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Psoriasis Risk Is Lower in Type 2 Diabetes Patients Using Dipeptidyl Peptidase-4 Inhibitors or Thiazolidinediones Compared to Sulfonylureas

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ABSTRACT

The risk of psoriasis in diabetic patients has rarely been explored. This study aims to compare the risk of incident psoriasis in patients with Type 2 diabetes (T2D) who initiate dipeptidyl peptidase-4 inhibitors (DPP-4is) or thiazolidinediones (TZDs) with those who initiate sulfonylureas, the most common second-line glucose-lowering therapy, in addition to metformin monotherapy. This sequential, propensity-score-matched, new-user comparative effectiveness study utilized a target trial emulation framework. It included adults with T2D receiving metformin monotherapy, using data from 2006 to 2015 from a general population database in Taiwan. The primary outcome was the incidence of psoriasis, determined through diagnoses recorded in urgent care, hospital, and outpatient department records. Cox proportional hazards and Poisson regressions with 1:4 propensity score matching was employed to evaluate the risk factors for psoriasis after adjusting for comorbidities and the use of other medications. In 49,810 propensity score-matched adults with T2D (27,630 men [55.4%]; mean age 57.5 years) identified in the database, the incidence rate of psoriasis in DPP-4i users was 188 cases per 100,000 person-years, lower than in sulfonylurea users (467 cases per 100,000 person-years), with a hazard ratio(HR) of 0.422 (95% CI, 0.273–0.716). For the TZD vs. sulfonylurea comparison, the HR was 0.35, but the smaller matched dataset resulted in wide confidence intervals. The findings suggest that the use of DPP-4is is associated with a lower risk of psoriasis compared to sulfonylureas in patients with T2D. These results can guide the selection of glucose-lowering therapies in T2D patients who are at risk of developing psoriasis.

1 | Introduction

Patients with Type 2 diabetes (T2D) have an increased risk of developing psoriasis [1, 2], but the question of whether this risk could be affected by antidiabetic medications remains underexplored. In particular, the role of dipeptidyl peptidase-4 inhibitors (DDP-4is) and of thiazolidinediones (TZDs), commonly used in the treatment of T2D [3, 4], has not been extensively investigated.

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Summary

- What is the current knowledge on the topic?
- The incidence of psoriasis may vary with different glucose-lowering drugs.
- DPP-4 inhibitors (DPP4i) and thiazolidinediones (TZD) have mechanisms that might be beneficial for psoriasis.
- However, no studies have specifically compared these drugs with sulfonylureas when used in conjunction with metformin.
- What question did this study address?
- This study found that DPP4i use was associated with a lower risk of psoriasis compared to sulfonylureas (aHR: 0.422).
- What does this study add to our knowledge?
- DPP-4is may be an option to mitigate the risk of developing psoriasis for individuals requiring a second-line agent following metformin therapy.
- How might this change clinical pharmacology or translational science?
- These findings may guide the choice of glucose-lowering therapies for T2D patients at risk for psoriasis.

Psoriasis, a chronic inflammatory skin disorder, exhibits complex interactions with metabolic disorders such as diabetes mellitus [5]. Therefore, understanding the influence of antidiabetic medications on psoriasis risk is crucial for optimizing treatment strategies and improving patient outcomes. A growing body of evidence suggests that several hypoglycemic agents used to treat T2D, such as glucagon-like peptide-1 receptor agonists, DPP-4is, TZDs, and biguanides, exert beneficial effects on psoriasis [6, 7]. Some population-based studies have suggested that patients with T2D who are prescribed DPP-4is and TZDs have a lower incidence of psoriasis than those who are not do [8, 9]. The incidence and severity of psoriasis in patients with T2D may vary depending on the antidiabetic medications used [6–9]. Mechanistically, DPP-4is inhibit T cell activation [10], while TZDs reduce the inflammatory response of psoriasis through PPAR-γ activation and suppress keratinocyte overproliferation [11]. Some mechanisms of these antidiabetic drugs are closely linked to the pathogenesis of psoriasis and may influence its occurrence and treatment. However, it remains unclear whether different second-line antidiabetic medications, such as DPP-4is, TZDs, and sulfonylureas (the most commonly used antidiabetic agents after metformin), have varying effects on the risk of psoriasis in patients with T2D [12, 13].

This study explored the potential benefits of older antidiabetic medications from a drug repurposing perspective. We employed target trial emulation to compare the risk of incident psoriasis among T2D patients already on metformin therapy who initiated either DPP-4is or TZDs versus those who initiated sulfonylureas. The findings of this study can inform treatment decisions and contribute to the development of personalized therapeutic approaches for patients with T2D. By elucidating the association between antidiabetic medications and psoriasis risk, this study advances the understanding of the complex interplay between metabolic and inflammatory disorders, enabling the development of targeted interventions to improve patient care.

2 | Research Design and Methods

2.1 | Data Source

Taiwan's NHI system, which was initiated by the Taiwanese Government in March 1995, provides universal compulsory coverage to more than 96% of the population. Participation in the NHI program is mandatory for individuals registered in the census for more than 6 months, and it provides them with access to outpatient, urgent care, and inpatient services. Taiwan's National Health Research Institute maintains extensive computerized administrative datasets from the NHI program that are accessible to researchers following the deidentification of individual health information. The protocol for this nationwide, population-based retrospective cohort study was approved by the Ethics Institutional Review Board of Taipei Memorial Hospital (approval number: N201509007). The present study adhered to the principles outlined in the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

2.2 | Study Population

We enrolled patients aged 20 years or older with a diagnosis of T2D (*International Classification of Diseases, Ninth Revision, Clinical Modification* code [*ICD-9-CM*]: 250.XX) with an initial prescription for either DPP-4is or sulfonylureas recorded between January 2006 and June 2015 after at least 1 year of continuous enrollment in the database. Furthermore, included patients were required to have no history of receiving other glucose-lowering medications. The diagnosis of T2D was established on the basis of the presence of at least one symptom with an *ICD-9-CM* code. Notably, the accuracy of the diagnosis was confirmed using data from the NHIRD [14].

The study population consisted of newly diagnosed diabetes patients who were using metformin. We emulated two target trials: [1] The exposure group comprised patients newly using DPP-4is, while the control group included those newly using sulfonylureas. Both groups excluded the use of TZDs; [2] The exposure group consisted of patients newly using TZDs, while the control group included those newly using sulfonylureas. Both groups excluded the use of DPP-4is. To avoid effects between the target drugs DPP-4is and TZDs, we excluded combinations of these two medications to minimize confounding bias. The DPP-4is of interest were sitagliptin, vildagliptin, saxagliptin, and linagliptin. The index date for the exposure group was defined as the earliest date of target drug prescriptions. For the control group, the index date was randomly assigned with consideration of the duration from the day of T2D diagnosis to the target drug prescription date in the exposure group. This matching of prescription time distribution was conducted to mitigate imbalances in prescription times between the groups, which could cause survival bias.

The exclusion criteria were having received a diagnosis of Type 1 diabetes mellitus, being younger than 20 years, having a diagnosis of acquired psoriasis or chronic kidney disease (CKD), having received a diagnosis of HIV or malignancy before enrollment, and having used disease-modifying antirheumatic drugs (DMARDs) or insulin before the index date. The study cohort was continually followed until December 31, 2015.

2.3 | Study Outcomes

The primary outcome of interest in this study was the incidence of psoriasis. Psoriasis was defined on the basis of a patient having at least two visits for symptoms consistent with the disease-specific diagnostic codes in the ICD-9-CM of 696.0, 696.1, 696.5, and 696.8. The observation period for psoriasis onset was defined as 365 days following each patient's index date.

2.4 | Statistical Analysis

The study conducted a sequential, time-stratified, propensity-score-matched cohort study to account for secular trends in prescription patterns, medical utilization, and disease management. The propensity-score-matching method utilized logistic regression to calculate propensity scores for the exposed and control groups. If the propensity score of a control group patient closely matched that of an exposed group patient, the two were considered comparable and paired to minimize confounding bias. Matching was conducted using a 1:4 ratio, ensuring comparability based on variables such as sex, age, medications, and comorbidities. During the matching process, individuals in the control group were not allowed to be selected more than once. This ensured that the control patients in each risk set were distinct from those in other risk sets. A caliper width of 0.25 times the standard deviation of the propensity score was adopted in this study. Patients in the exposed and control groups with propensity scores within this range were considered similar in characteristics and were matched accordingly.

Given the complexity of diabetes treatment regimens and the high frequency of medication changes, the study aimed to accurately assess the risk of psoriasis associated with DPP-4is, TZDs, and sulfonylureas without interference from frequent treatment switches. To ensure this, patients were tracked for 365 days following their index date to observe psoriasis incidence, during which their medication regimens were kept consistent to maintain adherence.

We applied a Cox proportional hazards model to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for psoriasis between the two treatment groups [15]. Covariates in the model included medications and comorbidities. Medications were modeled as time-varying covariates to account for dynamic changes in drug usage. These medications included angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), antiepileptics, antipsychotics, beta-blockers, calcium channel blockers, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, and statins. Comorbidities were identified using ICD-9-CM codes within 1 year prior to the index date and included hypertension, cardiovascular disease, stroke, congestive heart failure, dyslipidemia, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), thyroid disease, and obesity. When estimating the Cox proportional hazards model, we employed a cluster-robust sandwich variance estimator to adjust for potential estimation bias caused by the dependency introduced by PSM between the two groups. The study used the standard mean difference (SMD) to compare the differences in characteristics between the two groups before and after matching. An absolute SMD value of less than 0.2 was considered indicative of no significant differences between the groups. The results of all statistical tests were deemed significant at $p < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The analysis was conducted from January to March 2019.

3 | Result

3.1 | Study Population Characteristics

Figure 1 presents the study flowchart. A total of 1,949,860 patients were identified as having a new diagnosis of T2D between 2006 and 2015. We excluded the following patients: (1) those with unknown sex or age, (2) those given a diagnosis of T2D before 2001, (3) those with CKD, (4) those given a diagnosis of psoriasis before their T2D diagnosis, (5) those with cancer, (6) those with HIV, (7) those who used insulin within 1 year before the index date, (8) those who used DMARDs within 1 year before the index date, and (9) those younger than 20 years. The included patients were divided into 2 groups, with one comprising DPP-4i users ($N = 22,721$) and sulfonylurea users ($N = 227,684$) and the other comprising TZD users ($N = 3704$) and sulfonylurea users ($N = 282,769$).

Before propensity score matching, we identified a cohort of 250,405 patients with T2D who were prescribed metformin monotherapy and initiated either DPP-4is or sulfonylurea during the study period. Before matching, the DPP-4i initiators tended to be older, were more likely to be women, and had lower diabetes complications severity index (DCSI) scores compared with the sulfonylurea initiators (Table 1). However, their baseline characteristics were effectively balanced after matching, with all standardized mean differences being less than 0.2. Consequently, the final study cohort included 9962 initiators of DPP-4is and 39,848 initiators of sulfonylurea (Table 1). In the cohort, 27,630 individuals (55.47%) were men, with a mean (standard deviation) age at the index date of 57.48 (11.8) years. The final study cohort also included 1066 initiators of TZD and 4264 initiators of sulfonylurea (Table 2). In the cohort, 3135 individuals (58.82%) were men, with a mean (standard deviation) age at the index date of 57.18 (12.3) years.

3.2 | Psoriasis Outcome

Among the 9962 propensity-score-matched patients who initiated DPP-4is, 17 incident cases of psoriasis were observed, indicating an incidence rate of 188 per 100,000 person-years. By contrast, among the 39,848 propensity-score-matched patients who initiated sulfonylurea, 178 cases of incident psoriasis were observed, with an incidence rate of 467 per 100,000

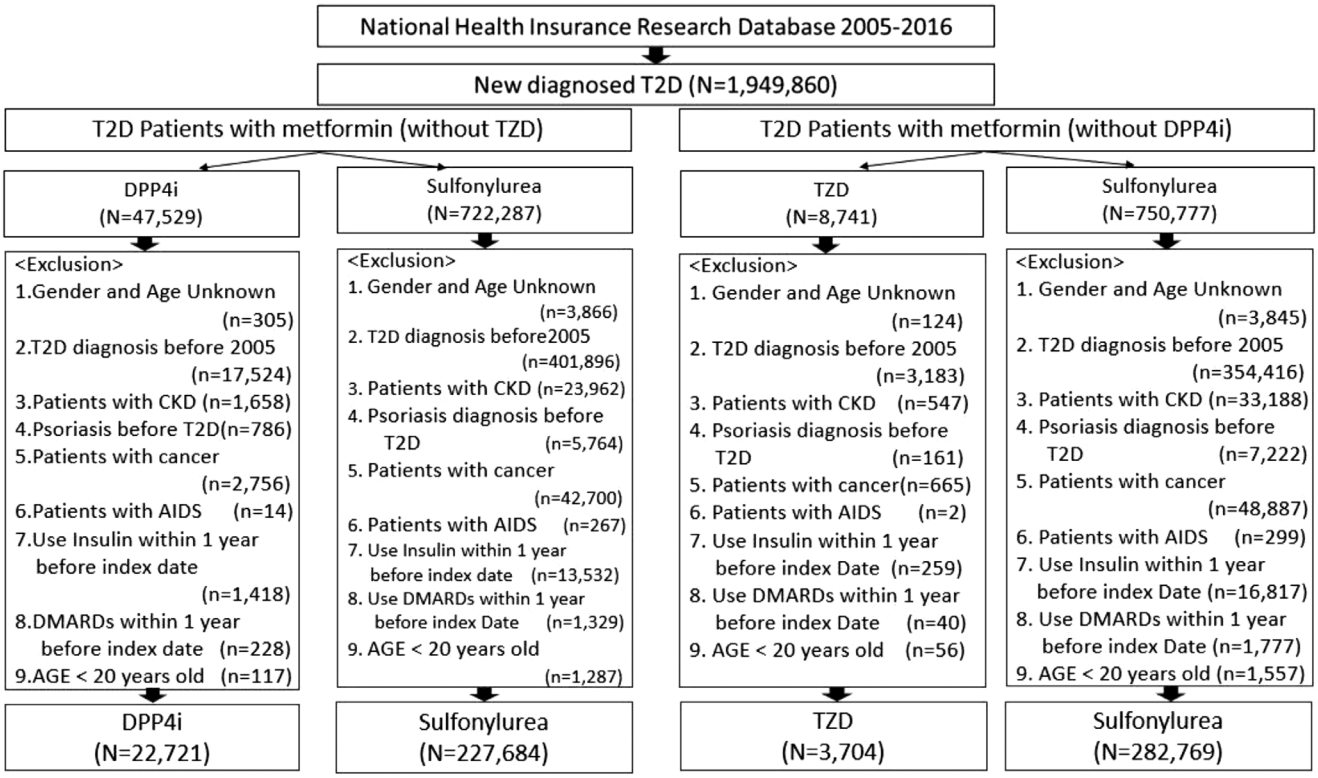

FIGURE 1 | Study flowchart. AIDS, Acquired Immunodeficiency Syndrome; CKD, Chronic kidney disease; DMARDs, Disease-modifying antirheumatic drugs; DPP-4i, Dipeptidyl peptidase-4 inhibitors; T2D, Type 2 diabetes mellitus; TZD, Thiazolidinediones.

person-years. The adjusted HR was 0.42 (95% CI, 0.27–0.72) for initiators of DPP-4is when compared with initiators of sulfonylureas (Table 3). Our Kaplan–Meier analysis, conducted to estimate the cumulative incidence of psoriasis, revealed that in the T2D cohort, DPP-4i users had a lower risk of psoriasis ($p < 0.001$) compared to sulfonylurea users (Figure 2A).

Among the 1064 propensity score-matched patients who initiated TZD, 2 incident cases of psoriasis were observed, indicating an incidence rate of 197 per 100,000 person-years. By contrast, among the 4624 propensity score-matched patients who initiated sulfonylurea, 19 cases of incident psoriasis were observed, with an incidence rate of 458 per 100,000 person-years. The adjusted HR was 0.35 (95% CI, 0.04–3.05) for TZD initiators when compared with sulfonylurea initiators (Table 3). However, the matched dataset was smaller with a limited number of events, resulting in wide confidence intervals for the estimated HR due to insufficient sample size. The Kaplan–Meier analysis illustrates the cumulative incidence of psoriasis among TZD users and sulfonylurea users (Figure 2B).

4 | Discussion

This is the first study to compare the risk of psoriasis in patients with T2D using different glucose-lowering medications in combination with metformin therapy. DPP-4i use was associated with a 58% reduction in the risk of incident psoriasis in patients treated with metformin monotherapy. Although TZDs were associated with a lower incidence of psoriasis than sulfonylureas the small number of observed events may have resulted in an overly wide 95% CI. The findings of psoriasis benefits related to the use of DPP-4is in these target trial emulations can be used to guide the selection of hypoglycemic therapy for patients with T2D who are at risk of psoriasis and require a second-line agent after metformin.

DPP-4 is a transmembrane glycoprotein that can be expressed in keratinocytes [16, 17] and is upregulated in psoriasis [17, 18]. Inhibition of DPP-4 suppresses keratinocyte proliferation in vitro and partially restores keratinocyte differentiation in vivo [19]. Several case reports have documented improvements in the severity of psoriasis with DPP-4i treatment [10–21]. A small-scale randomized controlled trial conducted in 2022 demonstrated that combining DPP-4is with narrow-band UV-B (NB-UVB) therapy is more effective than using NB-UVB therapy alone [22]. Additionally, no significant difference in psoriasis improvement after DPP-4i treatment compared with that after gliclazide treatment was observed. However, studies have generally primarily focused on the therapeutic effects of DPP-4is on psoriasis severity; only two have analyzed the risk of psoriasis incidence by comparing users and nonusers [8, 23].

Because metformin is the most commonly used first-line antihyperglycemic medication, and no studies have analyzed the difference in psoriasis risk between adding DPP-4is or sulfonylureas in patients already prescribed metformin, the present study employed a comparative design to address this gap in the literature. Our findings indicate that adding DPP-4is to

TABLE 1 | Baseline characteristics of patients with Type 2 diabetes initiating DPP-4is versus sulfonylureas before and after 1:4 propensity matching.

	Before matching			After matching		
	DPP-4i (*N* = 22,721)	Sulfonylurea (*N* = 227,684)		DPP-4i (*N* = 9962)	Sulfonylurea (*N* = 39,848)	
	N (%)	*N* (%)	SMD	*N* (%)	*N* (%)	SMD
Gender						
Female	10,107 (44.48%)	94,045 (41.31%)	0.0906	4436 (44.53%)	17,744 (44.53%)	0.0000
Male	12,614 (55.52%)	133,639 (58.69%)		5526 (55.47%)	22,104 (55.47%)	
Age						
20–29	310 (1.36%)	3401 (1.49%)	0.0675	104 (1.04%)	406 (1.02%)	0.1080
30–39	1466 (6.45%)	16,399 (7.2%)		589 (5.91%)	2359 (5.92%)	
40–49	3845 (16.92%)	47,981 (21.07%)		1692 (16.98%)	6799 (17.06%)	
50–59	7204 (31.71%)	74,479 (32.71%)		3272 (32.84%)	13,129 (32.95%)	
60–69	6052 (26.64%)	50,048 (21.98%)		2720 (27.30%)	10,856 (27.24%)	
70–79	2858 (12.58%)	27,168 (11.93%)		1254 (12.59%)	4988 (12.52%)	
≥80	986 (4.34%)	8208 (3.6%)		331 (3.32%)	1311 (3.29%)	
Mean (SD)	57.59 (12.44)	56.18 (12.51)	0.1130	57.49 (11.83)	57.48 (11.81)	0.0008
Median (IQR)	58 (15)	56 (16)		58 (15)	58 (15)	
DCSI						
0	12,726 (56.01%)	109,706 (48.18%)	0.1948	5809 (58.31%)	23,236 (58.31%)	0.0000
1	5757 (25.34%)	51,985 (22.83%)		2537 (25.47%)	10,148 (25.47%)	
2	2906 (12.79%)	34,565 (15.18%)		1152 (11.56%)	4608 (11.56%)	
≥3	1332 (5.86%)	31,428 (13.8%)		464 (4.66%)	1856 (4.66%)	
Mean (SD)	0.71 (0.99)	1.060 (1.38)	−0.2914	0.64 (0.92)	0.64 (0.92)	0.0000
Median (IQR)	0 (1)	1 (2)		0 (1)	0 (1)	
Other medication						
Insulin	1581 (6.96%)	32,129 (14.11%)	−0.3294	490 (4.92%)	1960 (4.92%)	0.0000
ACEIs/ARBs	12,586 (55.39%)	93,921 (41.25%)	0.4002	5500 (55.21%)	19,873 (49.87%)	0.1512
Beta blocking agents	7255 (31.93%)	61,468 (27%)	0.1529	3111 (31.23%)	10,305 (25.86%)	0.1682
Calcium channel blockers	7009 (30.85%)	86,875 (38.16%)	−0.2175	2703 (27.13%)	11,876 (29.8%)	−0.0837
Diuretics	2835 (12.48%)	43,449 (19.08%)	−0.2560	1102 (11.06%)	4035 (10.13%)	0.0427
Other anti-hypertensive agents	1005 (4.42%)	15,526 (6.82%)	−0.1474	411 (4.13%)	1469 (3.69%)	0.0321
Statins	12,112 (53.31%)	82,067 (36.04%)	0.4913	5192 (52.12%)	19,141 (48.04%)	0.1154
Glinides	1401 (6.17%)	8115 (3.56%)	0.1716	214 (2.15%)	856 (2.15%)	0.0000

(Continues)

TABLE 1 | (Continued)

	Before matching			After matching		
	DPP-4i (*N* = 22,721)	Sulfonylurea (*N* = 227,684)		DPP-4i (*N* = 9962)	Sulfonylurea (*N* = 39,848)	
	N (%)	*N* (%)	SMD	*N* (%)	*N* (%)	SMD
Alpha-glucosidase inhibitors	1876 (8.26%)	17,288 (7.59%)	0.0351	539 (5.41%)	2156 (5.41%)	0.0000
Systematic corticosteroids	4932 (21.71%)	56,549 (24.84%)	−0.1047	2090 (20.98%)	8360 (20.98%)	0.0000
Anti-epileptics	1534 (6.75%)	16,512 (7.25%)	−0.0277	589 (5.91%)	1914 (4.80%)	0.0697
Anti-psychotics	1763 (7.76%)	24,763 (10.88%)	−0.1518	694 (6.97%)	2401 (6.03%)	0.0539
NSAIDs	13,849 (60.95%)	156,527 (68.75%)	−0.2310	6104 (61.27%)	25,082 (62.94%)	−0.0487
Comorbidities						
Hypertension	135,757 (60.55%)	117,038 (51.4%)	0.2607	6064 (60.87%)	22,895 (57.46%)	0.0981
Cardiovascular disease	4406 (19.39%)	28,971 (12.72%)	0.2569	1816 (18.23%)	5302 (13.31%)	0.1909
Stroke	1987 (8.75%)	17,602 (7.73%)	0.0525	829 (8.32%)	2621 (6.58%)	0.0937
Congestive heart failure	1002 (4.41%)	7898 (3.47%)	0.0683	426 (4.28%)	1078 (2.71%)	0.1209
Dyslipidemia	13,503 (59.43%)	101,652 (44.65%)	0.4184	5887 (59.09%)	22,908 (57.49%)	0.0459
Chronic obstructive pulmonary disease	1514 (6.66%)	17,486 (7.68%)	−0.0559	649 (6.51%)	2169 (5.44%)	0.0638
Chronic kidney disease	16 (0.07%)	182 (0.08%)	−0.0052	9 (0.09%)	5 (0.01%)	0.0506
Chronic liver disease	2449 (10.78%)	27,343 (12.01%)	−0.0547	1118 (11.22%)	3869 (9.71%)	0.0698
Thyroid disease	179 (0.79%)	578 (0.25%)	0.1062	66 (0.66%)	104 (0.26%)	0.0836
Obesity	518 (2.28%)	1997 (0.88%)	0.1588	191 (1.92%)	460 (1.15%)	0.0886
Medical utilization						
Num. of HbA1c Measurements						
Mean (SD)	3.77 (2.24)	2.49 (2.02)	0.6001	3.68 (2.32)	2.59 (1.84)	0.5206
Median (IQR)	4 (3)	2 (3)		3 (3)	2 (3)	
Num. of outpatients						
Mean (SD)	26.33 (16.35)	27.00 (18.35)	−0.0386	25.33 (16.02)	20.87 (12.62)	0.3093
Median (IQR)	23 (18)	23 (19)		22 (18)	19 (14)	
Duration						
Mean (SD)	338.55 (65.94)	358.94 (34.80)	−0.3867	330.71 (73.52)	349.37 (54.39)	−0.2886
Median (IQR)	365 (0)	365 (0)		365 (0)	365 (0)	

Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; DPP-4i, DPP4is: dipeptidyl peptidase-4 inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; SMD, Standardized mean difference; IQR, interquartile range; SD, standard deviation; TZDs, thiazolidinedion.

TABLE 2 | Baseline characteristics among patients with Type 2 diabetes initiating TZD versus sulfonylureas before and after 1:4 propensity matching.

	Before matching			After matching		
	TZD ($N=3704$)	Sulfonylurea ($N=282,769$)		TZD ($N=1066$)	Sulfonylurea ($N=4264$)	
	N (%)	*N* (%)	SMD	*N* (%)	*N* (%)	SMD
Gender						
Female	121,547 (41.77%)	117,343 (41.50%)	0.0077	439 (41.18%)	1756 (41.18%)	0.0000
Male	2157 (58.23%)	165,426 (58.50%)		627 (58.82%)	2508 (58.82%)	
Age						
20–29	60 (1.62%)	4237 (1.50%)	0.0416	7 (0.66%)	29 (0.68%)	0.1090
30–39	287 (7.75%)	21,148 (7.48%)		83 (7.79%)	323 (7.58%)	
40–49	680 (18.36%)	60,074 (21.24%)		179 (16.79%)	714 (16.74%)	
50–59	1261 (34.04%)	93,348 (33.01%)		381 (35.74%)	1539 (36.09%)	
60–69	864 (23.33%)	61,768 (21.84%)		237 (22.23%)	946 (22.19%)	
70–79	403 (10.88%)	32,685 (11.56%)		125 (11.73%)	494 (11.59%)	
≥80	149 (4.02%)	9509 (3.36%)		54 (5.07%)	219 (5.14%)	
Mean (SD)	56.41 (12.52)	55.95 (12.44)	0.0369	57.18 (12.36)	57.20 (12.33)	−0.0016
Median (IQR)	56 (15)	55 (16)		57 (16)	57 (15.5)	
DCSI						
0	2115 (57.10%)	129,128 (45.67%)	0.2206	602 (56.47%)	2408 (56.47%)	0.0000
1	904 (24.41%)	66,806 (23.63%)		264 (24.77%)	1056 (24.77%)	
2	418 (11.29%)	45,113 (15.95%)		126 (11.82%)	504 (11.82%)	
≥3	267 (7.21%)	41,722 (14.75%)		74 (6.94%)	296 (6.94%)	
Mean (SD)	0.72 (1.05)	1.12 (1.39)	−0.3247	0.73 (1.05)	0.73 (1.05)	0.0000
Median (IQR)	0 (1)	1 (2)		0 (1)	0 (1)	
Other medication						
Insulin	234 (6.32%)	39,409 (13.94%)	−0.3572	62 (5.82%)	248 (5.82%)	0.0000
ACEIs/ARBs	1938 (52.32%)	120,799 (42.72%)	0.2719	578 (54.22%)	2198 (51.55%)	0.0756
Beta blocking agents	1042 (28.13%)	78,459 (27.75%)	0.0120	334 (31.33%)	1150 (26.97%)	0.1357
Calcium channel blockers	1293 (34.91%)	107,262 (37.93%)	−0.0888	341 (31.99%)	1433 (33.61%)	−0.0488
Diuretics	505 (13.63%)	52,222 (18.47%)	−0.1865	148 (13.88%)	516 (12.1%)	0.0749
Other anti-hypertensive agents	160 (4.32%)	18,618 (6.58%)	−0.1408	43 (4.03%)	160 (3.75%)	0.0205
Statins	1943 (52.46%)	105,726 (37.39%)	0.4285	528 (49.53%)	1951 (45.76%)	0.1068
Glinides	388 (10.48%)	9607 (3.4%)	0.3940	47 (4.41%)	188 (4.41%)	0.0000
Alpha-glucosidase inhibitors	351 (9.48%)	21,177 (7.49%)	0.1010	62 (5.82%)	248 (5.82%)	0.0000

(Continues)

TABLE 2 | (Continued)

	Before matching			After matching		
	TZD (*N* = 3704)	Sulfonylurea (*N* = 282,769)		TZD (*N* = 1066)	Sulfonylurea (*N* = 4264)	
	N (%)	*N* (%)	SMD	*N* (%)	*N* (%)	SMD
Systematic corticosteroids	708 (19.11%)	68,804 (24.33%)	−0.1790	196 (18.39%)	784 (18.39%)	0.0000
Anti-epileptics	222 (5.99%)	20,305 (7.18%)	−0.0679	69 (6.47%)	227 (5.32%)	0.0691
Anti-psychotics	320 (8.64%)	3957 (10.46%)	−0.0876	98 (9.19%)	303 (7.11%)	0.1075
NSAIDs	2345 (63.31%)	192,152 (67.95%)	−0.1382	671 (62.95%)	2761 (64.75%)	−0.0530
Comorbidities						
Hypertension	2199 (59.37%)	146,727 (51.89%)	0.2129	651 (61.07%)	2508 (58.82%)	0.0649
Cardiovascular disease	529 (14.28%)	38,136 (13.49%)	0.0323	182 (17.07%)	573 (13.44%)	0.1428
Stroke	225 (6.07%)	21,934 (7.76%)	−0.0942	79 (7.41%)	255 (5.98%)	0.0809
Congestive heart failure	97 (2.62%)	10,186 (3.60%)	−0.0798	24 (2.25%)	82 (1.92%)	0.0327
Dyslipidemia	2218 (59.88%)	129,920 (45.95%)	0.3947	626 (58.72%)	2394 (56.14%)	0.0738
Chronic obstructive pulmonary disease	246 (6.64%)	20,940 (7.41%)	−0.0426	72 (6.75%)	226 (5.30%)	0.0862
Chronic kidney disease	7 (0.19%)	212 (0.07%)	0.0471	0 (0%)	0 (0%)	NA
Chronic liver disease	420 (11.34%)	34,217 (12.1%)	−0.0334	116 (10.88%)	395 (9.26%)	0.0761
Thyroid disease	25 (0.67%)	840 (0.30%)	0.0753	6 (0.56%)	10 (0.23%)	0.0744
Obesity	63 (1.7%)	3097 (1.1%)	0.0722	12 (1.13%)	35 (0.82%)	0.0446
Medical utilization						
<Num. of HbA1c easurements>						
Mean (SD)	3.33 (2.20)	2.68 (2.09)	0.3029	3.48 (2.27)	2.72 (1.90)	0.3631
Median (IQR)	3 (3)	3 (3)		3 (3)	3 (3)	
<Num. of outpatients>						
Mean (SD)	25.85 (15.80)	27.03 (18.16)	−0.0693	26.38 (15.93)	23.37 (14.09)	0.2002
Median (IQR)	22 (18)	23 (19)		23 (17)	21 (16)	
Duration						
Mean (SD)	352.30 (48.53)	359.76 (32.35)	−0.1809	347.49 (56.20)	355.46 (42.58)	−0.1599
Median (IQR)	365 (0)	365 (0)		365 (0)	365 (0)	

Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; DPP-4is, dipeptidyl peptidase-4 inhibitors; IQR, interquartile range; NA, Not available; NSAIDs, nonsteroidal anti-inflammatory drugs; Num, number; SD, standard deviation; SMD, Standardized mean difference; TZDs, thiazolidinediones.

metformin therapy substantially reduces the incidence of psoriasis compared with that achievable by adding sulfonylureas. Because patients with T2D have a higher risk of developing psoriasis than the general population does, this comparison provides valuable information that can guide clinicians in selecting the most appropriate antihyperglycemic agents for their patients.

Several clinical studies have revealed that TZDs (peroxisome proliferator-activated receptor gamma [PPAR-γ] agonists) possess

TABLE 3 | Incidence rates, incidence rate ratios, and hazard ratios for psoriasis of DPP4i, TZD, and sulfonylurea.

A. DPP-4i versus sulfonylurea							
Group	**Events**	**Person years**	**Incidence rate**	**IRR**	**95% C.I. for IRR**	**Adj. HR**	**95% C.I. for HR**
DPP-4i	17	9019.80	188.47	0.404**	(0.245–0.664)	0.422**	(0.273–0.716)
Sulfonylurea	178	38115.25	467	Ref.		Ref.	
B. TZD Group versus sulfonylurea							
Group	**Events**	**Person years**	**Incidence rate**	**IRR**	**95% C.I. for IRR**	**Adj. HR**	**95% C.I. for HR**
TZD	2	1014.16	197.21	0.430	(0.100–1.849)	0.347	(0.039–3.049)
Sulfonylurea	19	4149.68	457.87	Ref.		Ref.	

Note: aHR (adjusted hazard ratio) was derived using the Cox proportional hazards model, accounting for the effects of various covariates. These covariates included gender, age, 13 medications and 10 comorbidities (listed in Table 1). The *p* value and 95% C.I. for the IRR is calculated using a Poisson distribution.
Abbreviations: DPP-4i, dipeptidyl peptiase-4 inhibitor; HR, hazard ratio; IR, Incidence rate per 100,000 person-years; IRR, incidence rate ratio; TZD, thiazolidinedione.
**Indicates *p* value < 0.05.

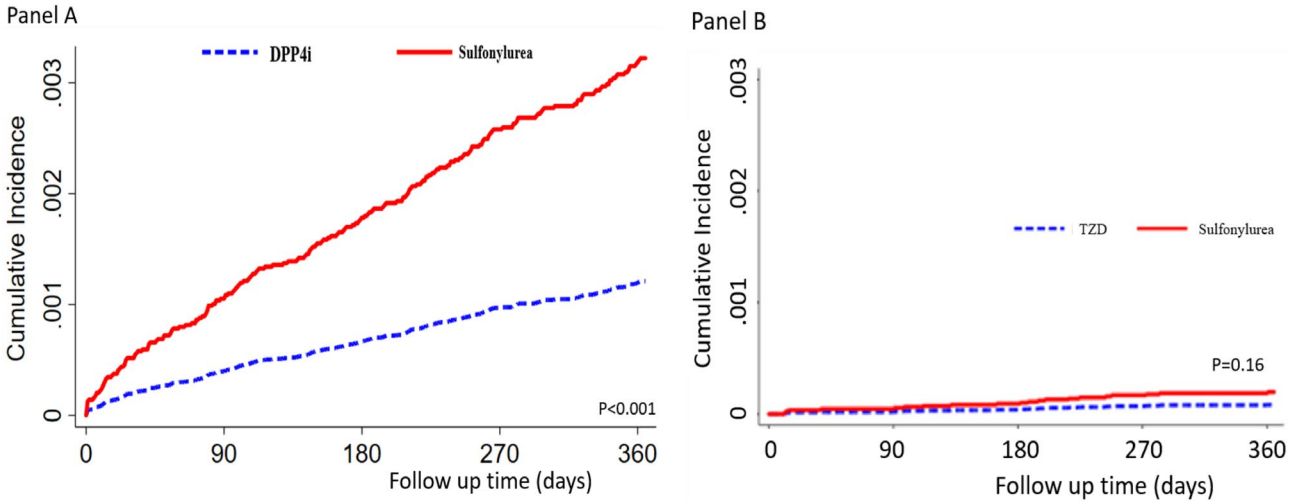

FIGURE 2 | (A) Cumulative incidence of psoriasis (DPP-i versus sulfonylurea). DPP-4i, Dipeptidyl peptidase-4 inhibitors. (B) Cumulative incidence of psoriasis (TZD versus sulfonylurea). TZD, Thiazolidinediones.

immunomodulatory and anti-inflammatory properties. Multiple pathophysiological mechanisms underlie the antipsoriatic effects of TZDs. First, TZDs suppress excessive proliferation of human keratinocytes and enhance their differentiation [11]. Second, TZDs may alleviate psoriasis by reducing the inflammatory response mediated by PPAR-γ [24]. Third, TZDs influence the histology of psoriatic skin by interfering with calcium channels and mitogen-activated protein kinase signaling pathways, although this effect is not directly related to PPAR activation [25]. These mechanisms can explain the improvement in psoriasis severity observed in studies on TZDs [26, 27]. Although one population-based study observed that patients with T2D who have never used insulin but who use TZDs have a lower risk of psoriasis [9], no studies have compared the risk of psoriasis between patients who use TZDs and those who use other hypoglycemic agents. The current study is thus the first to compare the incidence rate of psoriasis between TZDs and sulfonylureas. However, because warnings have been issued regarding the risks associated with using TZDs, such as heart failure, liver function impairment, and bladder cancer [28], the number of patients using TZDs has markedly decreased. This may explain the relatively small number of cases available in our analysis. Because of this small number, although the incidence rate of psoriasis was lower in the TZD group than in the sulfonylurea group, the 95% CI was too wide to reach significance.

4.1 | Limitations

As is true for all observational studies, we cannot exclude the possibility of residual unmeasured confounding variables. Despite our inclusion of several proxy measures of diabetes disease severity in the propensity scores, such as diabetes duration, complications, and DCSI scores, laboratory measures such as hemoglobin A1c, uric acid levels, and kidney function tests were not accessible. Furthermore, the data did not include information on environmental and lifestyle factors, such as body mass index, alcohol consumption, or smoking status. Nevertheless, these unmeasured factors are unlikely to have substantially influenced the selection of DPP-4is and sulfonylureas for patients at risk of developing psoriasis because neither medication class was approved or clinically recognized for its association with psoriasis risk or management during the study period. The outcome of

this study involves rare events, and even minor variations can significantly impact HR estimates, necessitating cautious interpretation of the analysis results. However, by employing propensity score matching and the Cox proportional hazards model, we effectively controlled for potential biases, thereby enhancing the precision of the analysis and supporting the credibility of the conclusions. In this study, unobserved confounding factors, such as healthcare quality and patients' dietary habits, could potentially lead to biased estimates. However, we calculated the E-values [29] for the DPP-4i and TZD groups as 4.17 and 5.21, respectively. This indicates that unobserved confounders are unlikely to cause significant bias in the results of this study. Since the observation period is relatively distant, medication use patterns may have changed with medical advancements. For example, the use of TZDs has declined over time, which is one of the limitations of this study. Furthermore, race and ethnicity data were unavailable in our datasets. Future studies with analyses stratified by laboratory parameters and demographic factors such as race and ethnicity may offer valuable insights into potential heterogeneous treatment effects.

5 | Conclusion

This study focused on patients with T2D undergoing metformin monotherapy and revealed that initiating DPP-4is was associated with a decreased risk of psoriasis compared with initiating sulfonylureas. These findings suggest that DPP-4is may be an option to mitigate the risk of developing psoriasis for individuals requiring a second-line agent following metformin therapy.

Author Contributions

W.-S.C., Y.-S.C., T.-M.L., J.-H.C., and C.-C.C. wrote the manuscript. W.-S.C., T.-M.L., and C.-C.C. designed the research. W.-S.C., Y.-S.C., Y.-C.S., T.-M.L., H.-C.H., T.-T.K., S.-C.C., J.-H.C., and C.-C.C. performed the research. T.-T.K. and J.-H.C. analyzed the data.

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Ethics Statement

The present study was approved by the Institutional Review Board of Taipei Medical University (TMU JIRB-N201509007).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used or analyzed in the present study are available from the corresponding author upon reasonable request.

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