio tests were significant for all analysis to which this variable was added. In a sensitivity multivariate analysis, the number of hospitalizations in the 5 years of follow-up after the index date were used as an alternative proxy for healthcare consumption. This analysis showed comparable effects as were seen after adjusting for the unique number of ATC codes. After adjustment only anti-hypertensives (adjusted OR = 1.13; 95% CI 1.07–1.20) and nitrates (adjusted OR = 1.17; 95% CI 1.07–1.29) were significantly associated with psoriasis. Because the distribution of unique number of ATC codes was less skewed than the number of hospitalizations (64% of the psoriasis population and 56% of the reference population were not hospitalized during these 5 years), the results of the analyses that included number of ATC codes were presented.

One of the strengths of this study is that the study outcome (i.e. drug use) is well documented because a pharmacy database that records filling of prescriptions has been used. However, prescription rates are likely to underestimate the true prevalence of CVDs because of undiagnosed cases, under-treatment and/or poor compliance (20, 26, 27). The applied algorithm to select psoriasis patients from this population-based database only included definite psoriasis patients in order to reduce the number of false-positive cases. The 5-year psoriasis prevalence was 0.4%, which is lower than

the lifetime prevalence in other Western populations, of approximately 2–3% (28). This discrepancy may be due to the period prevalence, the strict selection criteria of the algorithm, the high percentages of patients not seeking healthcare and/or patients not having received vitamin D derivatives (in a US general population sample of psoriasis patients almost 80% never used calcipotriol) (29). To avoid that false-negative cases (e.g. patients who had received topical corticosteroids, cyclosporine and methotrexate, but without vitamin D derivatives, PUVA, efalizumab or inpatient treatments) would pollute the reference group, all possible and probable psoriasis patients were excluded from the analyses. The 5-year follow-up of all eligible subjects was chosen to select the most optimal time-frame to prevent the exclusion of a substantial proportion of subjects with insufficient follow-up. This time-span increases the likelihood that our study results are reliable representation of the actual prevalence of CVD drug use in the psoriasis patients from the general population. Although the use of CVD drugs is probably one of the first available parameters of a different cardiovascular profile of psoriasis patients, it cannot be excluded that for a significant effect of systemic inflammation on the occurrence of cardiovascular events perhaps even longer follow-up time may had been required. Unfortunately, this algorithm could not include UVB (ultraviolet B), which is among the most commonly used therapies for moderate to severe psoriasis in the Netherlands, since its use does not require a pharmacy visit and was not recorded in one of the other available databases (24). The lack of UVB information may not have reduced the number of psoriasis patients because most patients who have been exposed to UVB are likely to have used vitamin D derivatives, but may have led to a misclassification bias in psoriasis severity (i.e. patients who have used topical drugs and UVB were categorized as mild and not moderate to severe disease). To minimize the selection of false-positive cases, the study was restricted to definite psoriasis cases. Validating a subsample of the eligible cases showed that 98.2% of the patients who had psoriasis according to the general physician files were also recognized as definite psoriasis patients. This remarkably high sensitivity was accompanied by a reasonable specificity of 80.2%. However, 547 patients (20%) who were classified as definite psoriasis by our algorithm were also not identified as such by their GP, implicating either that our algorithm was not sufficiently specific or that not every psoriasis patient is registered as such in the GPs' files. Since the patient records were anonomized, we were not able to contact the patients or had any other options for testing the positive predictive value to validate our algorithm. A limitation of using a pharmacy database is that several patients and disease characteristics, such as type and extent of psoriasis, BMI, HRQoL impairment, depression and lifestyle factors, were not available. Because the variable unique number of ATC codes included lipid-lowering, anti-diabetic and anti-depressive drugs, diabetes, depression and, in part, obesity were corrected for in the multivariate model. Adjustment for important confounders remains challenging for each of the epidemiological studies that assessed the association between psoriasis and CVD (1, 8, 9, 30, 31).

Although the proportion of psoriasis patients using cardiovascular drugs is higher than that of controls, the findings of this large population-based study may indicate that there is no direct relationship between psoriasis and CVD or metabolic syndrome. The discrepancy between the univariate and multivariate analyses illustrates the complexity of studies assessing co-morbidities in psoriasis and suggests that medical surveillance bias, in addition to HRQoL impairment and depression, therapies and lifestyle factors, is an important confounder. Unfortunately, none of the other observational studies that demonstrated psoriasis as an independent risk factor for CVD adjusted for healthcare-seeking behaviour or exposure (8, 9). The ideal study design to further examine the relationship between psoriasis and co-morbidities is to conduct a large prospective cohort study with long follow-up specifically designed to investigate this relationship in patients first diagnosed with psoriasis.

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