Original Article

The bidirectional association between type 2 diabetes and psoriasis: Two retrospective cohort studies

Hsien-Yi Chiu[1,2,3], Chu-Ju Hung[4,5], Chih-Hsin Muo[6,7], Kang-Chih Fan[8], Fung-Chang Sung[7,9]

[1]Department of Dermatology, National Taiwan University Hospital Hsin-Chu Branch, Hsinchu, [2]Department of Dermatology, National Taiwan University Hospital, Taipei, [3]Department of Dermatology, College of Medicine, National Taiwan University, Taipei, [4]Department of Dermatology, Chung Shan Medical University Hospital, Taichung, [5]Department of Dermatology, School of Medicine, Chung Shan Medical University, Taichung, [6]College of Medicine, China Medical University, Taichung, [7]Department of Health Services Administration, China Medical University, Taichung, [8]Department of Internal Medicine, Division of Endocrinology and Metabolism, National Taiwan University Hospital Hsin-Chu Branch, Hsinchu, [9]Department of Food Nutrition and Health Biotechnology, Asia University, Taichung, Taiwan

Abstract

Background: Inflammation plays a crucial role in both type 2 diabetes mellitus (T2DM) and psoriasis pathogenesis; thus, a bidirectional association between them is likely suspected.

Aims: We investigated the possible bidirectional association between T2DM and psoriasis.

Methods: Using the Taiwan National Health Insurance Research Database, we conducted two retrospective cohort studies. The analysis of psoriasis onset in relation to T2DM status included 31,697 patients with diabetes and 126,788 nondiabetic control subjects (Analysis 1). The analysis of T2DM onset in relation to psoriasis status included 1,947 psoriatic patients and 7,788 nonpsoriatic control subjects (Analysis 2). The follow-up period was from 2000 to the date of the outcome of interest, date of death, or December 31, 2013. Cox proportional models were used to estimate the relative hazards.

Results: In Analysis 1, Kaplan–Meier (KM)-based cumulative incidence of psoriasis was higher in the T2DM cohort than that in the non-T2DM cohort (1.2% vs. 0.7%). The covariate-adjusted hazard ratio (HR) was 1.40 [95% confidence interval (CI), 1.20–1.63] for patients with T2DM. Analysis 2 revealed KM-based cumulative T2DM incidences of 18.7% and 13.1% in psoriatic and nonpsoriatic subjects, respectively. The adjusted HR for incident T2DM was higher in patients with psoriasis (1.38; 95% CI, 1.20–1.58).

Limitation: This article may not represent the population worldwide and patient selection bias may exist.

Conclusion: Our results provide evidence for a bidirectional T2DM–psoriasis association. T2DM and psoriasis are common worldwide; thus, our findings have public health implications for the early identification and management of these comorbid diseases.

Key words: Epidemiology, inflammation, psoriasis, type 2 diabetes mellitus

Correspondence:
Prof. Fung-Chang Sung, Department of Health Services Administration, China Medical University, 91 Hseuh Shih Road, Taichung 404, Taiwan.
E-mail: fcsung1008@yahoo.com

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Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin resistance and impaired islet beta cell function.[1] Psoriasis is a chronic immune-mediated inflammatory disorder that affects 0.1%–3.0% of adults worldwide.[2-4] T2DM and psoriasis are among the most prevalent diseases and are associated with a number of comorbidities.[5-8] The rapid worldwide increase in the prevalence of T2DM and psoriasis has had substantial adverse effects on healthcare systems and affected patients.[1,9]

Accumulating evidence suggests that inflammation has a crucial intermediary role in T2DM development and progression.[10] Inflammation is also thought to be a key component in the pathogenic mechanism of psoriasis.[2,11] Inflammatory mediators such as C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α are frequently elevated in patients with T2DM, as well as in patients with psoriasis.[10-15] Moreover, subclinical inflammation in psoriasis can trigger psoriatic disease recurrence.[16] These findings suggest that T2DM and psoriasis share an inflammatory mechanism and may be linked.

Some studies have reported that diabetes was prevalent among patients with psoriasis.[17-19] However, the underlying link between psoriasis and diabetes is not well understood. Studies examining whether persons with diabetes have an elevated risk of psoriasis have been limited in scope and have yielded inconclusive findings.[10,20,21] A recent study found that T2DM increased the risk of developing rheumatoid arthritis (RA), which, like psoriasis, is an immune-mediated chronic inflammatory disease.[22]

We hypothesized that chronic low-grade inflammation in T2DM may trigger psoriasis development in genetically susceptible individuals and, conversely, that persons with psoriasis have a higher risk of subsequently developing T2DM. This study investigated the potential bidirectional association between T2DM and psoriasis in a large, nationally representative, population-based cohort of predominantly Chinese patients in Taiwan.

Methods

Data source

This retrospective cohort study used data from the Taiwan Longitudinal Health Insurance Database (LHID) 2000, which is a subset of the National Health Insurance Research Database (NHIRD). NHIRD data are compiled from the Taiwan National Health Insurance (NHI) system, which was launched in 1995 to finance healthcare for all citizens. The NHI provides care for approximately 99.5% of the 23.74 million citizens of Taiwan. In LHID 2000, approximately 1,000,000 representative individuals were randomly sampled from all those in NHIRD in 2000. The database comprises comprehensive information on insured subjects, such as demographic data, dates of clinical visits, diagnostic codes, prescription details, and expenditures. A multistage stratified systematic sampling design was used and there were no statistically significant differences in sex, age, or average insured payroll-related amount between the LHID sample and the entire NHIRD population (http://nhird.nhri.org.tw/en/Data_Subsets.html). All subject information was anonymized and deidentified to protect privacy. The study protocol was approved by the local investigational research bureau of National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan (103-024-E).

Study subjects

In the first analysis, we identified patients who received a new diagnosis of T2DM and those without a T2DM diagnosis (control group). We randomly selected four control subjects without a T2DM diagnosis per patient with psoriasis, matched for age, sex, and index date from LHID 2000. A T2DM diagnosis was defined as at least two ambulatory claims or at least one inpatient claim with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 250.xx, except for type 1 diabetes (ICD-9-CM codes 250.01, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.81, and 250.93), between 2000 and 2004. In the second analysis, we selected individuals with a new psoriasis diagnosis (ICD-9-CM codes 696.0, 696.1, and 696.8) and those without a psoriasis diagnosis as the control group. For each psoriasis patient, four subjects without psoriasis, matched for age, sex, and index date, were randomly selected from LHID 2000. To ensure the accuracy of the psoriasis diagnoses, subjects were selected only if they had received at least two diagnoses of psoriasis by dermatologists during ambulatory visits or inpatient care between 2000 and 2004. The dates of newly diagnosed T2DM (in Analysis 1) and psoriasis (in Analysis 2) were designated as the index dates from which follow-up began. To ascertain the temporal association between the risk factor and the subsequent development of outcome, we had excluded cases with outcome at enrolment. In Analysis 1, we excluded patients who had received a psoriasis diagnosis before a T2DM diagnosis. Similarly, patients with a T2DM diagnosis before a psoriasis diagnosis were excluded from Analysis 2.

Outcome and relevant variables

All subjects were followed from the index date until the incidence of psoriasis (Analysis 1) or T2DM (Analysis 2), until they were censored at the end of the study period (December 31, 2013), or until the date of disenrollment (usually because of death). The primary outcome was the first ambulatory visit or hospitalization for any psoriasis (Analysis 1) or T2DM (Analysis 2), regardless of whether the patient survived or died after the outcome event.

We adjusted for potential confounders by including medical history and medication use in the preceding year. The medical history included hypertension (ICD-9-CM codes 401–405), hepatitis C (070.41, 070.44, 070.51, 070.54, and V02.62), depression (296.2, 296.3, 300.4, 309.1, and 311), coronary artery disease (410–414), hyperlipidemia (272), obesity (278), gout (274), chronic kidney disease (403, 404, 582, 583, 585, 586, 588, V42.0, V45.1, and V56), alcoholic liver disease (571.0, 571.1, 571.2, and 571.3), and chronic obstructive pulmonary disease (490–496). Prior medication use included statins, steroids, diuretics, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs, hydroxychloroquine, interferon, lithium, and antipsychotic drugs.

Statistical analysis

Intergroup differences were evaluated by independent-samples *t*-tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. In Analysis 1, we calculated the incidence density (cases per 10,000 person-years) of psoriasis stratified by sex, age, and comorbidities. Cox regression models were used to estimate the T2DM cohort to non-T2DM cohort hazard ratio (HR) of psoriasis development. The multivariable model including the variables of age, sex, degree of urbanization, income group, comorbidities, medications used, and number of outpatient visits in the first year after the index date was used to estimate the adjusted HR (aHR). The cumulative incidence of psoriasis was computed using Kaplan–Meier (KM) method, and differences between two cohorts were examined by log-rank tests. Similar data analysis procedures were used for Analysis 2. We also conducted a test for interaction to evaluate for statistically significant differences in subgroups. If the *P* value was significant, we concluded that the effect of T2DM/psoriasis on the outcome differed within the subgroups. The data were managed and statistical analysis was performed using SAS Version 9.3 (SAS Institute, Cary, NC, USA). A two-tailed *P* value of less than 0.05 was considered to indicate statistical significance.

Results

Analysis 1: Cohort analysis of the psoriasis risk in relation to diabetes status

During 2000–2004, we identified 31,697 diabetic patients and 126,788 matched control subjects. The distributions of age and sex were similar between the cohorts. The mean age was approximately 55 years, and most patients in both groups were male. Patients with T2DM were more likely than the matched control subjects to have comorbidities including hypertension, coronary artery disease, cerebrovascular disease, depression, hyperlipidemia, hepatitis C, obesity, gout, chronic obstructive pulmonary disease, chronic kidney disease, and alcoholic liver disease (all $P < 0.001$) [Table 1].

The median follow-up periods were 10.1 years in the diabetic group and 10.6 years in the nondiabetic control group. The incidence of psoriasis was higher in the diabetic cohort than that in the nondiabetic cohort, with KM-based cumulative incidences of 1.2% and 0.7%, respectively [Figure 1]. The diabetic cohort remained associated with a significantly higher risk for psoriasis after adjusting for age, sex, degree of urbanization, income group, comorbidities, medications used, and number of outpatient visits in the first year after the index date [aHR 1.40; 95% confidence interval (CI), 1.20–1.63; Table 2]. The aHRs for psoriasis were significantly higher in both sexes. In subgroup analysis, although the interaction *P* value was not statistically significant, the aHR among diabetic patients was highest for patients age 50–64 years (1.58; 95% CI, 1.23–2.20), and the aHR for psoriasis was higher in diabetic patients with comorbidities than that in those without comorbidities [Table 2].

Analysis 2: Cohort analysis of diabetes risk in relation to psoriasis status

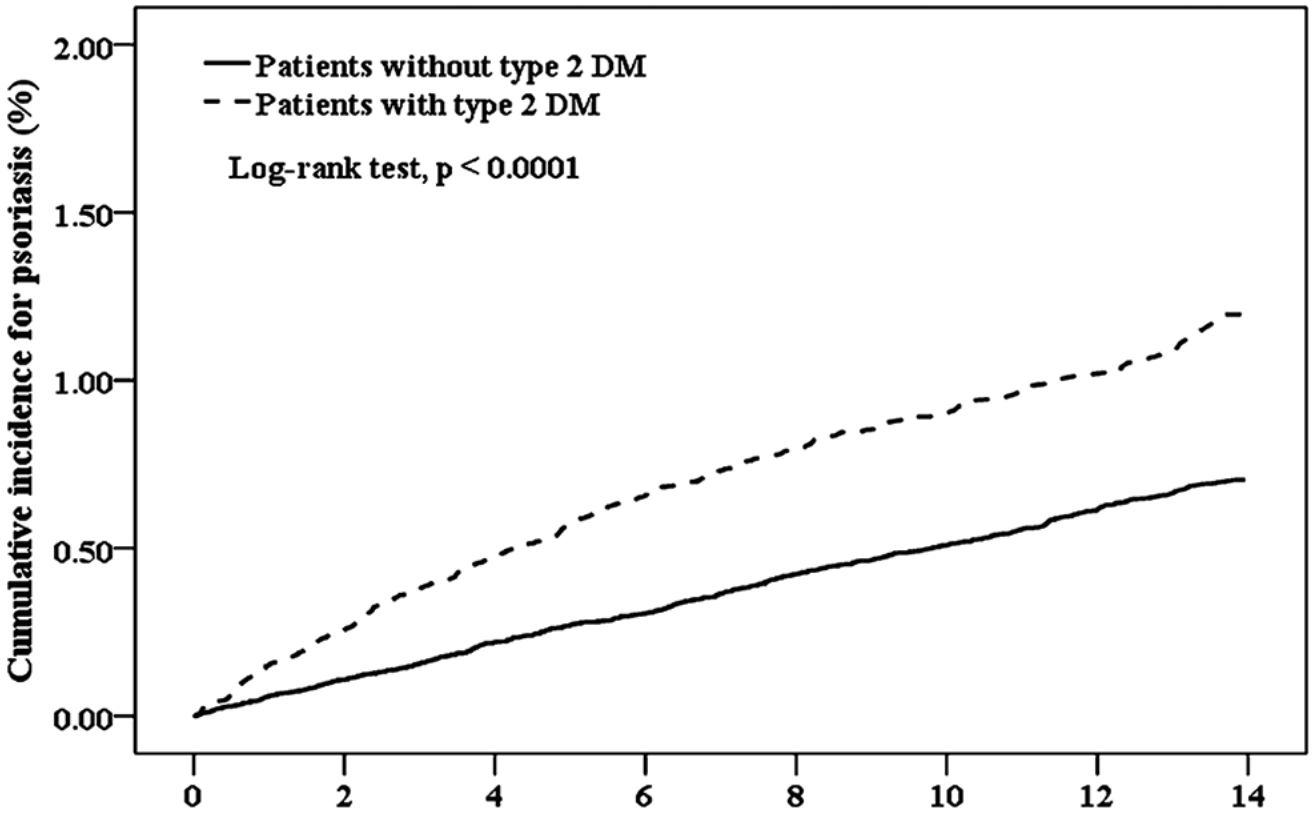
The distributions of baseline characteristics in the psoriasis and nonpsoriasis cohorts are summarized in Table 3. Patients with psoriasis had lower incomes and more comorbidities than those in the nonpsoriasis group. The KM-based cumulative incidence of T2DM was 18.7% in patients with psoriasis and 13.1% in controls during mean follow-up periods of 9.98 and 10.5 years, respectively [Figure 2].

After adjusting for age, sex, degree of urbanization, income group, comorbidities, medication use in the previous year, and number of outpatient visits in the first year after the index date, the aHR for diabetes during the 10-year follow-up period for subjects with psoriasis was 1.38 (95% CI, 1.20–1.58) when compared with nonpsoriatic subjects [Table 4]. Among patients with psoriasis, although the interaction *P* value was not statistically significant, the risk of T2DM was higher for men than that for women. In age-stratified analysis, the risk of diabetes after a psoriasis diagnosis was highest for patients age 50 years or older (aHR, 1.40; 95% CI, 1.17–1.68) [Table 4].

Discussion

Analysis 1: T2DM and subsequent psoriasis risk

The relationship between diabetes and psoriasis is likely to be complex. Unfortunately, few studies have investigated the risk of psoriasis in patients with T2DM. Recent research indicates that T2DM increases blood levels of inflammatory markers such as TNF-α and IL-6.[10,12] Elevations of these inflammatory markers may be pathogenetic factors in psoriasis.[11,13,23] Moreover, hyperglycemia has been reported to drive secretion of several proinflammatory cytokines, including TNF-α, IL-1 β, IL-6, and IL-22, by macrophages and T cells in adipose tissue, which have also been implicated in psoriasis pathogenesis.[2,4,14,24,25] Elevated circulating glucose concentrations activate the NLRP3 inflammasome, which may play a pivotal role



Follow-up year	0	2	4	6	8	10	12	14
Patients without type 2 DM								
No at risk	126788	121930	117518	113446	109499	84771	42744	
Event no	0	136	132	99	131	90	70	27
Cumulative incidences (95% CI)	0.00	0.11 (0.09-0.13)	0.22 (0.20-0.25)	0.31 (0.28-0.34)	0.42 (0.39-0.46)	0.51 (0.47-0.55)	0.61 (0.57-0.66)	0.70 (0.65-0.77)
Patients with type 2 DM								
No at risk	31697	29989	28840	27675	26424	20252	10145	
Event no	0	78	65	51	40	26	18	7
Cumulative incidences (95% CI)	0.00	0.25 (0.20-0.32)	0.47 (0.40-0.56)	0.65 (0.57-0.75)	0.80 (0.70-0.91)	0.90 (0.80-1.02)	1.02 (0.90-1.15)	1.20 (0.99-1.44)

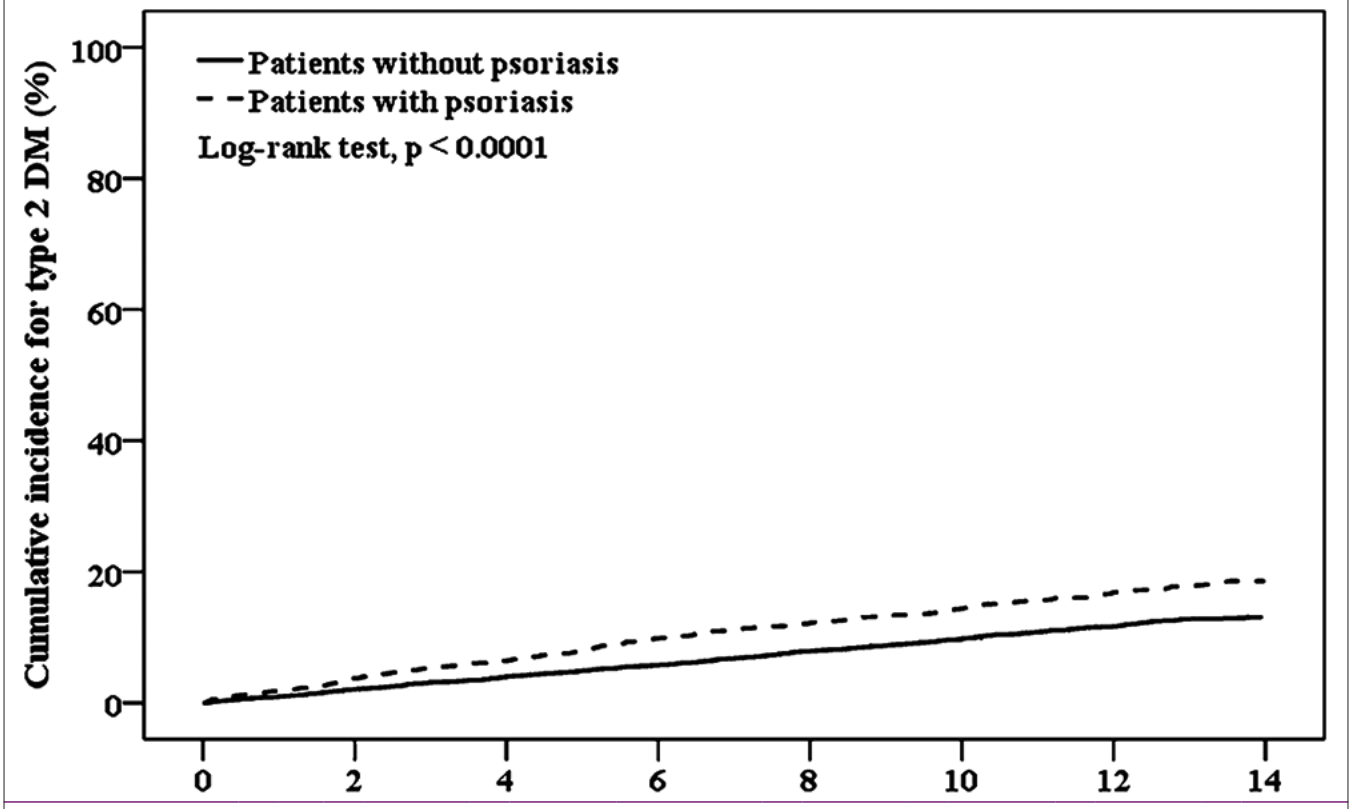
Figure 1: Cumulative incidence of psoriasis in type 2 diabetes and control cohorts (general population without diabetes)

in psoriasis susceptibility.[10,26] Furthermore, increases in Th17 and CD8+ T cells in both T2DM and psoriasis may explain the link between these diseases.[27,28] Emerging evidence suggests that the chronic inflammatory state of T2DM could induce release of cryptic "self" antigens upon destruction of inflammation-induced tissue, thereby leading to autoimmune activation.[27,29] This hypothesis is further supported by a recent nationwide, population-based, case–control study that showed a 3.6-fold increased risk of developing RA in patients age 20–44 years with T2DM than that in those without T2DM.[22] The increased risk of the autoimmune disorder RA in patients with T2DM might be attributable to chronic inflammation in T2DM.[22]

Existing evidence indicates that psoriasis and diabetes have a common genetic background. Genetic variations in T-lymphocyte antigen 4, Toll-like receptor 3, IL-12B, IL-23R, and IL-23A increase the risks of both diseases.[30,31] Wolf *et al*. reported that psoriasis is associated with pleiotropic susceptibility loci identified in T2DM.[32] The present findings showed that the psoriasis risk was 40% higher in patients with T2DM than that in individuals without T2DM after adjusting for confounding variables.

Analysis 2: Psoriasis and subsequent T2DM risk

Several observational studies reported increased prevalence and incidence of T2DM among patients with psoriasis,[18,19,33] although several studies found no association between psoriasis and diabetes.[34-36] Systemic inflammation is a potential mechanistic link between these diseases.[18,19] Chronic inflammation is detrimental to β-cell function and may increase insulin resistance, which commonly precedes the



Follow-up year	0	2	4	6	8	10	12	14
Patients without psoriasis								
No at risk	7788	7429	7130	6875	6594	5001	2277	
Event no	0	159	142	131	156	131	89	32
Cumulative incidences (95% CI)	0.00	2.07 (1.78-2.41)	3.96 (3.55-4.33)	5.74 (5.24-6.29)	7.90 (7.31-8.54)	9.78 (9.12-10.5)	11.6 (10.9-12.4)	13.1 (12.2-14.0)
Patients with psoriasis								
No at risk	1947	1863	1773	1678	1604	1200	537	
Event no	0	72	1	65	42	37	26	6
Cumulative incidences (95% CI)	0.00	3.72 (2.96-4.66)	6.39 (5.38-7.57)	9.84 (8.59-11.3)	12.1 (10.7-13.7)	14.3 (12.8-16.0)	16.8 (15.1-18.7)	18.7 (16.3-21.1)

Figure 2: Cumulative incidence of type 2 diabetes in the psoriasis and control cohorts (general population without psoriasis)

development of T2DM.[22,37] A meta-analysis of 10 prospective studies that evaluated data from 19,709 participants showed that elevated levels of CRP and IL-6 significantly increased the risk of T2DM.[12,22] Elevated CRP and IL-6 levels were also observed in patients with psoriasis.[11,15] One study reported that psoriatic keratinocytes release proinflammatory cytokines, including IL-1β, that induce insulin resistance and may favor the development of diabetes.[28] Moreover, the use of salsalate to modulate inflammatory reactions in patients with T2DM improved glycemic control, which suggests that inflammation contributes to insulin resistance and diabetes development.[22] Our results showing that subjects with psoriasis have a higher risk of developing T2DM are consistent with these earlier findings. Although the incidence of diabetes among psoriasis cases seemed higher than that of psoriasis among diabetes subjects, the aHR for diabetes among psoriasis cases was 1.38 (95% CI, 1.20–1.58), which was close to that for psoriasis among T2DM cases (adjusted HR 1.40; 95% CI, 1.20–1.63).

Strengths and limitations

Our study has several limitations. First, as is the case for other epidemiologic studies, the identification of exposure and outcome were based on claims data. To increase the validity and accuracy of the diagnoses, we selected only subjects with repeated coding, thereby minimizing this bias. Furthermore, the NHI of Taiwan has established an *ad hoc* committee to monitor the accuracy of claims data, prevent violations, and verify the accuracy of medical records.[38] The Bureau of NHI of Taiwan imposes heavy fines for false claims, overcharging, or malpractice for fraudulent claims. However, it was possible that the diagnosis of diabetes or psoriasis was not made in patients who did not report the disease symptoms and signs or did not visit medical facilities; thus, they might have been

Table 1: Demographic characteristics of patients with T2DM and the comparison group without T2DM

Groups	Patients with T2DM (*n*=31,697), *n* (%)	Patients without T2DM (*n*=126,788), *n* (%)	*P*
Demographic data			
Age, mean (SD)	55.4 (14.8)	55.4 (14.8)	0.82
Sex			
Male	16,527 (52.1)	66,108 (52.1)	>0.99
Female	15,170 (47.9)	60,680 (47.9)	
Degree of urbanization			
Urban	18,501 (58.4)	74,264 (58.6)	0.01
Suburban	9619 (30.4)	28,953 (30.7)	
Rural	3577 (11.3)	13,571 (10.7)	
Income group			
Low	10,188 (32.1)	40,368 (31.8)	<0.0001
Medium	10,713 (33.8)	39,633 (31.3)	
High	10,796 (34.1)	46,787 (36.9)	
Comorbidities			
Hypertension	1568 (49.5)	32,513 (25.6)	<0.0001
Coronary artery disease	7334 (23.1)	15,704 (12.4)	<0.0001
Cerebrovascular disease	4801 (15.2)	10,729 (8.5)	<0.0001
Depression	1287 (4.1)	3164 (2.5)	<0.0001
Hyperlipidemia	11,541 (36.4)	12,536 (9.9)	<0.0001
Hepatitis C	527 (1.7)	915 (0.7)	<0.0001
Obesity	347 (1.1)	248 (0.2)	<0.0001
Gout	4709 (14.9)	6953 (5.5)	<0.0001
Chronic obstructive pulmonary disease	11,063 (34.9)	31,960 (25.2)	<0.0001
Chronic kidney disease	2,083 (6.6)	3615 (2.9)	<0.0001
Alcoholic liver disease	529 (1.7)	532 (0.4)	<0.0001
Medications used			
NSAIDs	21,891 (69.1)	65,669 (51.8)	<0.0001
Antihypertensives	16,391 (51.7)	32,492 (25.6)	<0.0001
Hydroxychloroquine	66 (0.2)	317 (0.3)	0.18
Lithium	70 (0.2)	78 (0.1)	<0.0001
No. of outpatient visits in the year after the index date, mean (SD)	28.3 (21.1)	15.5 (16.5)	<0.0001
Years of follow-up, mean (SD)	10.1 (3.3)	10.6 (3.2)	<0.0001

T2DM: type 2 diabetes mellitus; SD: standard deviation; NSAID: nonsteroidal anti-inflammatory drug

Table 2: Incidences and hazard ratios for psoriasis in subgroups within the T2DM cohort, with the non-T2DM cohort as reference

Variables	Patients with T2DM			Patients without T2DM			95% CI		Interaction (*P*)
	Event	Person-years	Rate†	Event	Person-years	Rate†	Crude HR	Adjusted HR	
Total	285	320,103	8.90	685	1,339,005	5.12	1.73 (1.5-1.99)***	1.40 (1.20-1.63)***	
Sex									
Male	178	161,526	11.02	438	681,482	6.43	1.70 (1.43-2.03)***	1.39 (1.14-1.68)***	0.74
Female	107	158,577	6.75	247	657,523	3.76	1.79 (1.43-2.25)***	1.42 (1.10-1.83)**	
Age (years)									
0-49	99	128,548	7.70	234	538,283	4.35	1.746 (1.39-2.23)***	1.49 (1.13-1.96)**	0.28
50-64	1110	119,851	9.18	232	495,226	4.68	1.95 (1.56-2.45)***	1.58 (1.23-2.02)***	
>65	76	71,704	10.60	219	305,495	7.17	1.47 (1.13-1.91)**	1.15 (0.87-1.52)	
Comorbidity									
No	47	73,629	6.38	320	746,552	4.29	1.49 (1.09-2.02)*	1.33 (0.97-1.84)	0.75
Yes	238	246,475	9.66	365	592,453	6.16	1.57 (1.33-1.85)***	1.46 (1.21-1.74)***	

T2DM: type 2 diabetes mellitus; CI: confidence interval; HR: hazard ratio. †Rate, per 10,000 person-years, ‡Manually adjusted for age, sex, degree of urbanization, income group, comorbidities, medications used, and number of outpatient visits in the first year after the index date. *P<0.05, **P<0.01, ***P<0.001

Table 3: Demographic characteristics of patients with psoriasis and the comparison group without psoriasis

Demographic data	Patients with psoriasis (*n*=1947), *n* (%)	Patients without psoriasis (*n*=7788), *n* (%)	*P*
Age, mean (SD)	40.5 (19.0)	40.5 (19.0)	0.97
Sex			
Male	1167 (59.9)	3120 (59.9)	>0.99
Female	780 (40.1)	4668 (40.1)	
Degree of urbanization			
Urban	1245 (63.9)	4640 (59.6)	0.0001
Suburban	580 (29.8)	2386 (30.6)	
Rural	122 (6.3)	762 (9.8)	
Income group			
Low	1020 (52.4)	3743 (48.1)	0.002
Medium	454 (23.3)	1913 (24.6)	
High	473 (24.3)	2132 (27.4)	
Comorbidities			
Hypertension	330 (17.0)	1125 (14.5)	0.006
Coronary artery disease	117 (9.1)	499 (6.4)	<0.0001
Cerebrovascular disease	94 (4.8)	370 (4.8)	0.89
Depression	43 (2.2)	119 (1.5)	0.04
Hyperlipidemia	186 (9.6)	508 (6.5)	<0.0001
Hepatitis C	18 (0.9)	34 (0.4)	0.008
Obesity	8 (0.4)	17 (0.2)	0.13
Gout	130 (6.7)	334 (4.3)	<0.0001
Chronic obstructive pulmonary disease	455 (23.4)	1472 (19.0)	<0.0001
Chronic kidney disease	46 (2.4)	135 (1.7)	0.07
Alcoholic liver disease	13 (0.7)	24 (0.3)	0.02
Medications used			
Statins	44 (2.3)	85 (1.1)	<0.0001
Steroids	740 (38.0)	1699 (21.8)	<0.0001
Antihypertensives	365 (18.8)	1212 (15.6)	0.0006
Antipsychotics	75 (3.9)	198 (2.5)	0.002
No. of outpatient visits in the year after the index date	22.9 (18.2)	12.7 (14.3)	<0.0001
Follow-up years	9.98 (3.3)	10.5 (3.3)	<0.0001

SD: standard deviation

Table 4: Incidences and hazard ratios for type 2 diabetes mellitus in the subgroups of psoriasis cohort, with the nonpsoriasis cohort as reference

Variables	Patients with psoriasis			Patients without psoriasis			95% CI		Interaction (*P*)
	Event	Person-years	Rate†	Event	Person-years	Rate†	Crude HR	Adjusted HR	
Total	299	19,423	153.9	840	81,872	102.6	1.49 (1.31-1.70)***	1.38 (1.20-1.58)***	
Sex									
Male	211	11,318	186.4	556	48,118	115.5	1.61 (1.37-1.88)***	1.53 (1.29-1.81)***	0.12
Female	88	8105	108.6	284	33,753	84.1	1.28 (1.01-1.63)*	1.11 (0.86-1.43)	
Age (years)									0.31
0-29	17	7336	23.2	55	29,979	18.3	1.26 (0.73-2.18)	1.14 (0.65-2.02)	
30-49	104	7633	136.3	294	32,385	90.8	1.51 (1.20-1.88)***	1.26 (0.99-1.60)	
>50	178	4454	399.6	491	19,508	251.7	1.58 (1.33-1.88)***	1.40 (1.17-1.68)***	
Comorbidity									0.82
No	105	12,845	81.7	330	57,886	57.0	1.43 (1.15-1.78)**	1.49 (1.18-1.89)***	
Yes	194	6578	294.9	510	23,985	212.6	1.38 (1.17-1.63)***	1.36 (1.15-1.62)***	

CI: confidence interval; HR: hazard ratio. †Rate, per 10,000 person-years, ‡Manually adjusted for age, sex, degree of urbanization, income group, comorbidities, medications used, and number of outpatient visits in the first year after the index date. *P<0.05, **P<0.01, ***P<0.001

misclassified as control subjects. Second, more frequent hospital visits by psoriasis or diabetic patients, when compared with those in the general population, could result in potential surveillance bias. To address that issue, the multivariable regression model was further adjusted for the frequency of ambulatory care visits. The results were consistent with those of the primary models, which indicated that increased healthcare consumption and attendant surveillance bias were unlikely to contribute significantly to the results. Third, the NHIRD does not provide detailed information on smoking or drinking habits, physical activity, body mass index, dietary preferences, laboratory data, or family history, although these are potential confounding factors. However, our data analysis used the comorbidity variables of chronic obstructive pulmonary disease, alcoholic liver disease, obesity, and sociodemographic status as part of the controlling variables to substitute these unmeasured confounders. Fourth, based on the ICD-9-CM codes for psoriasis diagnosis (696.0, 696.1, and 696.8) used in this study, pustular psoriasis or arthropathic psoriasis could not be completely ruled out, though most included patients had psoriasis vulgaris.

Conclusion

The results of this study show the bidirectional association between T2DM and psoriasis. T2DM and psoriasis are more than coincidental comorbidities: T2DM increases the risk of subsequent psoriasis and psoriasis onset increases the risk of T2DM. Given the corresponding healthcare burden and adverse clinical outcomes of these medical conditions, public health and medical professionals need to be informed of the bidirectional association between T2DM and psoriasis. Knowledge of this relationship will assist in early identification and prompt management strategies which could increase the quality of life and improve outcomes of concomitant psoriasis and T2DM among patients with diabetes and psoriasis, respectively.

Declaration of patient consent

The authors used Taiwan National Health Insurance Research Database, which had encrypted the names of patients, health care providers, and medical institutions with unique and anonymous identifiers, to conduct this study. Thus, the waiver of consent from each patient and the study protocol were approved by the local investigational research bureau of National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan (103-024-E).

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Conflicts of interest

There are no conflicts of interest.

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