RESEARCH ARTICLE

Association Between GLP-1 Receptor Agonist Use and Epilepsy Risk in Type 2 Diabetes

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Abstract

Background and Objectives

Individuals with type 2 diabetes mellitus (T2DM) are at an increased risk of developing epilepsy, particularly in later life. While preclinical studies suggest neuroprotective properties of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), real-world comparative effectiveness data remain limited. We aimed to evaluate whether GLP-1 RA use is associated with a lower risk of incident epilepsy compared with dipeptidyl peptidase-4 inhibitor (DPP-4i) use in adults with T2DM.

Methods

We conducted a retrospective cohort study using the TriNetX network from 2015 to 2023, including adults aged 18 years or older with T2DM who were new users of either GLP-1 RAs or DPP-4is. Patients with a previous diagnosis of epilepsy or seizure, or those using antiepileptic drugs, were excluded. The primary outcome was incident epilepsy, identified using ICD-10-CM codes. Propensity score matching (1:1) was performed based on demographics, socioeconomic status, body mass index, comorbidities, and baseline medications. Cox proportional hazard models estimated hazard ratios (HRs) with 95% CIs. We also conducted prespecified subgroup and sensitivity analyses to assess the robustness of the findings.

Results

After matching, 452,766 patients were included (226,383 in each group; mean age 60.5 years; 47.1% female). During follow-up, 1,670 individuals in the GLP-1 RA group and 1,886 in the DPP-4i group developed epilepsy, corresponding to cumulative incidences of 2.35% vs 2.41%. GLP-1 RA use was associated with a significantly lower risk of epilepsy (HR 0.84, 95% CI 0.78–0.90), with protective associations evident at 1 year (HR 0.71, 95% CI 0.62–0.80), 3 years (HR 0.81, 95% CI 0.74–0.88), and 5 years (HR 0.82, 95% CI 0.76–0.88). Among individual agents, semaglutide showed the strongest association (HR 0.68, 95% CI 0.60–0.77). The results were consistent across major subgroups, including both age and sex. Sensitivity analyses excluding patients with overlapping or switching exposure yielded similar findings (HR 0.71, 95% CI 0.64–0.78).

Discussion

GLP-1 RA therapy was associated with a significantly lower epilepsy risk compared with DPP-4i use in adults with T2DM. These results support the hypothesis that GLP-1 RAs may exert neurologic benefits beyond glycemic control. Limitations include the observational design and potential residual confounding.

Classification of Evidence

This study provides Class III evidence that the use of GLP-1 RAs in people with T2DM results in a lower risk of developing epilepsy compared with those treated with DPP-4i.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Supplementary Material

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Glossary

BMI = body mass index; **CSMUH** = Chung Shan Medical University Hospital; **CVD** = cardiovascular disease; **HR** = hazard ratio; **PSM** = propensity score matching; **SMD** = standardized mean difference; **T2DM** = type 2 diabetes mellitus.

Introduction

Epilepsy is a neurologic disorder characterized by the brain's persistent predisposition to generate seizures, leading to neurobiological, psychological, and social consequences. While several pharmacologic treatment strategies have been developed, such as γ-aminobutyric acid type A receptor agonists and voltage-gated sodium channel inhibitors, more than 30% of patients with epilepsy remain unresponsive to conventional antiseizure medications.[1] This underscores the importance of identifying novel therapeutic targets. Among patients with epilepsy, a considerable proportion of new-onset cases occur in individuals aged 60 years and older, a condition referred to as late-onset epilepsy.[2] This condition predominantly presents as focal-onset seizures and is often associated with cardiovascular disease (CVD) and neurodegenerative disorders such as Alzheimer disease.[3] Type 2 diabetes mellitus (T2DM) is recognized as a key risk factor of CVD,[4] suggesting that some antidiabetic medications may exert pleiotropic effects that influence epilepsy risk.

GLP-1 receptor agonists (GLP-1 RAs) are a class of glucose-lowering agents that exert effects beyond glycemic control, including actions on the CNS.[5] GLP-1 receptors are widely expressed in the brain, and GLP-1 analogs have demonstrated the ability to cross the blood-brain barrier.[6] These characteristics have prompted growing interest in their potential neuroprotective effects. Preclinical studies and animal models suggest that GLP-1 RAs reduce oxidative stress and inflammation[7,8] while modulating neurotransmitter systems, including enhancing gamma-aminobutyric acid signaling and inhibiting excitotoxic glutamatergic activity. However, despite promising mechanistic rationale, clinical evidence linking GLP-1 RAs to reduced epilepsy risk remains sparse. Most data arise from cardiovascular outcome trials where seizure events were recorded as adverse events rather than predefined end points.[9] GLP-1 RAs have shown the greatest potential in reducing seizure frequency based on these indirect findings among newer glucose-lowering drugs.[5]

Given the neuroprotective and anti-inflammatory properties of GLP-1 RAs and the hints of reduced seizure risk in previous studies, we hypothesized that GLP-1 RA use in patients with T2DM is associated with a lower risk of developing epilepsy relative to an active comparator. In the absence of head-to-head trial data on this question, we undertook a large observational study in a US real-world cohort. Using DPP-4i as the comparison group (a second-line medication class without known neuroprotective effects), we examined the incidence of epilepsy among GLP-1 RA users vs DPP-4i users. We herein report the results of this cohort study, which provide new evidence on the potential neurologic benefits of GLP-1 RAs in patients with T2DM.

Methods

Data Source and Study Population

We used the TriNetX US research network, a large federated electronic health record database containing deidentified data from multiple health care organizations. We identified all adults aged 18 years and older with a diagnosis of T2DM (ICD-10-CM code E11.x) recorded between January 1, 2015, and March 31, 2023. Within this T2DM population, we identified "new users" of either a GLP-1 RA or a DPP-4i. A new user was defined as a patient who had a first prescription or administration of a GLP-1 RA (including all Food and Drug Administration-approved analogs) or a DPP-4i during the study period, with no previous use of the other class in the year before the index date.

Exposure and Outcome Definitions

The GLP-1 RA exposure group included any patient who started treatment with an injectable or oral GLP-1 analog, and the comparator group included those who started any DPP-4i (identified by Anatomical Therapeutic Chemical codes). The index date was defined as the date of first prescription for the respective drug class. The primary outcome was incident epilepsy, defined by the first occurrence of an ICD-10-CM diagnosis code for epilepsy or recurrent seizures (G40.x) during follow-up. Follow-up began the day after the index date and continued until the earliest of an epilepsy diagnosis or the last available medical record. This study followed an intention-to-treat (ITT) approach, in which patients were followed according to their initial treatment assignment regardless of subsequent switching or overlap. This coding algorithm has been validated in previous research, with a sensitivity of 84.4% (95% CI 80.8%–87.5%), specificity of 79.4% (95% CI 62.1%–91.3%), and positive predictive value of 98.3% (95% CI 96.6%–99.3%).[10] Although combining diagnostic codes with antiepileptic medication use can improve specificity in some settings, this approach was not feasible in our study because of platform limitations. Nevertheless, we excluded patients with previous epilepsy diagnoses or antiepileptic drug use to ensure capture of new-onset epilepsy.

Covariates

We collected a comprehensive set of baseline covariates measured before cohort entry, including demographic characteristics (age, sex, race/ethnicity), indicators of socioeconomic status (using ICD-10 Z55–Z65 codes for social

determinants of health), and clinical variables. Clinical covariates included body mass index (BMI), baseline hemoglobin A1c, and medication. While duration of T2DM was not directly available in TriNetX, our use of a new-user design and adjustment for baseline glycemic control and medication use helped mitigate potential bias related to diabetes duration.

Comorbidities were selected based on their known associations with epilepsy risk or their potential influence on antidiabetic prescribing. These included CVD, cerebrovascular disease, neurodegenerative and psychiatric disorders, and alcohol-related conditions. Baseline medication use was also captured, including antidiabetic drugs (e.g., insulin, metformin, and sulfonylureas) and cardiovascular agents (e.g., beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonist, calcium channel blockers, diuretics, aspirin, clopidogrel, and warfarin).

Statistical Analysis

We performed 1:1 propensity score matching (PSM) to balance the GLP-1 RA and DPP-4i cohorts. The propensity score (probability of receiving a GLP-1 RA vs a DPP-4i) was estimated by logistic regression including all covariates listed above. Patients who started GLP-1 RAs were matched to those who started DPP-4is using nearest neighbor matching without replacement, with a caliper of 0.1 SD of the logit of the propensity score. Balance after matching was assessed using standardized mean differences (SMDs), with SMD <0.1 indicating adequate balance. All covariate definitions and ICD-10/ATC codes used are provided in eTable 1.

Baseline characteristics were summarized as means ± SD for continuous variables and counts (percentages) for categorical variables, before and after matching. Incidence of epilepsy was estimated using Kaplan-Meier survival analysis; curves for the matched cohorts were compared by the log-rank test. We used Cox proportional hazard models to estimate the hazard ratio (HR) for incident epilepsy associated with GLP-1 RA use (vs DPP-4i use), reporting HRs with 95% CIs and 2-sided *p* values. Cox models were stratified by matched pair. Primary analyses were conducted in the matched cohort.

We also conducted prespecified subgroup analyses by repeating the Cox regression within strata defined by age (18–64 vs ≥ 65 years), sex, race (White, Black, Asian), baseline BMI category (<30 vs ≥ 30 kg/m^2), and key comorbid conditions (e.g., hypertension, CVD, and neurologic disorders). To evaluate potential confounding related to the COVID-19 pandemic, we conducted a stratified analysis by calendar period (prepandemic: 2015–2019 vs pandemic/postpandemic: 2020–2023). All analyses used a significance level of 0.05. Statistical analyses were performed using TriNetX's built-in tools, and we followed the Strengthening the Reporting of Observational studies in Epidemiology guidelines for reporting observational studies.[11] Competing risk analysis was not available within the TriNetX platform, which may modestly affect absolute event estimates but not relative comparisons.

As a sensitivity analysis, we repeated the analysis excluding patients with overlapping or switching exposure. In this stricter "no-switch" cohort, individuals with crossover drug use were excluded both at baseline and during follow-up (eTables 2–4).

Standard Protocol Approvals, Registrations, and Patient Consents

To ensure patient confidentiality, all data sets within TriNetX are fully deidentified in compliance with the Health Insurance Portability and Accountability Act and the General Data Protection Regulation. The deidentification process involves the removal of personal identifiers such as names, addresses, and any direct patient identifiers, with data aggregated at the cohort level to prevent re-identification. In addition, this study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (CSMUH), under approval number CS2-24180.

Data Availability

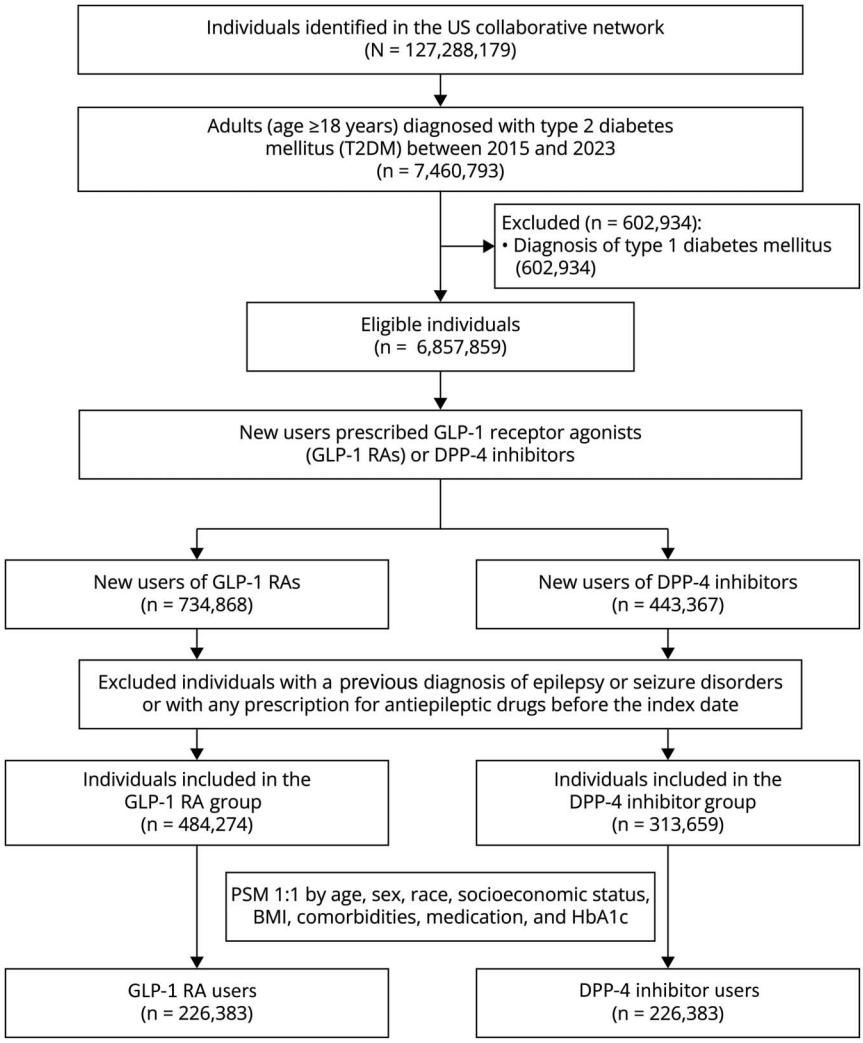
This population-based study obtained data from the TrinetX platform (accessible at trinetx.com/), for which third-party restrictions apply to the availability of these data. The data were used under license for this study, with restrictions that do not allow for data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs might be incurred, and a data-sharing agreement would be necessary.

Results

Figure 1 shows the flowchart of cohort assembly. In the TriNetX network, we identified 7,460,793 adults with T2DM (2015–2023). Of these, 1,178,235 patients had a new prescription for a GLP-1 RA or a DPP-4i. After applying study eligibility criteria and excluding individuals with previous epilepsy, seizure diagnoses, or antiepileptic drug use, 734,868 patients remained in the GLP-1 RA cohort and 443,367 in the DPP-4i cohort. Subsequent 1:1 PSM yielded 226,383 GLP-1 RA users matched to 226,383 DPP-4i users (total N = 452,766).

After matching, the GLP-1 RA and DPP-4i groups were well balanced on baseline covariates (Table 1). The mean age was 60.47 ± 11.92 years in the GLP-1 RA group and 60.70 ± 12.95 years in the DPP-4i group (SMD = 0.018). The proportion of female patients was similar (47.08% vs 47.34%; SMD = 0.005). Race and ethnicity were also balanced (60.6% White, 16.6%–17.2% Black, 6.3% Asian in both groups; SMD <0.05 for all). Mean BMI was modestly higher in the GLP-1 RA group (33.86 vs 33.36 kg/m^2; SMD = 0.066). All other covariates (comorbidities, medication use, social determinants) had SMD <0.05, indicating excellent balance. Baseline characteristics are summarized in Table 1.

Figure 1 Flow Diagram of This Study



We observed a total of 3,556 new cases of epilepsy in the matched cohort (Table 2). Epilepsy incidence was lower among GLP-1 RA users (n = 1,670) than among DPP-4i users (n = 1,886). This corresponded to a cumulative incidence of 2.35% in the GLP-1 RA cohort vs 2.41% in the DPP-4i cohort by the end of follow-up. These estimates reflect Kaplan-Meier cumulative incidence percentages. Owing to platform limitations, person-time and median follow-up duration were not available.

Figure 2 shows early separation of the event curves: by 1 year, the incidence was 0.20% vs 0.28%; by 3 years, it was 0.57% vs 0.69%; and by 5 years, it was 0.94% vs 1.31%, favoring GLP-1 RA use at each time point (Table 2). The overall HR for epilepsy with GLP-1 RA vs DPP-4i use was 0.84 (95% CI 0.78–0.90).

When examining individual GLP-1 RA agents, we observed heterogeneity in the magnitude of association. Among liraglutide users (matched n = 36,489 each), the HR was 1.02 (95% CI 0.88–1.18). For dulaglutide (n = 115,818 each), the HR was 0.93 (95% CI 0.84–1.03), and for semaglutide (n = 114,676 each), the HR was 0.68 (95% CI 0.60–0.77). These findings, given in Table 3, suggest that semaglutide primarily drove the overall protective association, whereas liraglutide and dulaglutide showed neutral effects (Table 3).

The association between GLP-1 RA use and lower epilepsy risk was generally consistent across subgroups (Table 4). Patients aged 18–64 years had a HR of 0.79 (95% CI 0.72–0.86), whereas those aged 65 years and older had a HR of 0.90 (95% CI 0.81–0.99). Female and male patients had HRs of 0.82 (95% CI 0.75–0.91) and 0.84 (95% CI 0.76–0.92), respectively. Point estimates were directionally consistent across racial strata (White: HR 0.87, 95% CI 0.79–0.95; Black: HR 0.79, 95% CI 0.68–0.91; Asian: HR 0.74, 95% CI 0.52–1.06) and BMI categories (<30 kg/m^2: HR 0.92, 95% CI 0.81–1.05; ≥30 kg/m^2: HR 0.93, 95% CI 0.84–1.03). Among patients with hypertension, the HR was 0.84 (95% CI 0.78–0.91). Among those with CVD, the HR

Table 1 Baseline Demographic and Clinical Characteristics of GLP-1 Receptor Agonist and DPP-4i Users Before and After Propensity Score Matching (PSM)

	Patients, no. (%)					
	Before PSM			After PSM		
	GLP-1 RA users N = 484,274	DPP-4i users N = 313,659	SMD	GLP-1 RA users N = 226,383	DPP-4i users N = 226,383	SMD
Age at index	57.00 ± 12.97	62.42 ± 12.60	0.424	60.47 ± 11.92	60.70 ± 12.95	0.018
Sex						
Female	243,881 (50.36)	144,221 (45.98)	0.088	106,589 (47.08)	107,163 (47.34)	0.005
Male	224,757 (46.41)	160,857 (51.28)	0.098	111,137 (49.09)	113,723 (50.24)	0.023
Race						
White	303,071 (62.58)	183,135 (58.39)	0.086	137,283 (60.64)	137,152 (60.58)	0.001
Black or African American	83,205 (17.18)	53,266 (16.98)	0.005	37,488 (16.56)	38,955 (17.21)	0.017
Asian	22,699 (4.69)	25,848 (8.24)	0.145	14,306 (6.32)	14,290 (6.31)	<0.001
Other races	20,894 (4.31)	14,493 (4.62)	0.015	9,621 (4.25)	10,586 (4.68)	0.021
Unknown race	46,263 (9.55)	31,951 (10.19)	0.021	24,049 (10.62)	21,806 (9.63)	0.033
Socioeconomic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	6,825 (1.41)	4,061 (1.30)	0.010	3,033 (1.34)	3,024 (1.34)	<0.001
Problems related to education and literacy	291 (0.06)	208 (0.07)	0.002	146 (0.06)	150 (0.07)	0.001
Problems related to employment and unemployment	700 (0.15)	353 (0.11)	0.009	314 (0.14)	293 (0.13)	0.003
Problems related to housing and economic circumstances	2,744 (0.57)	1,647 (0.53)	0.006	1,093 (0.48)	1,309 (0.58)	0.013
BMI	327,053 (67.54)	202,158 (64.45)	0.547	143,063 (63.20)	144,708 (63.92)	0.066
BMI, mean ± SD	36.23 ± 8.07	31.96 ± 7.50	0.547	33.86 ± 7.75	33.36 ± 7.49	0.066
Comorbidities						
Hypertension						
Essential (primary) hypertension	300,722 (62.10)	204,590 (65.23)	0.065	145,109 (64.10)	145,172 (64.13)	0.001
Hypertensive heart disease	14,251 (2.94)	12,584 (4.01)	0.058	8,190 (3.62)	8,355 (3.69)	0.004
Hypertensive chronic kidney disease	19,441 (4.01)	22,519 (7.18)	0.138	13,045 (5.76)	13,159 (5.81)	0.002
Hypertensive heart and chronic kidney disease	6,503 (1.34)	9,767 (3.11)	0.120	5,036 (2.23)	5,116 (2.26)	0.002
Cardiovascular disease						
Angina pectoris	6,121 (1.26)	5,056 (1.61)	0.029	3,625 (1.60)	3,093 (1.37)	0.019
Acute myocardial infarction	9,564 (1.98)	10,385 (3.31)	0.083	5,774 (2.55)	6,322 (2.79)	0.015
Chronic ischemic heart disease	58,340 (12.05)	52,369 (16.70)	0.133	34,714 (15.33)	32,333 (14.28)	0.030
Heart failure	28,431 (5.87)	28,123 (8.97)	0.118	16,708 (7.38)	17,030 (7.52)	0.005
Alcohol-related disorders	4,839 (1.00)	4,216 (1.34)	0.032	2,695 (1.19)	2,674 (1.18)	0.001
Neurologic comorbidities						
Alzheimer disease	711 (0.15)	1742 (0.56)	0.069	642 (0.28)	662 (0.29)	0.002
Parkinson disease	960 (0.20)	1,568 (0.50)	0.051	739 (0.33)	754 (0.33)	0.001
Amyotrophic lateral sclerosis	26 (0.01)	72 (0.02)	0.015	14 (0.01)	45 (0.02)	0.012
Multiple sclerosis	986 (0.20)	603 (0.19)	0.003	443 (0.20)	465 (0.21)	0.002
Brain tumors						

Continued

Table 1 Baseline Demographic and Clinical Characteristics of GLP-1 Receptor Agonist and DPP-4i Users Before and After Propensity Score Matching (PSM) *(continued)*

	Patients, no. (%)					
	Before PSM			After PSM		
	GLP-1 RA users N = 484,274	DPP-4i users N = 313,659	SMD	GLP-1 RA users N = 226,383	DPP-4i users N = 226,383	SMD
Malignant neoplasm of brain	77 (0.02)	115 (0.04)	0.013	40 (0.02)	77 (0.03)	0.010
Benign neoplasm of brain and other parts of CNS	256 (0.05)	213 (0.07)	0.006	137 (0.06)	142 (0.06)	0.001
Arteriovenous malformation of cerebral vessels	43 (0.01)	50 (0.02)	0.006	27 (0.01)	32 (0.01)	0.002
Diffuse traumatic brain injury	14 (0.00)	43 (0.01)	0.012	10 (0.00)	23 (0.01)	0.007
Stroke						
Cerebral infarction	8,777 (1.81)	10,207 (3.25)	0.092	5,851 (2.59)	5,895 (2.60)	0.001
Nontraumatic intracerebral hemorrhage	509 (0.11)	812 (0.26)	0.036	379 (0.17)	386 (0.17)	0.001
Meningitis and encephalitis						
Bacterial meningitis, not elsewhere classified	20 (0.00)	39 (0.01)	0.009	12 (0.01)	28 (0.01)	0.008
Viral meningitis	31 (0.01)	21 (0.01)	<0.001	16 (0.01)	14 (0.01)	0.001
Encephalitis, myelitis, and encephalomyelitis	77 (0.02)	96 (0.03)	0.010	50 (0.02)	59 (0.03)	0.003
Other encephalitis and encephalomyelitis	15 (0.00)	18 (0.01)	0.004	10 (0.00)	14 (0.01)	0.002
Cerebral palsy	196 (0.04)	197 (0.06)	0.010	93 (0.04)	154 (0.07)	0.012
Neurodevelopmental disorders						
Autistic disorder	375 (0.08)	149 (0.05)	0.012	94 (0.04)	121 (0.05)	0.005
Intellectual disabilities	627 (0.13)	690 (0.22)	0.022	356 (0.16)	399 (0.18)	0.005
Medications						
Biguanides	259,081 (53.50)	189,947 (60.56)	0.143	136,361 (60.24)	133,848 (59.13)	0.023
Insulins and analogs	143,125 (29.56)	101,103 (32.23)	0.058	74,397 (32.86)	72,840 (32.18)	0.015
Sulfonylureas	92,870 (19.18)	88,753 (28.30)	0.216	58,179 (25.70)	57,290 (25.31)	0.009
Thiazolidinediones	19,071 (3.94)	14,371 (4.58)	0.032	10,564 (4.67)	10,380 (4.59)	0.004
Alpha-glucosidase inhibitors	860 (0.18)	985 (0.31)	0.028	594 (0.26)	608 (0.27)	0.001
Diuretics	137,323 (28.36)	101,387 (32.32)	0.086	69,219 (30.58)	69,721 (30.80)	0.005
Beta-blocking agents	118,231 (24.41)	105,936 (33.77)	0.207	67,258 (29.71)	68,066 (30.07)	0.008
Ace inhibitors, plain	126,579 (26.14)	97,480 (31.08)	0.109	67,501 (29.82)	66,922 (29.56)	0.006
Calcium channel blockers	94,793 (19.57)	80,157 (25.56)	0.143	51,800 (22.88)	52,547 (23.21)	0.008
Angiotensin II receptor blockers (ARBs), plain	108,181 (22.34)	73,466 (23.42)	0.026	52,370 (23.13)	52,662 (23.26)	0.003
Aspirin	64,253 (13.27)	74,293 (23.69)	0.271	43,114 (19.05)	43,531 (19.23)	0.005
Clopidogrel	18,580 (3.84)	20,967 (6.69)	0.128	12,399 (5.48)	12,420 (5.49)	<0.001
Warfarin	5,623 (1.16)	6,813 (2.17)	0.079	3,604 (1.59)	3,758 (1.66)	0.005
Laboratory results						
Hemoglobin A1c (%)	316,765 (65.41)	179,737 (57.30)	0.003	136,633 (60.36)	135,856 (60.01)	0.048
Hemoglobin A1c (%), mean ± SD	8.31 ± 2.05	8.31 ± 2.05	0.003	8.49 ± 2.04	8.39 ± 2.03	0.048

Abbreviations: PSM = propensity score matching; SMD = standardized mean difference.
The percentages do not sum to 100% because of missing data in the TriNetX database.

Table 2 Risk of Incident Epilepsy Among GLP-1 Receptor Agonist Users Compared With DPP-4i Users

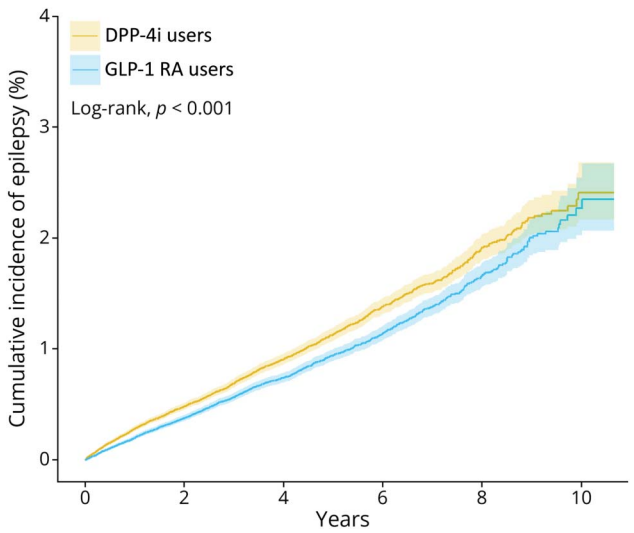
	No. of events (N = 226,383)		Cumulative incidence (%)		
	GLP-1 RA users	DPP-4i users	GLP-1 RA users	DPP-4i users	HR (95% CI)
All	1,670	1886	2.35	2.41	0.84 (0.78–0.90)
1 y	420	567	0.20	0.28	0.71 (0.62–0.80)
3 y	1,004	1,169	0.57	0.69	0.81 (0.74–0.88)
5 y	1,359	1,571	0.94	1.13	0.82 (0.76–0.88)

was 0.84 (95% CI 0.74–0.95). For those with previous stroke, the HR was 0.79 (95% CI 0.63–0.99). Subgroups with limited sample sizes, such as patients with brain tumor or cerebral palsy, were underpowered for reliable comparisons.

To assess potential confounding related to COVID-19, we stratified analyses by calendar period. The association between GLP-1 RA use and reduced epilepsy risk remained consistent: HR 0.89 (95% CI 0.81–0.97) during the prepandemic era (2015–2019) and HR 0.78 (95% CI 0.69–0.87) during the pandemic/postpandemic era (2020–2023). These results are presented in eTable 2.

In sensitivity analyses, we excluded patients with overlapping or switching exposure to evaluate the robustness of our findings. After PSM (N = 92,675 in each group), baseline characteristics remained well balanced (eTable 3). The association between GLP-1 RA use and reduced epilepsy risk remained consistent with the primary results. Specifically, the HR for incident epilepsy was 0.71 (95% CI, 0.64–0.78) over the entire follow-up period, with time-specific estimates of 0.63 (95% CI, 0.53–0.75) at 1 year, 0.69 (95% CI, 0.61–0.78) at 3 years, and 0.71 (95% CI, 0.64–0.80) at 5 years (eTable 4). These findings support the robustness of our main conclusions under alternative exposure assumptions.

Figure 2 Kaplan-Meier Plot for Risk of Epilepsy in GLP-1 RA Users Compared With DPP-4i Users



Owing to data access limitations of the TriNetX platform that provides the Kaplan-Meier curves, precise numbers at risk at each time point are not available. DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist.

Discussion

In this large observational study of adults with T2DM, use of GLP-1 RAs was associated with a substantially lower risk of developing epilepsy compared with use of DPP-4is. After matching 226,383 new users of each class, we found a 16% lower hazard of epilepsy (overall HR 0.84) among GLP-1 RA users. The risk reduction was apparent early (1-year HR 0.71) and persisted over long-term follow-up (5-year HR 0.82). These results extend mechanistic insights and preclinical findings about the neuroprotective properties of GLP-1 RAs to a real-world clinical context. By contrast, DPP-4is showed no known neuroprotective effect, which strengthens the interpretation that the observed difference may be attributable to intrinsic properties of GLP-1 RAs.

Notably, the apparent effect varied by specific GLP-1 RA agent. Liraglutide was not associated with a significant reduction in epilepsy risk (HR 1.02), and dulaglutide similarly showed a neutral effect (HR 0.93). By contrast, semaglutide demonstrated a strong protective association (HR 0.68). This heterogeneity might reflect differences in pharmacokinetics, blood-brain barrier penetration, receptor-binding profiles, or dosing regimens among the agents. For example, semaglutide has high potency and prolonged receptor activation, which may enhance CNS effects; conversely, liraglutide's shorter half-life or different CNS uptake may limit its impact on neuronal excitability. These agent-specific findings align with preclinical data: semaglutide has demonstrated neuroprotective effects in experimental models. However, confirmatory studies are needed to elucidate the reasons for these differences. In addition to these agent-specific observations, our study provides real-world evidence directly comparing GLP-1 RAs and DPP-4is in relation to epilepsy risk, using a validated outcome definition and excluding prevalent cases. This design enables a more clinically relevant assessment of drug-related differences under routine prescribing conditions, complementing and extending previous trial-based findings.

Table 3 Risk of Incident Epilepsy Associated With Individual GLP-1 Receptor Agonists Compared With DPP-4is

	GLP-1 RAs		DPP-4is		
	N	No. of events	N	No. of events	HR (95% CI)
Liraglutide	36,489	331	36,489	380	1.02 (0.88–1.18)
Dulaglutide	115,818	730	115,818	788	0.93 (0.84–1.03)
Semaglutide	114,676	455	114,676	636	0.68 (0.60–0.77)

Our findings align with a meta-analysis of cardiovascular trials showing a 24% reduction in seizures or epilepsy with newer glucose-lowering agents, predominantly driven by GLP-1 RAs.[5] The similar magnitude of risk reduction observed in both trials and real-world data supports the credibility of our findings. In contrast to DPP-4is, which seem neutral, GLP-1 RAs may confer a true protective effect.

Additional support comes from a complementary target trial emulation demonstrating a similar reduction in epilepsy risk reduction with SGLT-2 inhibitors.[12] That study, which compared SGLT-2is with DPP-4is, reported a nearly identical HR (HR 0.71, 95% CI 0.52–0.97). The convergence of findings across drug classes and across diverse populations strengthens the overall evidence.[12] It suggests that the observed neuroprotective effect might extend across newer antidiabetic agents with systemic benefits, rather than being a peculiarity of 1 study or population. However, it is worth noting that in the randomized controlled trial meta-analysis, SGLT-2 inhibitors did not show a significant seizure risk reduction, whereas GLP-1 RAs did.[5] One possible interpretation is that GLP-1 RAs have a direct CNS effect,

Table 4 Stratified Analysis of Epilepsy Risk Among GLP-1 Receptor Agonist Users Compared With DPP-4i Users

	GLP-1 RA users		DPP-4i users		
	N	No. of events	N	No. of events	HR (95% CI)
Age					
18–64	134,327	882	134,327	1,072	0.79 (0.72–0.86)
≥65	90,320	756	90,320	792	0.90 (0.81–0.99)
Sex					
Female	1,076	802	1,451	1,038	0.82 (0.75–0.91)
Male	112,625	769	112,625	874	0.84 (0.76–0.92)
Race					
White	129,572	949	129,572	1,037	0.87 (0.79–0.95)
Black or African American	37,954	337	37,954	404	0.79 (0.68–0.91)
Asian	13,714	55	13,714	69	0.74 (0.52–1.06)
BMI					
<30	54,881	435	54,881	445	0.92 (0.81–1.05)
≥30	88,801	710	88,801	735	0.93 (0.84–1.03)
Comorbidities					
Hypertension	151,219	1,244	151,219	1,395	0.84 (0.78–0.91)
Cardiovascular disease	42,023	458	42,023	510	0.84 (0.74–0.95)
Neurologic comorbidities	1,373	35	1,373	24	1.26 (0.75–2.12)
Alcohol-related disorders	2,589	49	2,589	48	0.93 (0.62–1.38)
Multiple sclerosis	431	10	431	11	0.85 (0.36–2.01)
Stroke	6,014	143	6,014	160	0.79 (0.63–0.99)
Neurodevelopmental disorders	467	11	467	15	0.70 (0.32–1.52)

whereas the benefits of SGLT-2 inhibitors might be secondary through vascular or metabolic improvements. Regardless, both observational studies point toward a real-world benefit of newer glucose-lowering drugs in reducing epilepsy incidence, with our study specifically highlighting the GLP-1 RA class. Mechanistically, GLP-1 receptors are distributed in the CNS and influence neurotransmitter signaling and neuronal excitability.[6] Animal studies show that GLP-1 RAs reduce inflammation, oxidative stress, and neurodegeneration.[13,14] The antiepileptogenic potential of GLP-1 RAs may relate to these neuroprotective mechanisms rather than metabolic control alone, especially because HbA1c levels were similar across treatment groups.

GLP-1 RAs have demonstrated benefits in reducing certain cardiovascular outcomes, including stroke, in some trials of liraglutide and semaglutide.[15,16] In our study, the subgroup of patients with previous stroke also showed a significant reduction in epilepsy risk (HR 0.79, 95% CI 0.63–0.99), reinforcing the possibility that GLP-1 RAs may confer benefits in populations already at high neurologic risk. It is important to note that this association suggests that the protective effect of GLP-1 RAs may extend beyond simple stroke prevention, potentially reflecting direct neuroprotective actions such as modulation of excitotoxicity, reduction of neuroinflammation, and preservation of neuronal integrity.[5]

Of interest, our comparison drug class, DPP-4is, in theory also raises endogenous GLP-1 levels and has some antioxidant and neuroprotective effects preclinically.[17] Yet, DPP-4is did not show a benefit in trials or our study. This might be due to DPP-4is having a weaker effect centrally.[18] This underscores that the finding is likely specific to GLP-1 RAs rather than all antidiabetics.[5]

Our strengths include the large sample, active comparator design, and extensive covariate adjustment. Postmatching balance was excellent. Diagnostic codes used to define epilepsy are specific, and seizure history was excluded to isolate incident cases. These factors support the validity of our effect estimates. In addition, to address potential confounding related to the COVID-19 pandemic, we conducted a sensitivity analysis stratified by period. The consistent results across pre–COVID-19 and post–COVID-19 eras further strengthen the robustness of our findings.

Several limitations of this observational study should be acknowledged. Although PSM was applied to minimize confounding, residual bias from unmeasured variables, such as genetic susceptibility, family history of epilepsy,[19] or lifestyle factors including sleep hygiene[20] and alcohol use,[21] may persist. We could not capture real-world prescribing determinants such as gastrointestinal tolerability, patient or provider preference, cost, or formulary restrictions, which may influence the choice between GLP-1 RAs and DPP-4is. These unmeasured factors may contribute to residual confounding in treatment allocation despite careful matching on observable covariates. Moreover, the early divergence of the Kaplan-Meier curves between groups may reflect residual confounding or selection bias, despite rigorous PSM. This pattern suggests that unmeasured factors such as disease severity, clinician prescribing preferences, or patient frailty could influence both treatment allocation and epilepsy risk. We lacked detailed information on treatment adherence, dosage, and potential therapy changes over time, which may have influenced outcomes. Furthermore, epilepsy diagnoses were based on administrative ICD-10-CM codes, which may misclassify isolated seizure events or fail to capture all relevant cases, potentially introducing misclassification bias.

This study used Kaplan-Meier methods for survival analysis; however, the TriNetX platform does not currently support competing risk models, such as Fine-Gray subdistribution hazard models. As a result, death as a competing event could not be accounted for, which may lead to a slight overestimation of epilepsy incidence. Nonetheless, the relative comparison between groups is unlikely to be meaningfully affected because of robust baseline matching and the large sample size. In addition, this study was conducted using an intention-to-treat approach, whereby patients were analyzed according to their initial treatment assignment. Owing to limitations in medication refill and adherence data in the TriNetX platform, we were unable to evaluate per-protocol or as-treated effects. This may attenuate the observed associations.

Another limitation of our study is that the PSM process excluded a substantial number of individuals from both treatment groups who did not have a suitable match within the specified caliper. Although this approach improved covariate balance and strengthened internal validity, it reduced the final sample size and may limit the generalizability of our findings to a broader population of GLP-1 RA or DPP-4i users. In addition, data for BMI and hemoglobin A1c were missing for a substantial portion of the cohort. Because missing values could not be imputed within the TriNetX platform, residual bias may exist in analyses involving these covariates. Finally, tirzepatide, a dual gastric inhibitory polypeptide and GLP-1 receptor agonist, was not included in our analysis. Although it was approved by the US FDA in May 2022, its recent introduction and limited follow-up time within the study window precluded meaningful inclusion. Therefore, our findings should not be extrapolated to this newer agent.

Future research should explore whether GLP-1 RA–related epilepsy risk reduction holds in other populations, whether effects vary by agent, and whether seizure reduction correlates with improvements in metabolic parameters. Mechanistic studies may help clarify whether GLP-1 directly alters neuroexcitation pathways. Inclusion of epilepsy outcomes in ongoing trials for Alzheimer and Parkinson diseases may offer insights.

In conclusion, in a large, matched cohort of patients with type 2 diabetes, use of GLP-1 RAs was associated with a significantly reduced risk of developing epilepsy compared with

DPP-4is. Although the absolute risk difference over time was modest, the consistent association across subgroups and alignment with previous trial data support the hypothesis that GLP-1 RAs may have neurobiological effects beyond glycemic control. These findings reflect a relative risk difference between 2 treatment strategies and do not imply that DPP-4is are harmful or that GLP-1 RAs are definitively neuroprotective. Further research is warranted to confirm these findings and explore their mechanistic basis. These results expand the potential utility of GLP-1 RAs, suggesting that they may contribute to reducing the burden of late-onset epilepsy in high-risk populations.

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Author Contributions

C-Y. Cheng: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. S-C. Lo: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; Analysis or interpretation of data. C-N. Huang: major role in the acquisition of data; analysis or interpretation of data. Y-S. Yang: major role in the acquisition of data; study concept or design; analysis or interpretation of data. Y-H. Wang: major role in the acquisition of data; study concept or design; analysis or interpretation of data. E. Kornelius: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Disclosure

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