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Glucagon-like peptide-1 receptor agonists and reduced mortality, cardiovascular and psychiatric risks in patients with psoriasis: a large-scale cohort study

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Abstract

Background Psoriasis is associated with a significant comorbidity burden, especially cardiovascular and metabolic complications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, used to treat obesity and diabetes, could potentially reduce comorbidities in patients with psoriasis.

Objectives To investigate all-cause mortality, cardiovascular, inflammatory and psychiatric outcomes, and adverse events in patients with psoriasis treated with GLP-1RAs.

Methods This retrospective population-based cohort study used real-world data from the US TriNetX database. Patients with psoriasis who were treated for diabetes or obesity with a GLP-1RA during the follow-up period of 2 years were compared with those treated with other systemic antidiabetic or antiobesity drugs. After 1 : 1 propensity score matching for relevant risk factors, 3048 participants were included in each cohort. Primary outcomes included the risk of cardiometabolic, psychiatric and autoimmune sequelae of psoriasis, as well as all-cause mortality and potential adverse drug events. The analysis was repeated using cohorts without psoriasis and the results were further validated through two sensitivity analyses involving (i) later follow-up periods or (ii) the exclusion of patients with pustular psoriasis.

Results In the matched cohorts of 3048 patients with psoriasis treated with a GLP-1RA [60.4% women, mean (SD) age 56.94 (12.02) years] vs. other antidiabetic and antiobesity drugs [61.9% women, mean (SD) age 56.42 (14.16) years], GLP-1RA treatment was associated with significantly decreased all-cause mortality [hazard ratio (HR) 0.219, 95% confidence interval (CI) 0.123–0.391; $P<0.001$] and reduced risk of major adverse cardiac events (HR 0.561, 95% CI 0.442–0.714; $P<0.001$). Additionally, lower risks for alcohol (HR 0.346, 95% CI 0.174–0.685; $P=0.009$) and substance abuse (HR 0.510, 95% CI 0.350–0.743; $P=0.002$) were found. Typical adverse drug events were not more frequent in the GLP-1RA cohort. The risk reductions were more pronounced in the cohorts with psoriasis than in those with obesity or diabetes without psoriasis. The findings were consistent across all sensitivity analyses.

Conclusions GLP-1RA treatment was safe and associated with reduced risks of cardiovascular and psychiatric comorbidities, as well as lower mortality in patients with psoriasis, with risk reductions markedly higher than in cohorts without psoriasis. Physicians should consider this drug class for patients with psoriasis and comorbid obesity or diabetes.

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Lay summary

Psoriasis is a common skin condition. It affects 2% to 3% of the world's population. People with psoriasis can have a higher risk of heart diseases and mental health conditions like depression. A new class of drugs called 'GLP-1RA' is being used to treat people with obesity and type 2 diabetes. These drugs have been effective in reducing risks of heart disease and suicidal thoughts.

We are researchers from Germany, Israel and Spain. We used data from the USA to investigate whether patients with psoriasis could benefit from GLP-1RA treatment. We analysed electronic records collected by healthcare providers in the USA. Patients with psoriasis were selected. We then identified who was treated with GLP-1RA or with other drugs for diabetes and obesity. Next, we looked at how many of these patients developed heart, mental health and autoimmune conditions. Afterwards, we performed the same analysis with patients without psoriasis. We found that patients with psoriasis treated with GLP-1RA had a lower risk of dying. They also had lower risks of heart disease and alcohol or drug abuse. However, the risk was no different for unwanted drug effects or other autoimmune diseases. The risk reductions were higher than in people without psoriasis.

Our study findings suggest that people with psoriasis could benefit from GLP-1RA treatment for obesity or type 2 diabetes. This could help lead clinicians to provide more treatment choices for people with psoriasis.

What is already known about this topic?

- Patients with psoriasis have higher risks of cardiometabolic diseases, including obesity, heart attacks, stroke and death due to cardiovascular events.
- Psychiatric conditions such as depression, and other autoimmune diseases are found more frequently in people with psoriasis.
- Glucagon-like peptide receptor-1 agonists (GLP-1RAs) are used to treat obesity and type 2 diabetes and reduce the risk of cardiometabolic comorbidities in individuals with obesity or diabetes mellitus.
- Lower risks of suicidal ideations and alcoholism have been found with GLP-1RA treatment.

What does this study add?

- We hypothesized that patients with psoriasis could benefit from GLP-1RA treatment due to their special comorbidity risk.
- Our US population-based study compared the risk of selected comorbidities in patients with psoriasis treated with GLP-1RA with those treated with other antidiabetic and antiobesity drugs.
- We found lower all-cause mortality, lower risk of major adverse cardiac events, particularly heart failure and stroke, and also a lower risk of alcohol abuse in people with psoriasis treated with GLP-1RAs.

Psoriasis is associated with higher risks of cardiometabolic diseases, including major adverse cardiovascular events (MACE) and metabolic syndrome.[1–3] Chronic inflammation mediated by circulating T helper (Th)1 and Th17 cells in patients with psoriasis aggravates atherogenesis, increasing the incidence of myocardial infarction, stroke and cardiovascular mortality.[4] Psoriasis is also associated with inflammatory comorbidities, such as inflammatory bowel syndrome and uveitis. Additionally, psychiatric comorbidity, such as depression and anxiety, are common, putatively driven not only by social stigmatization and low self-esteem due to the visible and chronic nature of the disease, but also by the neuropsychiatric action of proinflammatory cytokines. Patients with psoriasis are also more prone to alcohol abuse.[5]

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) mimicking the action of the hormone GLP-1 are used to treat type 2 diabetes and obesity. They have a pleiotropic action and mainly act by modulating the satiety centres of the hypothalamus, not only causing a reduction in food intake, but also affecting gastrointestinal organs, blood vessels, muscle and fat tissue. US Food and Drug Administration-approved GLP-1RAs include exenatide, dulaglutide, liraglutide and semaglutide. Their dual benefit of improving glycaemic control and facilitating weight reduction addresses two major health concerns, making GLP-1RAs a much-noted treatment choice in contemporary medical practice. Recent real-world data have also shown reduced risks of certain psychiatric complications, such as suicidal ideations and drug abuse,[6, 7] associated with GLP-1RA use.

In this study, we analysed real-world healthcare data to evaluate the association of GLP-1RAs with comorbidity risks in patients with psoriasis, focusing not only on cardiovascular and metabolic disorders, but also psychiatric outcomes and adverse events (AEs). The data will help clinical decision-making and could improve the holistic management of psoriasis.

Patients and methods

Study design and database

We conducted a global propensity-score matched real-world retrospective cohort study similar to previous protocols.[8, 9] Electronic health records (EHRs) from patients with psoriasis with concomitant obesity or type 2 diabetes and antipsoriatic systemic medication were identified in the US Collaborative Network of the federated TriNetX platform

(henceforth referred to as 'TriNetX'). The group was split into a cohort treated with GLP-1RAs and a control cohort treated with other drugs for type 2 diabetes or obesity. To assess the specific impact of GLP-1RA in patients with psoriasis on the studied outcomes, cohorts or persons with obesity or type 2 diabetes without psoriasis were analysed in parallel. Outcomes defined prior to data acquisition were analysed after propensity score matching (Figure 1).

Study population

Data were retrieved in October 2024 from TriNetX. The network was chosen for its high number of patient records and comprised EHRs of > 110 000 000 patients in the USA at the time of analysis. EHRs recorded in the 20 years before the timepoint of data collection from patients aged > 18 years with psoriasis [International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code: L40] and diabetes mellitus (ICD-10-CM code: E08–E13) or obesity (ICD-10-CM code: E65–E68) were retrieved (Table S1 lists the registration codes used; see Supporting Information). Only EHRs of patients noting systemic antipsoriatic treatment were included in the study, to ensure validity of the diagnosis. Systemic treatment encompassed acitretin, adalimumab, apremilast, brodalumab, certolizumab pegol, ciclosporin, deucravacitinib, dimethyl fumarate, etanercept, golimumab, guselkumab, infliximab, ixekizumab, methotrexate, risankizumab, secukinumab, tildrakizumab and ustekinumab. Patients who had undergone bariatric surgery were excluded. The group was split into a cohort treated with GLP-1RAs for ≥ 24 months [including all GLP-1RAs listed in ATC (Anatomical Therapeutic Chemical) chapter A10BJ] at any time after starting antipsoriatic medication, and a control cohort. Patients in the latter group were not treated with GLP-1RAs; instead, they had been treated for the same duration with any of the other approved systemic antidiabetic or obesity drugs, including α-glucosidase inhibitors, gliflozins, gliptins, glitazones, metformin, sulfonylureas, orlistat, the combination of bupropion with naltrexone, and the combination of phentermine with topiramate. The index event was defined by the first exposure to either GLP-1RA or alternative antidiabetic or antiobesity drugs. Additional cohorts with the exclusion of any codes for psoriasis were identified accordingly. The study design is shown in Figure 1. Baseline cohort characteristics are presented in Table 1.

Covariates

Propensity score matching (PSM) was performed to control for relevant confounding variables. PSM was previously considered advantageous over conventional multivariate Cox analysis.[10] We selected clinically relevant factors including demographic and socioeconomic information, cardiovascular risk factors, psychiatric diseases and other major diseases. We also matched for insulin use. Matching was performed 1 : 1 by the nearest neighbour greedy matching algorithm with a calliper distance of 0.1 SDs after establishing a propensity score for each EHR by logistic regression. Covariates included in the regression matrix, as well as baseline characteristics before and after matching, are presented in Table 1; definition codes for covariates are summarized in Table S1.

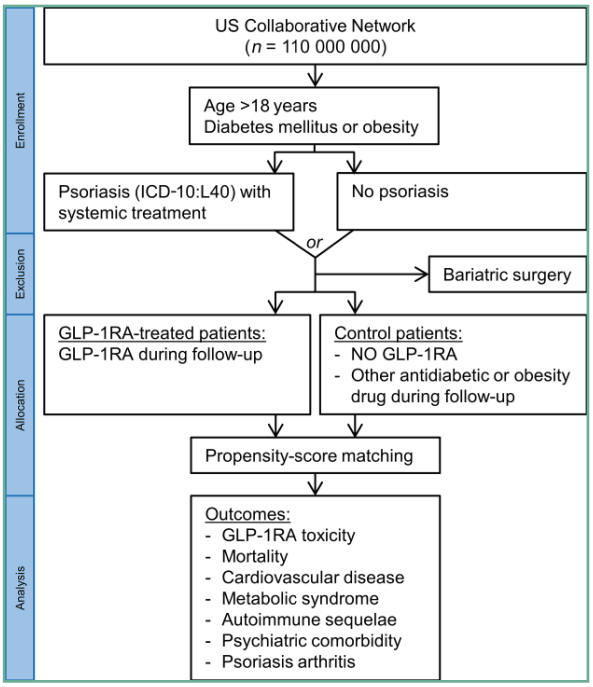


Figure 1 Flowchart of the study inclusion process. See Table S1 for definitions of registration codes. GLP-1RA, glucagon-like peptide-1 receptor agonists; ICD-10, International Classification of Diseases, Tenth Revision.

Statistical analysis

Psoriasis sequelae were analysed up to 2 years after the index event; the first month after treatment initiation was excluded. EHRs with an outcome prior to the index event were excluded from each analysis. Relative risks and risk differences were calculated. Patients were censored after the last available record. Survival analyses were performed by the Kaplan–Meier method and Aalen–Johansen plots. The proportionality assumption was tested based on Schoenfeld residuals. Kaplan–Meier curves were compared by log-rank tests. Hazard ratios (HRs) and confidence intervals (CIs) were expressed by univariate Cox regressions. To adjust for multiple testing, the Holm–Šidák correction was used. The significance level α was set at 0.05.

Results

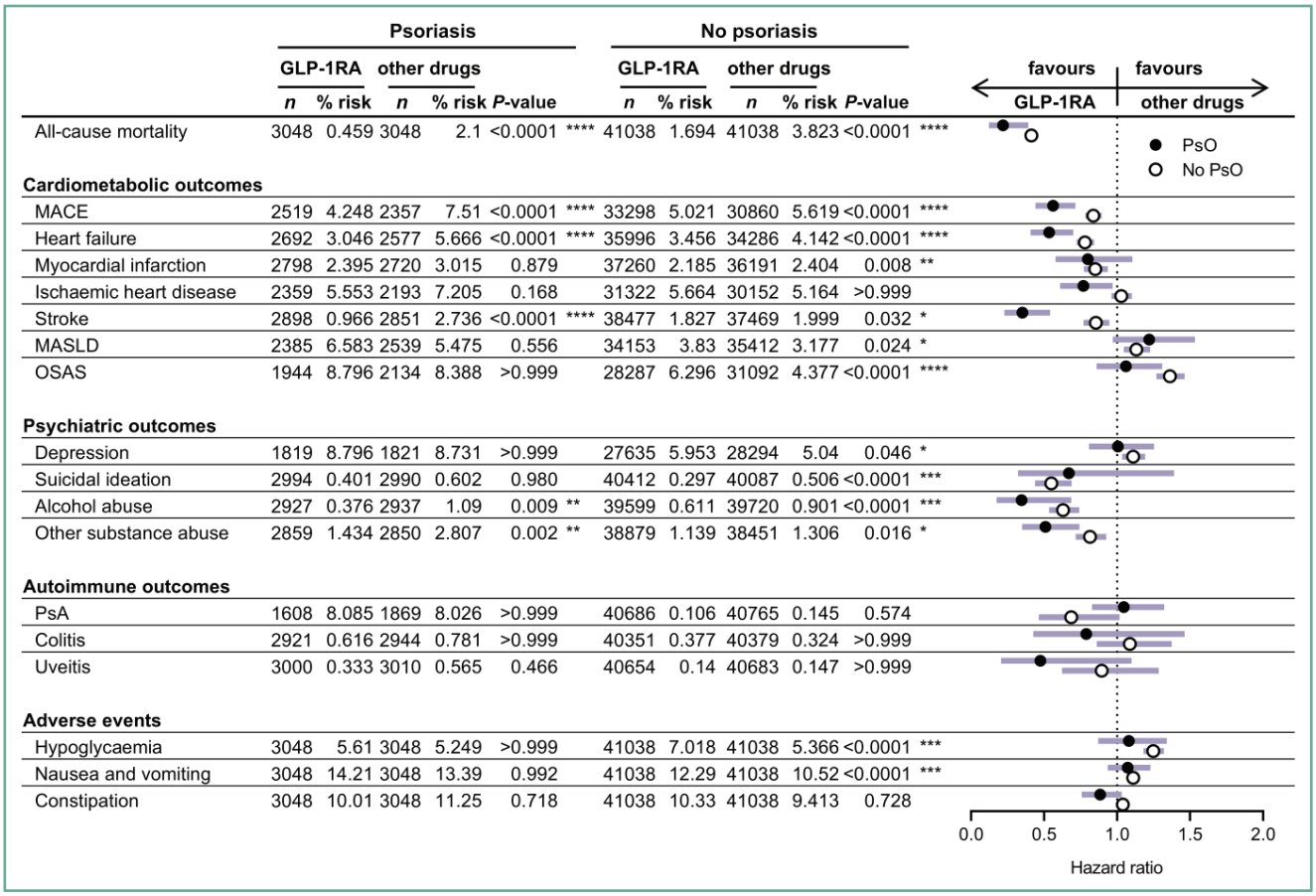
Study population characteristics

We identified 3636 patients with psoriasis treated with GLP-1RAs and 8410 patients with psoriasis who received other antidiabetic or antiobesity drugs. Before matching, the mean (SD) age of those in the GLP-1RA group was 56.44 (12.17) years and in the control group it was 58.98 (13.54) years ($P < 0.001$). The majority of individuals in both groups were women [GLP-1RA group, $n = 2261/3597$ (62.9%); control group, $n = 4438/8055$ (55.1%); $P < 0.001$]. Most people in both groups were non-Hispanic/Latino [GLP-1RA group, $n = 2770/3597$ (77.0%); control group, $n = 6039/8055$

Table 1 Baseline characteristics of patients with psoriasis treated with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and control patients treated with any other antidiabetic or obesity medication before and after propensity score matching (PSM)

		Before matching[a]				After matching[a]			
Characteristic	**ICD-10 code**	**GLP-1RA (*n* = 3597)**	**Other drug (*n* = 8055)**	***P*-value**	**SMD**	**GLP-1RA (*n* = 3048)**	**Other drug (*n* = 3048)**	***P*-value**	**SMD**
Age at index (years), mean (SD)[b]		56.44 (12.17)	58.98 (13.54)	0.00	0.197	56.94 (12.02)	56.42 (14.16)	0.12	0.040
Sex									
Female[b]		2261 (62.9)	4438 (55.1)	0.00	0.158	1840 (60.4)	1887 (61.9)	0.22	0.032
Male		1220 (33.9)	3449 (42.8)	0.00	0.184	1095 (35.9)	1111 (36.5)	0.67	0.011
Race									
White[b]		2764 (76.8)	5886 (73.1)	0.000	0.087	2320 (76.1)	2329 (76.4)	0.79	0.007
Black or African American		282 (7.8)	778 (9.7)	0.002	0.064	230 (7.5)	289 (9.5)	0.007	0.069
Asian		86 (2.4)	311 (3.9)	0.00	0.085	75 (2.5)	89 (2.9)	0.27	0.028
Ethnicity									
Not Hispanic or Latino[b]		2770 (77.0)	6039 (75.0)	0.02	0.048	2326 (76.3)	2324 (76.2)	0.95	0.002
Hispanic or Latino		367 (10.2)	742 (9.2)	0.09	0.033	308 (10.1)	279 (9.2)	0.21	0.032
Diagnoses and medication									
Overweight and obesity[b]	E66	2541 (70.6)	3506 (43.5)	0.00	0.570	1999 (65.6)	2030 (66.6)	0.40	0.021
Diabetes mellitus[b]	E08–E13	3074 (85.5)	5698 (70.7)	0.00	0.362	2530 (83.0)	2490 (81.7)	0.18	0.034
Essential (primary) hypertension[b]	I10	2833 (78.8)	5564 (69.1)	0.00	0.222	2344 (76.9)	2322 (76.2)	0.51	0.017
Disorders of lipoprotein metabolism and other lipidaemias[b]	E78	2771 (77.0)	5128 (63.7)	0.00	0.296	2275 (74.6)	2224 (73.0)	0.14	0.038
Neoplasms[b]	C00–D49	1806 (50.2)	3336 (41.4)	0.00	0.177	1463 (48.0)	1430 (46.9)	0.40	0.022
Chronic lower respiratory diseases	J40–J4A	1364 (37.9)	2487 (30.9)	0.00	0.149	1102 (36.2)	1081 (35.5)	0.58	0.014
Disorders of thyroid gland[b]	E00–E07	1201 (33.4)	1997 (24.8)	0.00	0.190	967 (31.7)	956 (31.4)	0.76	0.008
Chronic kidney disease[b]	N18	601 (16.7)	873 (10.8)	0.00	0.171	463 (15.2)	416 (13.6)	0.09	0.044
Personal history of nicotine dependence[b]	Z87.891	723 (20.1)	1296 (16.1)	0.00	0.104	601 (19.7)	567 (18.6)	0.27	0.028
Nicotine dependence[b]	F17	691 (19.2)	1487 (18.5)	0.34	0.019	583 (19.1)	575 (18.9)	0.79	0.007
Family history of ischaemic heart disease and other diseases of the circulatory system[b]	Z82.4	421 (11.7)	600 (7.4)	0.00	0.145	317 (10.4)	343 (11.3)	0.28	0.027
Alcohol related disorders[b]	F10	121 (3.4)	390 (4.8)	0.00	0.075	118 (3.9)	106 (3.5)	0.41	0.021
Other psychoactive substance related disorders[b]	F19	81 (2.3)	150 (1.9)	0.16	0.027	69 (2.3)	65 (2.1)	0.73	0.009
Family history of arthritis and other diseases of the musculoskeletal system and connective tissue[b]	Z82.6	67 (1.9)	99 (1.2)	0.008	0.051	47 (1.5)	50 (1.6)	0.76	0.008
Hyperuricemia without signs of inflammatory arthritis and tophaceous disease[b]	E79.0	59 (1.6)	84 (1.0)	0.007	0.052	42 (1.4)	46 (1.5)	0.67	0.011
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders[b]	F40–F48	1512 (42.0)	2401 (29.8)	0.00	0.257	1190 (39.0)	1188 (39.0)	0.96	0.001
Mood (affective) disorders[b]	F30–F39	1594 (44.3)	2544 (31.6)	0.00	0.265	1260 (41.3)	1250 (41.0)	0.80	0.007
Problems related to employment and unemployment[b]	Z56	19 (0.5)	28 (0.3)	0.16	0.027	13 (0.4)	16 (0.5)	0.58	0.014
Problems related to housing and economic circumstances[b]	Z59	62 (1.7)	69 (0.9)	0.00	0.077	40 (1.3)	43 (1.4)	0.74	0.008
Insulin[b]	HS501	1986 (55.2)	2148 (26.7)	0.00	0.607	1446 (47.4)	1409 (46.2)	0.34	0.024

P-values were calculated by *t*-tests for continuous variables and *z*-tests for categorical variables. ICD-10, International Classification of Diseases, Tenth Revision; SMD, standardized mean difference.
[a]Discrepancies from the column total arise from electronic health records coding as other categories than the ones included (e.g. 'other sex' or 'unknown sex'). [b]Covariates used for PSM.



	Psoriasis						No psoriasis					
	GLP-1RA		other drugs				GLP-1RA		other drugs			
	n	% risk	*n*	% risk	*P*-value		*n*	% risk	*n*	% risk	*P*-value	
All-cause mortality	3048	0.459	3048	2.1	<0.0001	****	41038	1.694	41038	3.823	<0.0001	****
Cardiometabolic outcomes												
MACE	2519	4.248	2357	7.51	<0.0001	****	33298	5.021	30860	5.619	<0.0001	****
Heart failure	2692	3.046	2577	5.666	<0.0001	****	35996	3.456	34286	4.142	<0.0001	****
Myocardial infarction	2798	2.395	2720	3.015	0.879		37260	2.185	36191	2.404	0.008	**
Ischaemic heart disease	2359	5.553	2193	7.205	0.168		31322	5.664	30152	5.164	>0.999	
Stroke	2898	0.966	2851	2.736	<0.0001	****	38477	1.827	37469	1.999	0.032	*
MASLD	2385	6.583	2539	5.475	0.556		34153	3.83	35412	3.177	0.024	*
OSAS	1944	8.796	2134	8.388	>0.999		28287	6.296	31092	4.377	<0.0001	****
Psychiatric outcomes												
Depression	1819	8.796	1821	8.731	>0.999		27635	5.953	28294	5.04	0.046	*
Suicidal ideation	2994	0.401	2990	0.602	0.980		40412	0.297	40087	0.506	<0.0001	***
Alcohol abuse	2927	0.376	2937	1.09	0.009	**	39599	0.611	39720	0.901	<0.0001	***
Other substance abuse	2859	1.434	2850	2.807	0.002	**	38879	1.139	38451	1.306	0.016	*
Autoimmune outcomes												
PsA	1608	8.085	1869	8.026	>0.999		40686	0.106	40765	0.145	0.574	
Colitis	2921	0.616	2944	0.781	>0.999		40351	0.377	40379	0.324	>0.999	
Uveitis	3000	0.333	3010	0.565	0.466		40654	0.14	40683	0.147	>0.999	
Adverse events												
Hypoglycaemia	3048	5.61	3048	5.249	>0.999		41038	7.018	41038	5.366	<0.0001	***
Nausea and vomiting	3048	14.21	3048	13.39	0.992		41038	12.29	41038	10.52	<0.0001	***
Constipation	3048	10.01	3048	11.25	0.718		41038	10.33	41038	9.413	0.728	

Figure 2 Cohorts of patients with psoriasis treated with glucagon-like peptide-1 receptor agonists (GLP-1RAs) or with other antidiabetic or obesity drugs, and similar cohorts without psoriasis, were analysed from 1 month to 2 years after starting treatment. We compared the occurrence of specific adverse effects of GLP-1R activation, as well as all-cause mortality, cardiovascular, metabolic, autoimmune and psychiatric complications of psoriasis, and psoriasis arthritis (PsA). GLP-1RAs in patients with psoriasis were not associated with a higher risk of known adverse drug effects or inflammatory psoriasis sequelae. On the contrary, patients with psoriasis treated with GLP-1RA showed significantly lower all-cause mortality and cardiovascular risks, as well as decreased risks of alcohol and substance abuse. The risk reductions were stronger in the cohorts with psoriasis than in those without. Bars show hazard ratios (HRs) with confidence intervals. *P*-values of log-rank tests adjusted for multiple testing are shown. MACE, major adverse cardiac events; MASLD, metabolic dysfunction-associated steatotic liver disease; OSAS, obstructive sleep apnoea syndrome; T2D, type 2 diabetes mellitus. **P*<0.05, ***P*<0.01, ****P*<0.001, *****P*<0.0001.

(75.0%); *P*=0.02] and White [GLP-1RA group, *n*=2764/3597 (76.8%); control group, *n*=5886/8055 (73.1%); *P*<0.001]. After 1 : 1 propensity score matching, demographic and socioeconomic factors, as well as the prevalence of type 2 diabetes, obesity and other major diseases, were balanced. Per group, 3048 EHRs were included (Table 1). Cohorts without psoriasis were matched accordingly and, here, 41 038 patients were included per group. The mean (SD) follow-up was 646.10 (185.85) days for the cohort with psoriasis and GLP-1RA treatment, and 649.62 (185.94) for those who received other treatments.

Drug safety of GLP-1RA in patients with psoriasis

Regarding possible adverse drug events related to GLP-1RA treatment in patients with psoriasis, no signals for increased risks of hypoglycaemia, nausea and vomiting, and constipation were noted in comparing patients with psoriasis (Figure 2). However, slightly higher risks were found for the cohorts without psoriasis, in line with the described AE profile of GLP-1RA.

Decreased risks of cardiovascular and psychiatric sequelae in patients with psoriasis treated with glucagon-like peptide-1 receptor agonists

We next analysed the impact of GLP-1RA treatment on mortality and cardiovascular risks in patients with psoriasis. All-cause mortality was significantly lower in patients with psoriasis treated with GLP-1RA (HR 0.219, 95% CI 0.123–0.391; *P*<0.001). Additionally, the risk of MACE analysed in a composite endpoint of heart failure, cardiogenic shock, stroke and acute myocardial infarction was lower in the GLP-1RA group (HR 0.561, 95% CI 0.442–0.714; *P*<0.001). Specifically, the risk of heart failure (HR 0.534, 95% CI 0.408–0.700; *P*<0.001) and stroke (HR 0.352, 95% CI 0.228–0.542; *P*<0.0001) were significantly reduced. Similar risk reductions for mortality, MACE and heart failure were also found in the cohorts without psoriasis. However, the risk reduction associated with GLP-1RA use was more pronounced for the cohorts with psoriasis. On the contrary, metabolic syndrome-associated diseases showed no difference in patients with psoriasis treated with GLP-1RA, or

even slightly higher risks in patients without psoriasis treated with GLP-1RAs, such as metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnoea syndrome (OSAS).

Lower risks were also marked for psychiatric endpoints, including alcohol abuse (HR 0.346, 95% CI 0.174–0.685; $P=0.009$) and other substance abuse (HR 0.510, 95% CI 0.350–0.743; $P=0.002$). Although the risk of suicidal ideation was also slightly lower, it was not statistically significant. Results were similar in the cohorts without psoriasis.

Autoimmune sequelae of psoriasis, including a composite endpoint of Crohn disease and ulcerative colitis, as well as uveitis, did not show different frequencies after GLP-1RA treatment. There were also no differences in incident psoriasis arthritis.

We conducted two sensitivity analyses: (i) to focus on late outcomes and to better exclude pre-existing chronic conditions, the analysis was repeated with a follow-up from 6 months to 2 years after the index event, yielding similar results to the primary analysis (Figure S1; see Supporting Information); (ii) excluding patients with pustular psoriasis from the analysis also confirmed the robustness of our findings in the cohorts with psoriasis (Figure S2; see Supporting Information). Aalen–Johansen analysis, including all outcomes with significant results in the primary survival analysis, showed no significant differences between raw event proportions and cumulative incidences, confirming that censoring or competing risks had minimal influence on the results (data not shown).

Discussion

Psoriasis is not only associated with well-established cardiovascular risk factors, such as smoking, hypertension and hyperlipidaemia, but also acts as an independent risk factor for myocardial infarction, stroke and MACE.[3] Elevated levels of circulating tumour necrosis factor-α and interleukin (IL)-17, along with increased local concentrations of IL-23, have been identified as key contributors to atherosclerosis. Imaging studies showed higher levels of vascular inflammation in patients with psoriasis.[11] Additionally, metabolic syndrome, which shares pathomechanistic links with psoriasis through activation of the IL-17/IL-23 axes in patients with obesity,[12] further exacerbates cardiovascular risks. Adipokines, such as leptin, which is elevated in the serum of patients with psoriasis,[13] can also promote vascular inflammation.[14] Thus, metabolic syndrome may synergistically increase cardiovascular risks in patients with psoriasis, and shared genetic predisposition factors have been identified. GLP-1RAs are known to reduce cardiovascular risks in patients with obesity or type 2 diabetes.[15, 16] Our study confirms that GLP-1RA treatment can not only mitigate the increased cardiovascular risk in patients with psoriasis, as reflected by reductions in cardiovascular disease incidence and all-cause mortality, but importantly, the extent of the risk reductions was larger than for cohorts without psoriasis treated with GLP-1RA. On the contrary, the risks for metabolic syndrome-associated conditions such as MASLD and OSAS were unaffected in patients with psoriasis in our study, despite prospective studies showing improvements of MASLD and OSAS.[17, 18] This could indicate miscoding or might be due to later onset or delayed registration in the database, or an initially higher severity of obesity or type 2 diabetes that led to the decision to treat with a GLP-1RA.

Psychiatric comorbidity in patients with psoriasis can be severe, with one meta-analysis showing a pooled odds ratio for suicidal ideation of 2.05.[19] A brain–skin axis has been postulated to reflect the interplay of common mediators of skin and systemic inflammation, psychological factors and psychiatric comorbidity in patients with psoriasis.[20] In patients treated with GLP-1RA for diabetes mellitus or obesity, decreased risks of suicidal ideations and drug addiction have been observed.[6, 21, 22] However, some pharmacovigilance reports suspected increased suicidal or self-injurious behaviours associated with GLP-1RA treatment, although larger studies did not confirm these associations.[23, 24] The mechanisms of the psychomodulatory action of GLP-1RA are not fully understood, but GLP-1 receptors are found in various brain tissues. The brain's dopamine reward system and the sympathoexcitatory system are notably affected by GLP-1.[25, 26] Our analysis indicated that patients with psoriasis experienced lower risks of alcohol and substance abuse when treated with GLP-1RA, in line with the results obtained for groups without psoriasis.

Regarding the direct effects of GLP-1RA on prevalent psoriasis, previous smaller prospective studies have shown significant improvements in psoriasis severity in patients treated with GLP-1RAs, as measured by the Psoriasis Area and Severity Index. Some studies have found significant reductions in body mass index, but other major comorbidities could not be evaluated in these studies due to small cohort sizes of a maximum of 32 patients.[27–31] Our study did not consider psoriasis severity as disease scores are not included in the database analysed. Positive effects of GLP-1RA on inflammation have also been demonstrated for rheumatoid arthritis and degenerative joint diseases.[32, 33] Considering psoriatic arthritis, no effects of GLP-1RA have been reported so far. In patients with psoriasis treated with GLP-1RAs, lower numbers and inhibited functions of invariant natural killer T cells,[34] γδ T cells and monocytes, as well as lower levels of IL-17, were found,[35] indicating that GLP-1 could suppress inflammation at the level of lymphocyte activation and trafficking in psoriasis. Immunomodulatory functions of GLP-1 were shown for several immune cells via activation of signal transducer and activator of transcription 3 (STAT3) and suppression of nuclear factor κB (NF-κB).[36] In cell culture, GLP-1RA could also inhibit NF-κB signalling directly in keratinocytes, which led to the lower secretion of inflammatory cytokines upon stimulation.[37] However, the role of GLP-1 in the pathophysiology of autoimmunity has not yet been fully elucidated.

The study is limited by its retrospective design. Associations of GLP-1RA treatment with lower comorbidity risks found here cannot be used to infer causality. Measured and unmeasured confounders might have distorted the results, despite extensive cohort matching. In particular, treatment adherence could not be fully controlled in the dataset. To partially address the potential bias imposed by unmeasured confounders, sensitivity analyses were performed. The observed consistency of the results affirm their validity but cannot completely negate bias by unmeasured confounding factors. Statistical significance levels were adapted for multiplicity; however, competing

risks, especially when analysing multiple cardiovascular and psychiatric outcomes, cannot be fully controlled as the underlying data can only be accessed in aggregated form. Miscoding or noncoding of diagnoses, events and medications is expected in real-world data; however, the primary inclusion criterion of prevalent psoriasis is solidified by only including participants with psoriasis-specific systemic treatments. Psychosocial, as well as geographical, factors might influence the level of engagement with healthcare providers; thus, some parts of the population might be underrepresented in the data.

In summary, this real-world cohort study showed lower mortality and lower risks of cardiovascular and psychiatric comorbidity in patients treated with GLP-1RAs compared with other antidiabetic or obesity drugs. Risk reductions were stronger than in patients without psoriasis. Mechanisms and causal factors have to be tested in prospective studies; however, the data could aid clinical decision-making in the treatment of patients with psoriasis and comorbid obesity or type 2 diabetes.

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Conflicts of interest

H.O., H.Z. and R.J.L. have received travel grants from TriNetX. G.H. is an employee of TriNetX. The other authors declare no conflicts of interest.

Data availability

All data relevant for this study are presented in the main text, figures and the Supporting Information.

Ethics statement

Our study did not require Institutional Review Board approval as all data were obtained in aggregated and deidentified form from the TriNetX database. Deidentification is compliant with the US deidentification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. Further, the study was a secondary analysis of existing data and did not involve intervention or interaction with human participants. The study was conducted and reported according to the STROBE guidelines.

Patient consent

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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Co-primary endpoints PASI 90 and IGA 0/1 at Week 16 were met.**Secondary endpoints. †N= mNRI, missing data were imputed with mNRI (patients with missing data following treatment discontinuation due to lack of efficacy or a TRAE were counted as non-responders; multiple imputation methodology was used for other missing data). ‡43.9% (n=189/431), and 43.4% (n=116/267) of biologic-naïve and TNFi-IR PsA patients achieved the primary endpoint of ACR 50 at Week 16 in BE OPTIMAL and BE COMPLETE, respectively (vs 10.0% [n=28/281] and 6.8% [n=9/133] placebo, p<0.0001); 54.5% (n=235/431) and 51.7% (n=138/267) maintained it at Week 52 (NRI).[4–6]

ACR 50, ≥50% response in the American College of Rheumatology criteria; **AS**, ankylosing spondylitis; **CRP**, C-reactive protein; **DMARD**, disease-modifying antirheumatic drug; **HS**, hidradenitis suppurativa; **IGA**, Investigator's Global Assessment; **(m)NRI**, (modified) non-responder imputation; **MRI**, magnetic resonance imaging; **nr-axSpA**, non-radiographic axial spondyloarthritis; **NSAID**, non-steroidal anti-inflammatory drug; **PASI 75/90/100**, ≥75/90/100% improvement from baseline in Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsD**, psoriatic disease; **PsO**, psoriasis; **TNFi-IR**, tumour necrosis factor-α inhibitor – inadequate responder; **TRAE**, treatment-related adverse event.

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