Psoriasis and the risk of incident diabetes mellitus: a population-based study

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Summary

Background Cross-sectional studies, mostly in hospitalized patients, reported a possible positive association between psoriasis and diabetes mellitus (DM). However, information on the temporal relation is scarce, and incidence rates of new-onset DM in patients with psoriasis are lacking.

Objectives To assess and compare incidence rates of new-onset DM between patients with psoriasis and a comparison group without psoriasis, and to explore the role of psoriasis severity and body mass index (BMI).

Methods We conducted a follow-up study with a nested case–control analysis within the U.K.-based General Practice Research Database. The study population consisted of patients with a first-time diagnosis of psoriasis between 1994 and 2005 and a matched group of psoriasis-free patients. We used psoriasis duration and treatment as proxy for disease severity, and we applied conditional logistic regression to obtain odds ratios (ORs) with 95% confidence intervals (CIs).

Results Within the study population of 65 449 patients we identified 1061 incident cases of DM. Of these, 59% had a history of psoriasis, yielding a crude incidence rate ratio of 1·36 (95% CI 1·20–1·53). The adjusted OR for patients with ≥ 2 years disease duration and > 2 prescriptions per year for oral psoriasis treatment was 2·56 (95% CI 1·11–5·92). In an analysis restricted to patients with normal BMI, the adjusted OR was 2·02 (95% CI 1·31–3·10).

Conclusions In this large observational study the risk of incident DM was increased for patients with psoriasis as compared with a psoriasis-free comparison group. The risk increased with psoriasis duration and severity and was not driven by high BMI alone.

Psoriasis is an immune-mediated inflammatory skin disease with an estimated prevalence of 1·5% in the U.K.[1] The prevalence varies across geographical regions of the world.[2] The disease is characterized by T cell-mediated hyperproliferation of keratinocytes and inflammatory processes based on a complex genetic background. After activation of naïve T cells by antigen-presenting cells, effector/memory T cells mainly of the Th1 and Th17 lineage are generated which produce cytokines such as interleukin (IL)-22, interferon-γ and tumour necrosis factor (TNF)-β, and IL-6, IL-17 and IL-22, respectively. These cytokines, which seem to play a central role in the pathogenesis of psoriasis, can activate keratinocytes directly or via macrophages/dendritic cells leading to increased proliferation of keratinocytes as well as production of other cytokines (TNF-α) and growth factors which sustain the inflammatory processes.[3] This inflammation is thought to be a reason for an increased cardiovascular risk in patients with psoriasis, as is thought to be the case for other diseases with systemic inflammation such as rheumatoid arthritis or lupus erythematosus.[4] Other possible reasons for an altered cardiovascular risk associated with psoriasis are an increased prevalence of smoking and high body mass index (BMI).[5] Previous studies on comorbidities of psoriasis reported an increased prevalence of diabetes mellitus (DM) among patients with psoriasis[6,7] including one study in which the effect was restricted to females.[6] TNF-α is involved in the pathogenesis of psoriasis and has been shown to induce insulin resistance, and inflammatory processes have also been hypothesized to play a role in the pathogenesis of DM.[8,9] One cross-sectional study in patients with a BMI < 30 kg m^{-2} did not provide evidence for a material difference in insulin secretion or sensitivity between patients with psoriasis and healthy controls, but a subanalysis related psoriasis duration with decreased insulin sensitivity, and the authors of another study described the metabolic state in patients with psoriasis to be shifted towards insulin resistance.[10,11] In addition, several epidemiological

studies[6,7,12–17] reported an increased prevalence of DM or metabolic syndrome (including central obesity, atherogenic dyslipidaemia, hypertension and glucose intolerance) in patients with psoriasis. However, all of the studies were cross-sectional, and most of them involved hospitalized patients. Furthermore, DM was the primary outcome of interest in only one of these studies.[14]

It was the aim of the present study to elucidate further the association between psoriasis and the risk of developing new-onset DM in a large population-based observational study.

Materials and methods

We conducted a matched follow-up study and a nested case–control analysis to quantify the risk of new-onset DM in patients with psoriasis and to compare it with that in a matched population without psoriasis.

Data source

We used the General Practice Research Database (GPRD), a large U.K.-based database established around 1987 which encompasses some 5 million patients who are actively enrolled with selected general practitioners (GPs). The GPs have agreed to provide data for research purposes to the GPRD. GPs have been trained to record medical information in a standard manner and to supply it anonymously. The patients enrolled in the GPRD are representative of the U.K. with regard to age, sex, geographical distribution and annual turnover rate. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, hospitalizations and all drug prescriptions, as the doctors generate prescriptions directly with the computer using a coded drug dictionary. Prescriptions contain the name of the preparation (active compound), the route of administration, the dose of a single unit, the number of units prescribed and, in most instances, the intake regimen prescribed by the GP. This database, which has been described in detail elsewhere[18,19] and validated extensively,[20–22] has been the source for numerous epidemiological studies published in peer-reviewed journals.

The study protocol was approved by the Independent Scientific Advisory Committee for the U.K. Medicines and Healthcare Products Regulatory Agency database research.

Study population

The study population consisted of all patients with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005, and of a comparison group of the exact same number of patients free of psoriasis, matched on calendar time (date of the psoriasis diagnosis), age (same year of birth), sex, general practice and years of history in the GPRD. We excluded patients with less than 3 years of history in the database prior to the first-time diagnosis of psoriasis (or the corresponding date in the comparison group). In previous GPRD-based studies on psoriasis, Gelfand *et al.* documented a high validity of psoriasis diagnoses in the GPRD,[1,23,24] and we therefore included all patients with a recorded psoriasis diagnosis in the analyses.

Follow-up and identification of incident diabetes cases

From the study population we excluded all patients with a prevalent diagnosis of DM as well as of cancer or human immunodeficiency virus (HIV) prior to the psoriasis diagnosis (or the corresponding date in the comparison group). We then followed all patients until they developed a first-time diagnosis of DM, died, or follow-up in the medical record ended, whichever came first. The date of the diagnosis of DM will subsequently be referred to as 'index date'. Cases with DM were included in the analyses if they had a first-time DM code recorded plus at least one prescription for an antidiabetic drug such as insulin, sulphonylureas, biguanides, thiazolidinediones, acarbose, glinides or guar gum within 30 days prior to or at any time after the first-time diagnosis of DM. In addition, patients with a recorded diagnosis of DM who did not receive any drug treatment but who were started on a diet were included. We excluded potential cases who did not fulfil these criteria as well as those who received antidiabetic drugs more than 30 days prior to the first recorded diagnosis of DM as they were considered to be prevalent rather than incident. We applied these criteria for inclusion or exclusion of potential cases of DM after having manually reviewed a random sample of computer profiles of potential cases of DM.

Nested case–control analysis

To each case patient with an incident diagnosis of DM we matched at random up to four control patients from the study population on age (same year of birth), sex and calendar time (same index date, i.e. the date when the case developed DM). We applied the same exclusion criteria to controls as we did to cases.

We compared the prevalence of diagnosed psoriasis prior to the index date between cases of DM and controls and stratified patients with psoriasis by severity of disease, thereby taking into account (i) duration of psoriasis (< 2 vs. ≥ 2 years), (ii) psoriasis treatment [no treatment, topical treatment only (emollients, salicylic acid, calcipotriol, coal tar, dithranol or tazarotene preparations or corticosteroids) and/or oral treatment (azathioprine, ciclosporin, methotrexate, acitretin, hydroxycarbamide, mycophenolate mofetil or ultraviolet/psoralen plus ultraviolet A therapy)] and (iii) intensity of psoriasis treatment (no treatment, ≤ 4 vs. > 4 prescriptions per year for topical treatment, ≤ 2 vs. > 2 prescriptions per year for oral treatment).

Statistical analysis

In the follow-up analysis we assessed person-time for all patients in the study population from the date of first psoriasis

diagnosis (or the corresponding date in the comparison group) until a patient developed DM, died, or follow-up in the medical record ended. We assessed the crude incidence rate (IR) of a first-time diagnosis of DM among patients with or without psoriasis, stratified by age and sex, as well as a crude incidence rate ratio (IRR) with 95% confidence interval (CI).

In the nested case–control analysis we conducted conditional logistic regression analyses using the SAS statistical software (version 9.1; SAS Institute, Cary, NC, U.S.A.). We displayed relative risk estimates as odds ratio (OR) with 95% CI. The analyses were controlled for the potential confounders age, sex and calendar time by matching. We further adjusted the OR for smoking status (non, current, ex, unknown) and BMI (< 18·5, 18·5–24·9, 25·0–29·9, 30+ kg m^{-2}, unknown) in the multivariate model, as well as for hyperlipidaemia (diagnosis or antihyperlipidaemic treatment recorded), hypertension, use of oral steroids (1–4 or ≥ 5 prescriptions) and previous infections (candidiasis/aspergillosis, cellulitis). We also tested potential confounding for a number of other covariates which were not included in the final model because they were not materially associated with the exposure or the outcome, such as ischaemic heart disease, congestive heart failure, arrhythmias, cerebrovascular diseases, arterial thrombosis, venous thrombosis, renal failure, schizophrenia, affective disorders, skin infections, respiratory/chest infections, viral infections, and use of aspirin, nonsteroidal anti-inflammatory drugs, antipsychotics, selective serotonin reuptake inhibitors, oral contraceptives and oestrogens.

Results

The initial study population consisted of 73 404 patients, 36 702 with psoriasis and 36 702 psoriasis-free patients in the matched comparison group [16 969 (46·2%) males and 19 733 (53·8%) females]. Patients with psoriasis were more likely to be current (23·9% vs. 18·8%) or ex-smokers (12·8% vs. 10·3%), and they tended to have a higher BMI (22·7% vs. 21·6% with BMI 25–29·9 kg m^{-2}, and 13·3% vs. 10·6% with BMI ≥ 30 kg m^{-2}) prior to the first-time psoriasis diagnosis than patients in the comparison group without psoriasis.

Incidence rates of diabetes in the person-time analysis

After the exclusion of patients with prevalent DM, cancer or HIV, the remaining study population consisted of 65 449 patients (32 593 cases and 32 856 controls). Within this population we identified 1061 cases with an incident diagnosis of DM of whom 626 (59%) had a history of psoriasis and 435 (41%) did not. The IR for DM was 4·06 (95% CI 3·75–4·39) per 1000 person-years in patients with psoriasis and 2·98 (95% CI 2·72–3·28) per 1000 person-years in the comparison group without psoriasis, yielding a crude IRR of 1·36 (95% CI 1·20–1·53) for patients with psoriasis compared with the comparison group. The crude IRs and IRRs, stratified by age and sex, are displayed in Table 1.

Nested case–control analysis

The nested case–control analysis encompassed 1061 incident cases of DM and 4244 matched control patients. The background characteristics of cases and controls are displayed in Table 2. As compared with patients without psoriasis, the relative risk estimate (OR) of developing DM associated with psoriasis was 1·31 (95% CI 1·13–1·51), adjusted for smoking status, BMI, hypertension, hyperlipidaemia, infections and use of systemic steroids. We found increasing ORs with increasing psoriasis severity, based on assessments of treatment type and

Table 1 Incidence rate (IR) and incidence rate ratio (IRR) stratified by age and sex

	Person-years	Cases	IR per 1000 person-years (95% CI)	IRR (95% CI)
Psoriasis (P)	154 316·1	626	4·06 (3·75–4·39)	1·36 (1·20–1·53)
No psoriasis (NP)	145 783·8	435	2·98 (2·72–3·28)	
Sex				
Male P	71 084·7	332	4·67 (4·20–5·20)	1·23 (1·04–1·44)
Male NP	66 270·5	252	3·80 (3·36–4·30)	
Female P	83 231·3	294	3·53 (3·15–3·96)	1·53 (1·28–1·83)
Female NP	79 513·4	183	2·30 (1·99–2·66)	
Age (years)				
0–29 P	40 246·0	18	0·45 (0·28–0·71)	2·75 (1·24–6·13)
0–29 NP	36 928·7	6	0·16 (0·07–0·35)	
30–59 P	70 072·0	237	3·38 (2·98–3·84)	1·33 (1·09–1·61)
30–59 NP	65 861·4	168	2·55 (2·19–2·97)	
60–79 P	37 008·4	330	8·92 (8·01–9·93)	1·43 (1·21–1·69)
60–79 NP	36 312·4	226	6·22 (5·47–7·09)	
80+ P	6989·7	41	5·87 (4·33–7·95)	1·12 (0·71–1·75)
80+ NP	6681·5	35	5·24 (3·77–7·28)	

CI, confidence interval.

Table 2 Background characteristics of diabetes cases and controls in the nested case–control analysis

	Cases (n = 1061), n (%)	Controls (n = 4244), n (%)	Adjusted[a] OR (95% CI)
Smoking status			
Nonsmoker	479 (45·2)	1937 (45·6)	1·00 reference
Current smoker	197 (18·6)	948 (22·3)	0·97 (0·79–1·20)
Ex-smoker	271 (25·5)	826 (19·5)	1·10 (0·90–1·34)
Unknown	114 (10·7)	533 (12·6)	1·11 (0·82–1·51)
BMI (kg m^{-2})			
12–18·4	2 (0·2)	49 (1·2)	0·47 (0·11–1·99)
18·5–24·9	97 (9·1)	1304 (30·7)	1·00 reference
25–29·9	320 (30·2)	1398 (32·9)	3·10 (2·41–3·99)
30–60	476 (44·9)	619 (14·6)	9·95 (7·68–12·89)
Unknown	166 (15·6)	874 (20·6)	2·53 (1·87–3·43)
Comorbidities			
Hypertension	494 (46·6)	1151 (27·1)	1·93 (1·64–2·28)
Hyperlipidaemia/ no antihyperlipidaemics	59 (5·6)	206 (4·9)	1·05 (0·75–1·47)
Hyperlipidaemia/ antihyperlipidaemics	230 (21·7)	477 (11·2)	2·13 (1·72–2·64)
Infections	419 (39·5)	1331 (31·4)	1·25 (1·06–1·47)

[a]Adjusted for all covariates listed in the table plus use of systemic corticosteroids. Infections include cellulitis, candidiasis and aspergillosis. BMI, body mass index; CI, confidence interval; OR, odds ratio.

duration (< 2 vs. ≥ 2 years) prior to the index date. An additional stratification of the duration of psoriasis prior to the index date into categories of < 2, 2 to < 4 or ≥ 4 years yielded increasing adjusted ORs with increasing psoriasis duration of 1·24 (95% CI 1·03–1·51), 1·26 (95% CI 1·01–1·59) and 1·43 (95% CI 1·16–1·76), respectively. The OR for patients with a history of psoriasis of ≥ 2 years who received > 2 prescriptions per year for oral psoriasis treatment was 2·56 (95% CI 1·11–5·92), as compared with those without psoriasis (Table 3).

Table 3 Diabetes risk and psoriasis stratified by severity, nested case–control analysis

	Cases (n = 1061), n (%)	Controls (n = 4244), n (%)	Adjusted[a] OR (95% CI)
No psoriasis	435 (41·0)	2154 (50·8)	1·00 reference
Psoriasis	626 (59·0)	2090 (49·2)	1·31 (1·13–1·51)
Short-term disease (< 2 years)	238 (22·4)	866 (20·4)	1·24 (1·03–1·51)
Long-term disease (≥ 2 years)	388 (36·6)	1224 (28·8)	1·35 (1·14–1·60)
Untreated psoriasis	32 (3·0)	132 (3·1)	1·20 (0·77–1·87)
Short-term	20 (1·9)	83 (2·0)	1·10 (0·64–1·90)
Long-term	12 (1·1)	49 (1·2)	1·41 (0·69–2·86)
Topical treatment	572 (53·9)	1909 (45·0)	1·30 (1·12–1·51)
Short-term	216 (20·4)	773 (18·2)	1·27 (1·04–1·55)
Long-term	356 (33·5)	1136 (26·8)	1·33 (1·11–1·58)
Low intensity	333 (31·4)	1212 (28·6)	1·20 (1·01–1·43)
High intensity	239 (22·5)	697 (16·4)	1·47 (1·21–1·80)
Long-term/high intensity	90 (8·5)	202 (4·8)	1·71 (1·27–2·32)
Oral treatment (± topical)	22 (2·1)	49 (1·1)	1·61 (0·90–2·88)
Short-term	2 (0·2)	10 (0·2)	0·55 (0·11–2·76)
Long-term	20 (1·9)	39 (0·9)	1·98 (1·06–3·70)
Low intensity	7 (0·7)	22 (0·5)	1·40 (0·55–3·60)
High intensity	15 (1·4)	27 (0·6)	1·77 (0·86–3·66)
Long-term/high intensity	13 (1·2)	18 (0·4)	2·56 (1·11–5·92)

[a]Adjusted for body mass index, smoking, hypertension, hyperlipidaemia, infections and use of oral corticosteroids. CI, confidence interval; OR, odds ratio.

Table 4 Diabetes risk and psoriasis, role of body mass index (BMI) and hyperlipidaemia

	Cases (n = 1061), n (%)	Controls (n = 4244), n (%)	Adjusted[a] OR (95% CI)
Psoriasis and BMI			
No psoriasis/BMI < 25	35 (3·3)	732 (17·3)	1·00 reference
Psoriasis/BMI < 25	64 (6·03)	621 (14·6)	2·02 (1·31–3·10)
No psoriasis/BMI ≥ 25	327 (30·8)	949 (22·4)	7·04 (4·86–10·19)
Psoriasis/BMI ≥ 25	469 (44·2)	1068 (25·2)	8·27 (5·75–11·90)
Psoriasis and hyperlipidaemia			
No psoriasis/no hyperlipidaemia	328 (30·9)	1841 (43·4)	1·00 reference
Psoriasis/no hyperlipidaemia	444 (41·9)	1720 (40·5)	1·33 (1·12–1·57)
No psoriasis/hyperlipidaemia	107 (10·1)	313 (7·4)	1·80 (1·35–2·39)
Psoriasis/hyperlipidaemia	182 (17·2)	370 (8·7)	2·23 (1·74–2·85)

[a]Adjusted for BMI or hyperlipidaemia, smoking, hypertension, infections and use of oral corticosteroids. Numbers of cases/controls in the model with BMI do not sum up to the total number of cases/controls as patients with unknown BMI are not in analysis. CI, confidence interval; OR, odds ratio.

We further analysed the role of BMI and hyperlipidaemia in the association of psoriasis and DM risk. As compared with patients without psoriasis and with normal BMI, the risk of developing DM was substantially elevated for overweight (BMI ≥ 25 kg m^{-2}) patients without psoriasis (adjusted OR 7·04, 95% CI 4·86–10·19), and the point estimate was even slightly higher for overweight patients with psoriasis (OR 8·27, 95% CI 5·75–11·90). In order to distinguish between the role of BMI and the role of psoriasis on the risk of developing DM, we restricted an analysis to patients with normal BMI. Among them, the DM risk was increased twofold for patients with psoriasis (OR 2·02, 95% CI 1·31–3·10) as compared with patients without psoriasis. As compared with patients without psoriasis and without hyperlipidaemia, the adjusted relative risk estimate for developing DM for patients with both psoriasis and hyperlipidaemia was 2·23 (95% CI 1·74–2·85) (Table 4).

Stratification by age < 60 and ≥ 60 years yielded similar risk estimates for developing DM (OR 1·31, 95% CI 1·03–1·68 and OR 1·26, 95% CI 1·05–1·52, respectively), and the ORs after stratification by sex were 1·17 (95% CI 0·96–1·41) for male and 1·54 (95% CI 1·23–1·94) for female patients with psoriasis, as compared with those without psoriasis.

In an additional analysis, we stratified cases of DM into type I and type II DM (type I DM was defined either by a diagnostic code for type I and/or by treatment with insulin only). We found a higher prevalence of type I DM in younger patients with psoriasis and a higher prevalence of type II DM in older patients. About two-thirds of the patients with type I DM had a history of psoriasis (Table 5). Only two of the patients with type I DM had oral psoriasis treatment (data not shown).

Table 5 Prevalence of psoriasis in patients with type I or type II diabetes stratified by age

	Type I diabetes (n = 32)		Type II diabetes (n = 1029)	
Age (years)	Psoriasis, n (%)	No psoriasis, n (%)	Psoriasis, n (%)	No psoriasis, n (%)
0–29	11 (34·4)	4 (12·5)	7 (0·7)	2 (0·2)
30–39	3 (9·4)	3 (9·4)	17 (1·7)	14 (1·4)
40–49	1 (3·1)	0 (0·0)	72 (7·0)	50 (4·9)
50–59	0 (0·0)	0 (0·0)	144 (14·0)	101 (9·8)
60–69	5 (15·6)	1 (3·1)	197 (19·1)	128 (12·4)
70–79	1 (3·1)	1 (3·1)	127 (12·3)	96 (9·3)
80+	0 (0·0)	2 (6·3)	41 (4·0)	33 (3·2)
Total	21 (65·6)	11 (34·4)	605 (58·8)	424 (41·2)

Discussion

The findings of this large population-based study suggest that the risk of developing DM is slightly increased in patients with psoriasis as compared with patients without psoriasis. The risk estimates were highest for patients with psoriasis with a longer psoriasis history who regularly received systemic treatment, possibly reflecting greater disease severity.

Unlike in previous cross-sectional studies, we were in a position to distinguish between prevalent DM and new-onset DM after the first psoriasis diagnosis. The overall DM incidence rate in the psoriasis-free comparison group (3 per 1000 person-years) is similar to the findings of another GPRD-based study reporting an IR of 3·3 per 1000 person-years[25] and slightly higher than the IR of 2·2 per 1000 person-years in a study from the Netherlands.[26] As previously reported,[26] we also observed an age-dependent increase in the DM incidence rate which again decreased in the highest age groups. In our study population the DM IR overall was higher than in the psoriasis-free comparison group, reaching a peak (8·92 per 1000 person-years) in patients aged 60–79 years. The rates were slightly higher among males than females, which is also

consistent with previous literature.[25] When we compared the DM IR between patients with or without psoriasis, the IRR was highest for patients < 30 years of age, most likely driven by cases with type I DM which tends to be increased in young patients with psoriasis. In a subgroup analysis encompassing 32 patients with type I DM, 11 (34·4%) had psoriasis and were < 30 years of age, as compared with four (12·5%) without psoriasis below 30 years of age. Like psoriasis, type I DM is considered to be an autoimmune disease mediated by Th1 helper T cells, and the two diseases may share mechanistic characteristics.[27]

In the nested case–control analysis, the prevalence of psoriasis was slightly higher among cases of DM than among controls (adjusted OR 1·31, 95% CI 1·13–1·51), and a BMI above 25 kg m^{-2} as well as comorbidities related to the metabolic syndrome were also more common in cases with DM than in controls. The slightly increased relative DM risk associated with psoriasis was similar to findings from previous studies in nonhospitalized patients and from cross-sectional designs.[14,16] Another cross-sectional study in hospitalized patients found an OR of 2·48 (95% CI 1·70–3·61); however, the result was not adjusted for BMI.[15] We compared the DM prevalence prior to the first-time psoriasis diagnosis in a previous analysis and did not find a substantial difference between patients with psoriasis and the comparison group without psoriasis.[28]

After stratification by psoriasis duration and type of treatment we found higher ORs for patients with a longer history of psoriasis and/or oral treatment, both markers of disease severity. The authors of another cross-sectional analysis on the GPRD who also used pharmacological treatment as a marker for disease severity reported an OR for DM of 1·62 (95% CI 1·30–2·01)[16] for patients with psoriasis using oral treatment, a similar finding to our OR of 1·61 (95% CI 0·90–2·88), and another study also reported increasing DM ORs with increasing psoriasis severity (defined by type of treatment).[14] In our study population, the DM risk for patients with psoriasis who received intensive topical treatment and had a longer disease duration was 1·71 (95% CI 1·27–2·32), and was 2·56 (95% CI 1·11–5·92) for patients with intensive oral treatment and longer disease duration.

As methotrexate has been shown to increase progression of DM in a randomized trial[29] and as ciclosporin has been associated with hyperglycaemia and acitretin with alterations in glucose tolerance,[30] we conducted several sensitivity analyses to explore the role of pharmacological treatment on the risk of developing DM. In a model restricted to patients with psoriasis without recorded use of oral treatment, the relative risk of developing DM remained higher for patients with psoriasis (adjusted OR 1·31, 95% CI 1·11–1·57) with a longer-term psoriasis history.

The herein reported association between the chronic inflammatory skin disease psoriasis and DM may support the notion that insulin resistance, DM and the metabolic syndrome are triggered by chronic inflammation, i.e. that they are associated with a cytokine-mediated activation of innate immunity.[31] C-reactive protein (CRP), a sensitive marker of inflammation, as well as other inflammatory mediators, have been related to insulin sensitivity as well as to BMI.[32,33] Cytokines (e.g. IL-1, IL-6 and TNF-α) stimulate hepatic production of acute-phase proteins, such as CRP,[31,32] which is also supposed to be increased in mild and severe psoriasis.[34] The beneficial effect of thiazolidinediones in both DM and psoriasis[28] additionally supports the link via inflammation between the two diseases, as these substances are supposed to have anti-inflammatory properties.[35]

Our study has several limitations. In large observational studies one can never rule out a certain degree of misclassification which may have led to the inclusion of cases of psoriasis or of cases of DM who in fact did not have such a diagnosis. However, in previous GPRD-based studies on psoriasis, Gelfand *et al.*[1,23,24] documented a high validity of this diagnosis. In order to reduce the likelihood of including cases of DM who did not have an incident diagnosis of DM, we applied a stringent previously defined algorithm and reviewed a large sample of case profiles so that we were confident that misclassification was not a major issue in this study. Nevertheless, it is possible that high blood glucose was detected by chance or due to increased medical attention in some cases, and that in some instances the index date may not have been accurate, or the person may not have had DM. The number of patients with psoriasis who were exposed to oral treatment is rather low in our study population. As this subgroup reflects patients with the highest disease severity, we do not have much information on this subgroup; most patients with psoriasis in our study population had mild to moderate psoriasis. In addition, it is possible that our classification of disease severity which was based on drug treatment is not always accurate as patients may have received some treatment on an irregular basis by the dermatologist, and this may not have been recorded for all patients by the GP.

Although we tested for a large number of potential confounding factors and included the most relevant ones in our model, we cannot exclude the possibility that unknown confounders or biases may have affected our results to some degree.

Particularly BMI is a strong risk factor for type II DM, and patients with psoriasis have been shown to have higher BMI. Thus, BMI is likely to confound the association between psoriasis and the risk of DM. We therefore adjusted the various models for BMI and ran sensitivity analyses to distinguish further between the role of BMI and of psoriasis as risk factors for new-onset DM. Nevertheless, we cannot rule out the possibility that a certain proportion of misclassified or missing BMI values may have led to some residual confounding. There was, however, substantial evidence from these various analyses that the association between psoriasis and an increased DM risk remained independent of BMI.

In conclusion, this is, to the best of our knowledge, the first study which explored the association between incident psoriasis and the risk of developing an incident diagnosis of DM. In our study population patients with psoriasis were at an increased risk of developing new-onset DM, and there was

a suggestion that the risk increased with psoriasis severity and duration. Finally, the risk of developing a diagnosis of DM did not seem to be explained by high BMI alone.

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