RESEARCH ARTICLE

Semaglutide and Risk of Adult-Onset Seizure

A Target Trial Emulation

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Abstract

Background and Objectives

Adult-onset seizure reflects the burden of acquired brain insults, but established disease-modifying preventive strategies are limited. We evaluated whether semaglutide initiation is associated with a lower incidence of adult-onset seizure compared with sodium-glucose cotransporter 2 inhibitors (SGLT2i) and other glucose-lowering drugs (GLDs) in adults with type 2 diabetes.

Methods

Using the *All of Us* Research Program, we emulated a population-based target trial in new-user, active-comparator cohorts from January 2018 to October 2023. We compared semaglutide vs other GLDs and semaglutide vs SGLT2i. Incident epilepsy or seizure was identified from diagnostic codes. Effects were estimated using inverse probability of treatment weighting with weighted Cox models and targeted maximum likelihood estimation (TMLE). Subgroup and sensitivity analyses with multiple outcome definitions and analytic approaches were conducted to assess the robustness of findings. We evaluated mediation through hemoglobin A1c (HbA1c) and body mass index (BMI) using the longitudinal Vansteelandt framework.

Results

We analyzed 10,213 patients in the semaglutide (n = 2,586, mean age, 60.1 years; 56.8% female) vs other GLDs cohort (n = 7,627, mean age, 63.7 years; 54.2% female) and 8,605 patients in the semaglutide (n = 2,814, mean age, 60.5 years; 66.2% female) vs SGLT2i cohort (n = 5,791, mean age, 64.4 years; 47.3% female). Semaglutide was associated with a lower risk of adult-onset seizure compared with other GLDs (weighted HR 0.44 [95% CI 0.25–0.79]; 4-year risk difference −1.78% [95% CI −2.58 to −0.98]) and SGLT2i (weighted HR 0.48 [95% CI 0.27–0.85]; 4-year risk difference −1.46% [95% CI −2.41 to −0.51]). TMLE estimated risk differences per 1,000 persons of −14.20 (95% CI −18.33 to −10.07) vs other GLDs and −7.62 (95% CI −11.65 to −3.60) vs SGLT2i, corresponding to numbers needed to treat of 70 and 131, respectively. Mediation was minimal for HbA1c (2.4% vs other GLDs; 6.5% vs SGLT2i) and BMI (0% vs other GLDs; 0.7% vs SGLT2i).

Discussion

Semaglutide initiation was associated with a lower risk of adult-onset seizure compared with SGLT2i and other GLDs in patients with type 2 diabetes, independent of glycemic and weight effects. Residual confounding, low event counts, and shorter follow-up limit causal interpretation.

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Supplementary Material

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Glossary

BMI = body mass index; **COVID-19** = coronavirus disease 2019; **GLD** = glucose-lowering drug; **GLP-1RA** = glucagon-like peptide 1 receptor agonist; **HbA1c** = hemoglobin A1c; **HR** = hazard ratio; **ICD-9-CM** = International Classification of Diseases, Ninth Revision, Clinical Modification; **ICD-10-CM** = International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification; **IPTW** = inverse probability of treatment weighting; **SGLT2i** = sodium-glucose cotransporter-2 inhibitors; **SMD** = standardized mean difference; **SNOMED-CT** = Systematized Nomenclature of Medicine Clinical Terms; **TMLE** = targeted maximum likelihood estimation.

Classification of Evidence

This study provides Class II evidence that semaglutide use was associated with a lower risk of adult-onset seizures compared with other GLDs and SGLT2i.

Introduction

Adult-onset seizure, defined as seizure onset at age 18 years or older, is increasingly recognized as a distinct clinical entity with causes that differ from childhood-onset seizures.[1,2] Acquired brain insults, including traumatic brain injury,[3] neurodegeneration,[4,5] and cerebrovascular disease,[6,7] are major contributors to its epileptogenesis. In this context, adult-onset seizure directly reflects brain health and strongly influences prognosis and quality of life.[1,5] However, beyond symptomatic management with antiseizure medication, disease-modifying therapies aimed at prevention have remained limited.

The glucagon-like peptide 1 receptor agonist (GLP-1RA) semaglutide is an incretin-based therapy that enhances glucose-dependent insulin secretion and suppresses glucagon.[8] Recent American Diabetes Association guidelines endorse semaglutide as a first-line treatment for adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease.[9,10] Beyond diabetes, semaglutide is approved for chronic weight management,[11] chronic kidney disease,[12] and metabolic dysfunction-associated steatohepatitis,[13] as well as for reduction of cardiovascular risk in overweight and obese patients without diabetes.[14] Emerging evidence suggests that, among GLP-1RAs, semaglutide may have distinctive neuroprotective effects relevant to CNS disorders,[15,16] yet large-scale, population-based studies evaluating the association between semaglutide and incident adult-onset seizure remain limited.

Accordingly, we used the large, population-based *All of Us* Research Program cohort to evaluate potential neurologic benefits of semaglutide for adult-onset seizure.[17] We used target trial emulation, a framework that applies the design principles of a hypothetical randomized trial to observational data, to enhance causal interpretation. Specifically, the primary research questions were whether semaglutide initiation was associated with a lower risk of incident adult-onset seizure compared with sodium-glucose cotransporter-2 inhibitors (SGLT2i) and other glucose-lowering drugs (GLDs), and whether any observed association was materially mediated by changes in hemoglobin A1c (HbA1c) or body mass index (BMI).

Methods

Data Sources and Study Cohorts

The study used data from the *All of Us* Research Program Curated Data Repository version 8, Controlled Tier, which includes longitudinal medical information from more than 633,000 participants (393,596 with electronic health records).[17] The *All of Us* Research Program is an open-access, large-scale, population-based resource enrolling a diverse group of individuals living in the United States with longitudinal follow-up. The data encompass health questionnaires, physical measurements, electronic health records, and biospecimen data, accessible through the cloud-based Researcher Workbench platform.

We constructed 5 active-comparator, new-user cohort studies to evaluate the effectiveness of semaglutide on preventing new-onset seizures or epilepsy in patients with type 2 diabetes. We used a target trial emulation framework to estimate the comparative effectiveness of semaglutide vs alternative GLDs on the outcome. This approach addresses methodological challenges inherent in observational studies, including immortal time bias, depletion-of-susceptible bias, and prevalent user bias.[18] By emulating a hypothetical randomized controlled trial using detailed eligibility criteria, treatment strategies, and follow-up protocols aligned at time zero, we aimed to approximate the causal effects that would be observed in a randomized setting (eFigure 1; eTable 1).

Study Population

The study included patients with type 2 diabetes who had a new-user prescription (no use of either class in the prior 183 days) between January 1, 2018, and October 1, 2023. For population selection, type 2 diabetes was defined as International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification (ICD-10-CM) code E11 or International Classification of

Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 250.x0 or 250.x2, with explicit exclusion of type 1 diabetes codes (ICD-10-CM E10; ICD-9-CM 250.x1 or 250.x3). Source diagnosis codes were harmonized to Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) concepts within the Observational Medical Outcomes Partnership Common Data Model. Prior validation studies have reported sensitivity of 76%–97% and specificity of 94%–99% for diagnosis code–based diabetes definitions[19] and sensitivity of 91.6% and specificity of 98.1% for diagnosis code–based type 2 diabetes identification against American Diabetes Association–based criteria.[20] We conducted 2 primary comparisons evaluating semaglutide vs other GLDs and semaglutide vs SGLT2i. To distinguish between a semaglutide-specific effect vs a GLP-1RA class effect, we additionally compared other GLP-1RAs (excluding semaglutide) with the same comparators. Finally, we compared SGLT2i vs other GLDs as a reference comparison between 2 non-GLP-1RA classes. The index date was the first prescription of the treatment or comparator medications (eFigure 1; eTable 1–3).

Study Outcomes and Follow-Up

The primary outcome was incident adult-onset seizure excluding hypoglycemic seizure events; specifically, seizure events with a hypoglycemia diagnosis on the same calendar day were excluded. Outcomes were identified through 1 or more diagnosis codes from the ICD-10-CM; the ICD-9-CM; or the SNOMED-CT (eTable 4). For the broad seizure/epilepsy code set using G40 and R56, published validation showed sensitivity 97.7%, specificity 44.1%, and positive predictive value 96.2%.[21] To address the limited specificity for epilepsy in the broad definition, we conducted sensitivity analyses using stricter epilepsy-oriented definitions: a G40-only definition with sensitivity 84.4%, specificity 79.4%, and positive predictive value 98.3%[21] and a recurrent-seizure definition requiring either an epilepsy diagnosis (G40) or at least 2 seizure events. Given the distinct etiologic profile of seizure among adults aged 60 years or older, we also examined late-onset seizure as a secondary outcome in a cohort restricted to patients aged 60 years or older at the index date. Patients were followed up from the index date until the earliest of the following events: occurrence of the outcome; death; last observation; or to the end of the study period on October 1, 2023. We used an intention-to-treat approach where patients were analyzed according to their initial treatment regardless of discontinuation or switching.

Covariates

The propensity score model incorporated 46 baseline covariates selected to capture clinically relevant factors that guide treatment selection among GLD classes (eTable 2, 3, and 5). Baseline covariates included demographics, comorbidities, medications, and HbA1c. Race and ethnicity data were extracted from the survey data. Race and ethnicity categories included Hispanic, non-Hispanic Black, non-Hispanic White, and Non-Hispanic Others (e.g., Middle Eastern/North African, Native Hawaiian/Pacific Islander, American Indian/Alaska Native). Comorbidities were defined using the modified Charlson Comorbidity Index,[22] a validated tool widely used in internal medicine to systematically assess patients' comorbidity burden and included conditions that directly influence prescribing decisions under current American Diabetes Association for the Study of Diabetes consensus algorithms.[9] Baseline HbA1c and BMI were included as primary metabolic parameters driving treatment intensification, and 18 comedication classes were captured to reflect concomitant cardiovascular and metabolic pharmacotherapy. Socioeconomic factors were included to account for differential access to newer agents. All comorbidities were assessed at or up to 2 years before index date, and medications were assessed at or up to 1 year before index date. The most recent BMI and HbA1c values measured before the index date were used and missing values were handled using the multiple imputation method.[23]

Statistical Analysis

Continuous variables were summarized as mean (±SD), while categorical variables were reported as counts and percentages. Baseline characteristics were compared between treatment groups using standardized mean differences (SMDs), with SMD <0.15 indicating adequate balance between groups. The Wilcoxon rank-sum test with continuity correction was used to compare follow-up times between groups when distributions were non-normal. Statistical analyses were performed using R version 4.3.1 within the Jupyter Notebook environment on the *All of Us* Researcher Workbench platform.

To estimate the causal effects of each drug group on epilepsy and seizure risk, we used 2 complementary methods within a target trial emulation framework: inverse probability of treatment weighting (IPTW) and targeted maximum likelihood estimation (TMLE).

IPTW cohorts were constructed to simulate randomized allocation across treatment groups. This method creates a pseudopopulation by weighting individuals according to the inverse probability of receiving their observed treatment, estimated from logistic regression models incorporating all baseline covariates, thereby balancing groups and reducing confounding.[24] Weights were truncated at the 1st and 99th percentiles to minimize the influence of extreme values, then standardized to maintain the original sample size. In this weighted pseudopopulation, we generated adjusted Kaplan–Meier curves to illustrate the time-to-event incidence of epilepsy and seizure and estimated adjusted hazard ratios (HRs) with 95% CIs using weighted Cox proportional hazards models.

TMLE was implemented to provide additional validation through a doubly robust approach. This semiparametric method combines propensity score and outcome regression models, enabling valid estimation when either is correctly

specified.[25] TMLE was fit in the unweighted emulated cohorts rather than in the inverse probability weighted pseudopopulation. We targeted the marginal risk difference for incident adult-onset seizure over the observed follow-up, with administrative censoring on October 1, 2023. Generalized linear models were used for the outcome and treatment mechanisms. Using TMLE, we calculated the risk difference and number needed to treat for each comparison. Bootstrap resampling (n = 1,000) was used to generate nonparametric bootstrap CI and distribution plots of the risk differences for key comparisons.

To investigate whether glycemic control and BMI reduction mediate the relationship between medication class and neurologic outcomes, we conducted a counterfactual mediation analysis for time-to-event outcomes with a repeatedly measured mediator, following the framework of Vansteelandt et al.[26] All analyses were performed on the unweighted raw cohort. To approximate the longitudinal mediator process, we divided follow-up into fixed 12-month windows up to 48 months. Within each window, we summarized the mediator as the mean of all measurements obtained before the subject's event or censoring; if no value was available in a window, we carried forward the last observed value from the prior window. We then fit a period-stratified Cox proportional hazards model that allowed the baseline risk to differ by window while adjusting for treatment and a baseline mediator value. Mediator trajectories were modeled using a linear model. We quantified uncertainty using a parametric bootstrap (n = 100) that accounts for uncertainty in the survival model and in the simulated mediator paths. Detailed method of the mediation analysis is described in eMethods.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was reviewed and approved by the *All of Us* Institutional Review Board.[27] This investigation involved secondary analysis of deidentified data, with no direct intervention or interaction with patients. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology and Transparent Reporting of Observational Studies Emulating a Target Trial guidelines. In accordance with the *All of Us* Data and Statistics Dissemination Policy, participant counts of 1–20 were suppressed to protect privacy.

Data Availability

The authors are third-party users of US claims data. The respective data use agreements and licensing agreements do not allow sharing of patient-level data with third parties. However, interested parties can contact the authors and request replication analyses. The core R source code for all analyses is publicly available on GitHub at github.com/yongeun/semaglutide-seizure-aou.

Results

Study Population and Baseline Characteristics

From 393,596 participants in the *All of Us* Research Program, we identified 10,213 eligible patients for the semaglutide (n = 2,586) vs other GLDs (n = 7,627) comparison and 8,605 patients for the semaglutide (n = 2,814) vs SGLT2i (n = 5,791) comparison (Figure 1; Table 1; eTable 6). Baseline characteristics for each cohort are presented in Table 1.

Across both cohorts, patients receiving semaglutide were younger, demonstrated lower baseline HbA1c levels, and exhibited higher BMI compared with their respective comparison groups. In the semaglutide vs other GLDs cohort, the mean age was 60.1 years (SD 12.0) for the semaglutide group vs 63.7 years (SD 11.9) for the other GLDs group. Baseline HbA1c was lower in the semaglutide group (7.48% [SD 1.85]) compared with the other GLDs group (8.05% [SD 1.97]), whereas baseline BMI was notably higher (38.4 kg/m^2 [SD 8.45] vs 34.2 kg/m^2 [SD 7.74], respectively). The semaglutide vs SGLT2i cohort exhibited similar patterns, with the semaglutide group demonstrating younger age (60.5 years [SD 12.0] vs 64.4 years [SD 11.4] years), lower baseline HbA1c (7.56% [SD 1.85] vs 8.07% [SD 1.87]), and higher BMI (38.3 kg/m^2 [SD 8.36] vs 34.6 kg/m^2 [SD 7.72]). After IPTW, baseline covariates were well balanced between groups (all SMD <0.15).

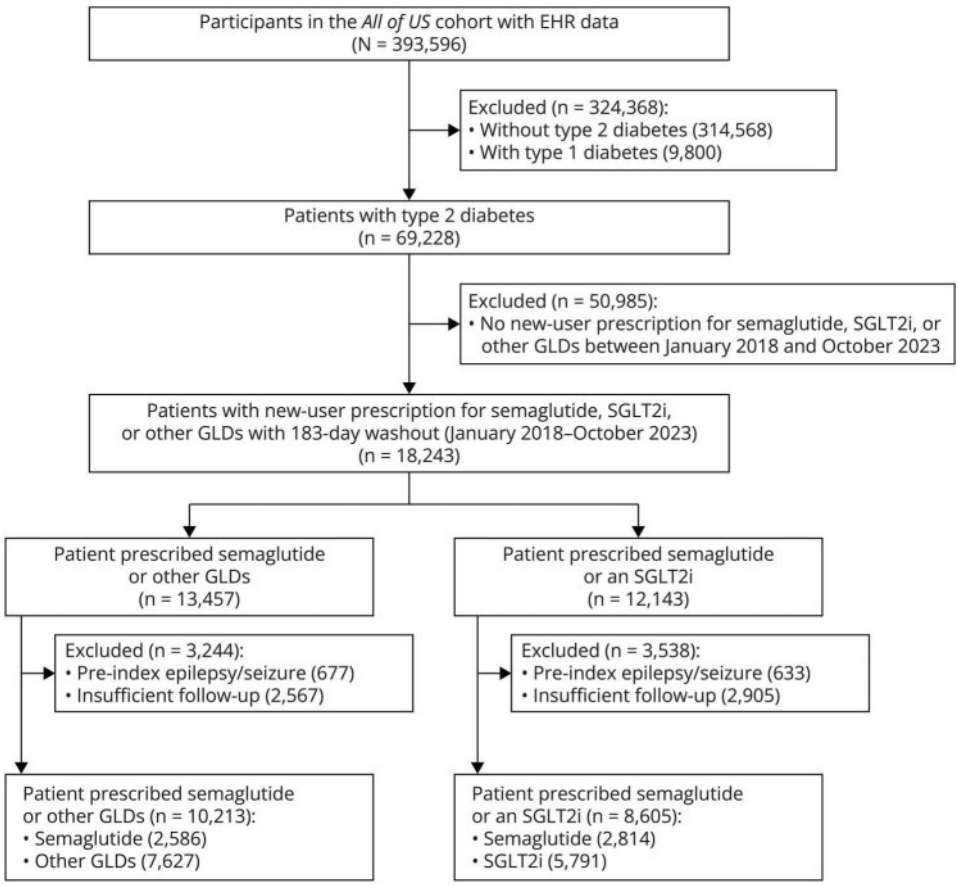
Semaglutide Showed Significantly Low Risk of Adult-Onset Seizure Occurrence

In the IPTW-weighted semaglutide vs other GLDs cohort, there were 24 events among 4,689 in the semaglutide group and 104 among 5,524 in the other GLDs group (Figure 2A; Table 2). Semaglutide use was associated with a significantly lower risk of adult-onset seizure, with a rate difference of −3.76 events per 1,000 person-years (95% CI −5.66 to −1.86), a 4-year risk difference of −1.78 percentage points (95% CI −2.58 to −0.98), and a weighted HR of 0.44 (95% CI 0.25–0.79, p = 0.006). Validation using TMLE analysis confirmed these results, showing 17 events in the 2,586 semaglutide group and 153 in the 7,627 other GLDs group, yielding a risk difference of −14.20 events per 1,000 persons over follow-up (95% CI −18.33 to −10.07, p < 0.001), corresponding to a number needed to treat of 70 (Figure 2, C and D; Table 2).

Semaglutide also demonstrated a significantly lower risk of adult-onset seizure compared with SGLT2i (Figure 2, B–D; Table 2). In the IPTW-weighted semaglutide vs SGLT2i cohort, there were 23 events among 4,235 in the semaglutide group and 56 among 4,370 in the SGLT2i group, with a rate difference of −3.26 events per 1,000 person-years (95% CI −5.38 to −1.13), a 4-year risk difference of −1.46 percentage points (95% CI −2.41 to −0.51), and a weighted HR of 0.48 (95% CI 0.27–0.85, p = 0.011) (Figure 2B; Table 2). TMLE produced consistent results, with 18 events in the 2,814 semaglutide group and 75 in the 5,791 SGLT2i group (risk difference −7.62 events per 1,000 persons over follow-up, 95% CI −11.65 to −3.60, p < 0.001; number needed to treat, 131) (Figure 2, C and D; Table 2).

In the secondary outcome analysis for late-onset seizure, the protective association of semaglutide with lower risk of epilepsy

Figure 1 Flow of Participants in the Study Cohort



Participants were identified from the *All of Us* Research Program (version 8) with available electronic health record data. Individuals with type 2 diabetes, excluding those with type 1 diabetes, were included if they had new-user prescriptions for semaglutide, SGLT2i, or other GLDs after a 183-day washout period between January 2018 and October 2023. Patients with preindex epilepsy or seizure diagnoses or insufficient follow-up were excluded. The final analytic cohorts consisted of patients prescribed semaglutide vs other GLDs and semaglutide vs other SGLT2i. GLD = glucose-lowering drug; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

and seizure was more pronounced (eFigure 2; eTable 7). Moreover, the observed protective effect on adult-onset seizure seemed to be specific to semaglutide. Other GLP-1RAs did not demonstrate significant protection effects compared with either other GLDs or SGLT2i (eFigure 3; eTable 8 and 9). Similarly, SGLT2i use was not associated with a significant risk difference in adult-onset seizure occurrence compared with other GLDs (eFigure 3; eTable 8 and 9).

Sensitivity and Subgroup Analyses

To further assess robustness, we performed 3 sets of sensitivity analyses. First, we repeated the analyses using stricter epilepsy-oriented outcome definitions, including a G40-only definition and a recurrent-seizure definition (≥2 seizure events) (eFigure 4). Second, to address temporal imbalance between the coronavirus disease 2019 (COVID-19) and non–COVID-19 periods and potential follow-up discrepancies related to staggered drug availability, we conducted exact calendar-year matching, a pre-COVID restricted analysis limited to 2018–2019, and an analysis restricted to patients with at least 2 years of follow-up (eFigure 5). Third, we evaluated alternative cohorts using propensity score matching with the original cohort and IPTW analysis excluding patients with severe renal disease and metastatic cancer (eFigure 6). Across all sensitivity analyses, the protective association of semaglutide vs other GLDs remained the most robust, with consistently significant or near-significant results across all analytic approaches (HR range 0.16–0.59). By contrast, SGLT2i showed inconsistent associations that varied across analytic approaches, and other GLP-1RAs showed modest but consistently nonsignificant associations.

In prespecified subgroup analyses, the comparison of semaglutide vs other GLDs showed significant heterogeneity by sex (p for interaction <0.001): The protective association was markedly stronger in men (HR 0.08; 95% CI 0.02–0.33; p < 0.001) than in women (HR 0.77; 95% CI 0.41–1.46; p = 0.426). No significant heterogeneity was observed by age (p for interaction = 0.406) or race/ethnicity (p for interaction = 0.140). For the comparison of semaglutide vs SGLT2i, no significant heterogeneity was detected across age (p = 0.547), sex (p = 0.271), or race/ethnicity (p = 0.890), with directionally consistent protective point estimates across all subgroups (eFigure 7).

Given the relatively small number of outcome events, we performed a leave-one-out analysis by refitting the IPTW-weighted Cox model after excluding each outcome event case in turn. In the semaglutide vs other GLDs comparison, the leave-one-out HRs ranged from 0.35 to 0.47, and in the

Table 1 Unweighted Baseline Characteristics of Patients With Type 2 Diabetes in the Adult-Onset Seizure Occurrence Analysis for Semaglutide vs Comparator Groups

	Semaglutide vs other GLDs (n = 10,213)				Semaglutide vs SGLT2i (n = 8,605)			
			SMD[a]				SMD[a]	
Characteristics	Semaglutide (n = 2,586)	Other GLDs (n = 7,627)	Before IPTW	After IPTW	Semaglutide (n = 2,814)	SGLT2i (n = 5,791)	Before IPTW	After IPTW
Demographics								
Age, y, mean (SD)	60.1 (12.0)	63.7 (11.9)	0.304	0.070	60.5 (12.0)	64.4 (11.4)	0.339	0.032
Sex, n (%)			0.212	0.038			0.388	0.019
Male	≥898 (34.7)	3,401 (44.6)			927 (32.9)	2,976 (51.4)		
Female	1,668 (64.6)	4,131 (54.2)			1,863 (66.2)	2,742 (47.3)		
Not specified/other	≤20 (0.8)	95 (1.3)			24 (0.9)	73 (1.3)		
Race and ethnicity, n (%)			0.185	0.059			0.150	0.027
Non-Hispanic White	1,465 (56.7)	3,617 (47.4)			1,629 (57.9)	2,958 (51.1)		
Non-Hispanic Black	504 (19.5)	1,704 (22.4)			559 (19.9)	1,198 (20.7)		
Hispanic	351 (13.6)	1,510 (19.8)			346 (12.3)	1,020 (17.6)		
Non-Hispanic others[b]	197 (7.6)	551 (7.2)			205 (7.3)	410 (7.1)		
Not specified/other	69 (2.7)	245 (3.2)			75 (2.7)	205 (3.5)		
Income, n (%)			0.198	0.046			0.138	0.020
<$50k	810 (31.3)	3,032 (39.8)			906 (32.2)	2,064 (35.6)		
$50k–100k	896 (34.6)	1,983 (26.0)			981 (34.9)	1,707 (29.5)		
>$100k	503 (19.5)	934 (12.2)			498 (17.7)	831 (14.3)		
Unknown[c]	377 (14.6)	1,678 (22.0)			429 (15.2)	1,189 (20.5)		
Education, n (%)			0.263	0.058			0.180	0.027
High school or less	612 (23.7)	2,712 (35.6)			682 (24.2)	1,870 (32.3)		
Some college	1,438 (55.6)	3,723 (48.8)			1,564 (55.6)	2,932 (50.6)		
Advanced degree	490 (18.9)	1,015 (13.3)			518 (18.4)	861 (14.9)		
Unknown[c]	46 (1.8)	177 (2.3)			50 (1.8)	128 (2.2)		
Insurance n (%)			0.266	0.055			0.226	0.013
None	68 (2.6)	469 (6.1)			76 (2.7)	263 (4.5)		
Public	1,188 (45.9)	4,287 (56.2)			1,320 (46.9)	3,277 (56.6)		
Private	1,071 (41.4)	2,197 (28.8)			1,139 (40.5)	1,722 (29.7)		
Unknown[c]	259 (10.0)	674 (8.8)			279 (9.9)	529 (9.1)		
Calendar year (index date), n (%)			0.743	0.107			0.139	0.017
COVID (2020–2022)	1,772 (68.5)	2,572 (33.7)			1,922 (68.3)	3,573 (61.7)		
Non-COVID (2018, 2019, 2023)	814 (31.5)	5,055 (66.3)			892 (31.7)	2,218 (38.3)		
Baseline HbA1c, %, mean (SD)	7.48 (1.85)	8.05 (1.97)	0.300	0.020	7.56 (1.85)	8.07 (1.87)	0.276	0.053
Baseline BMI, kg/m^2, mean (SD)	38.4 (8.45)	34.2 (7.74)			38.3 (8.36)	34.6 (7.72)		
Baseline BMI category, n (%)			0.389	0.083			0.349	0.078
Underweight (≤18.5)	0 (0.0)	32 (0.4)			0 (0.0)	21 (0.4)		
Normal (>18.5–≤25)	50 (1.9)	606 (7.9)			42 (1.5)	387 (6.7)		

Continued

Table 1 Unweighted Baseline Characteristics of Patients With Type 2 Diabetes in the Adult-Onset Seizure Occurrence Analysis for Semaglutide vs Comparator Groups *(continued)*

Characteristics	Semaglutide vs other GLDs (n = 10,213)				Semaglutide vs SGLT2i (n = 8,605)			
			SMD[a]				SMD[a]	
	Semaglutide (n = 2,586)	Other GLDs (n = 7,627)	Before IPTW	After IPTW	Semaglutide (n = 2,814)	SGLT2i (n = 5,791)	Before IPTW	After IPTW
Overweight (>25–≤30)	320 (12.4)	1,767 (23.2)			361 (12.8)	1,342 (23.2)		
Obese I (>30–≤35)	622 (24.1)	2,170 (28.5)			701 (24.9)	1,632 (28.2)		
Obese II (>35–≤40)	646 (25.0)	1,566 (20.5)			689 (24.5)	1,206 (20.8)		
Obese III (>40)	948 (36.7)	1,486 (19.5)			1,021 (36.3)	1,203 (20.8)		
Smoking			0.100	0.023			0.077	0.022
Never	1,402 (54.2)	3,963 (52.0)			1,521 (54.1)	2,907 (50.2)		
Former	821 (31.7)	2,326 (30.5)			888 (31.6)	1,946 (33.6)		
Current	275 (10.8)	1,057 (13.9)			294 (10.4)	729 (12.6)		
Unknown[c]	87 (3.4)	277 (3.6)			111 (3.9)	209 (3.6)		
Alcohol			0.138	0.041			0.117	0.012
Low risk	1,735 (67.1)	4,614 (60.5)			1,903 (67.6)	3,593 (62.0)		
Increased risk	118 (4.6)	408 (5.3)			119 (4.2)	326 (5.6)		
High risk	30 (1.2)	107 (1.4)			30 (1.1)	80 (1.4)		
Dependent	≤20 (0.8)	21 (0.3)			≤20 (0.7)	≤20 (0.3)		
Unknown[c]	≥672 (26.4)	2,468 (32.5)			≥734 (26.4)	≥1,756 (30.7)		
Diabetic complications								
Diabetic retinopathy, n (%)	237 (9.2)	560 (7.3)	0.066	0.007	242 (8.6)	595 (10.3)	0.055	0.016
Diabetic neuropathy, n (%)	526 (20.3)	1,479 (19.4)	0.024	0.000	578 (20.5)	1,456 (25.1)	0.109	0.020
Hypoglycemia, n (%)	88 (3.4)	204 (2.7)	0.042	0.005	90 (3.2)	196 (3.4)	0.007	0.006
Hyperglycemic emergency, n (%)	52 (2.0)	135 (1.8)	0.018	0.004	59 (2.1)	123 (2.1)	0.001	0.009
Comorbidities								
Myocardial infarction, n (%)	119 (4.6)	438 (5.7)	0.052	0.006	103 (3.7)	572 (9.9)	0.185	0.064
Congestive heart failure, n (%)	285 (11.0)	783 (10.3)	0.021	0.027	264 (9.4)	1,312 (22.7)	0.369	0.047
Peripheral vascular disease, n (%)	240 (9.3)	674 (8.8)	0.013	0.011	249 (8.8)	788 (13.6)	0.152	0.028
Cerebrovascular disease, n (%)	160 (6.2)	564 (7.4)	0.048	0.003	177 (6.3)	567 (9.8)	0.129	0.022
Dementia, n (%)	29 (1.1)	116 (1.5)	0.033	0.013	32 (1.1)	106 (1.8)	0.060	0.013
Chronic pulmonary disease, n (%)	676 (26.1)	1,757 (23.0)	0.078	0.019	732 (26.0)	1,439 (24.8)	0.032	0.004
Connective tissue rheumatic disease, n (%)	123 (4.8)	276 (3.6)	0.056	0.008	136 (4.8)	221 (3.8)	0.048	0.001
Peptic ulcer disease, n (%)	47 (1.8)	124 (1.6)	0.010	0.011	47 (1.7)	103 (1.8)	0.011	0.017
Liver disease[d]			0.102	0.033			0.039	0.015
Mild, n (%)	396 (15.3)	887 (11.6)			432 (15.4)	808 (14.0)		
Moderate to severe, n (%)	27 (1.1)	80 (1.1)			27 (1.0)	75 (1.3)		
Hemiplegia or paraplegia, n (%)	≤20 (0.8)	61 (0.8)	0.016	0.009	≤20 (0.7)	62 (1.1)	0.047	0.023

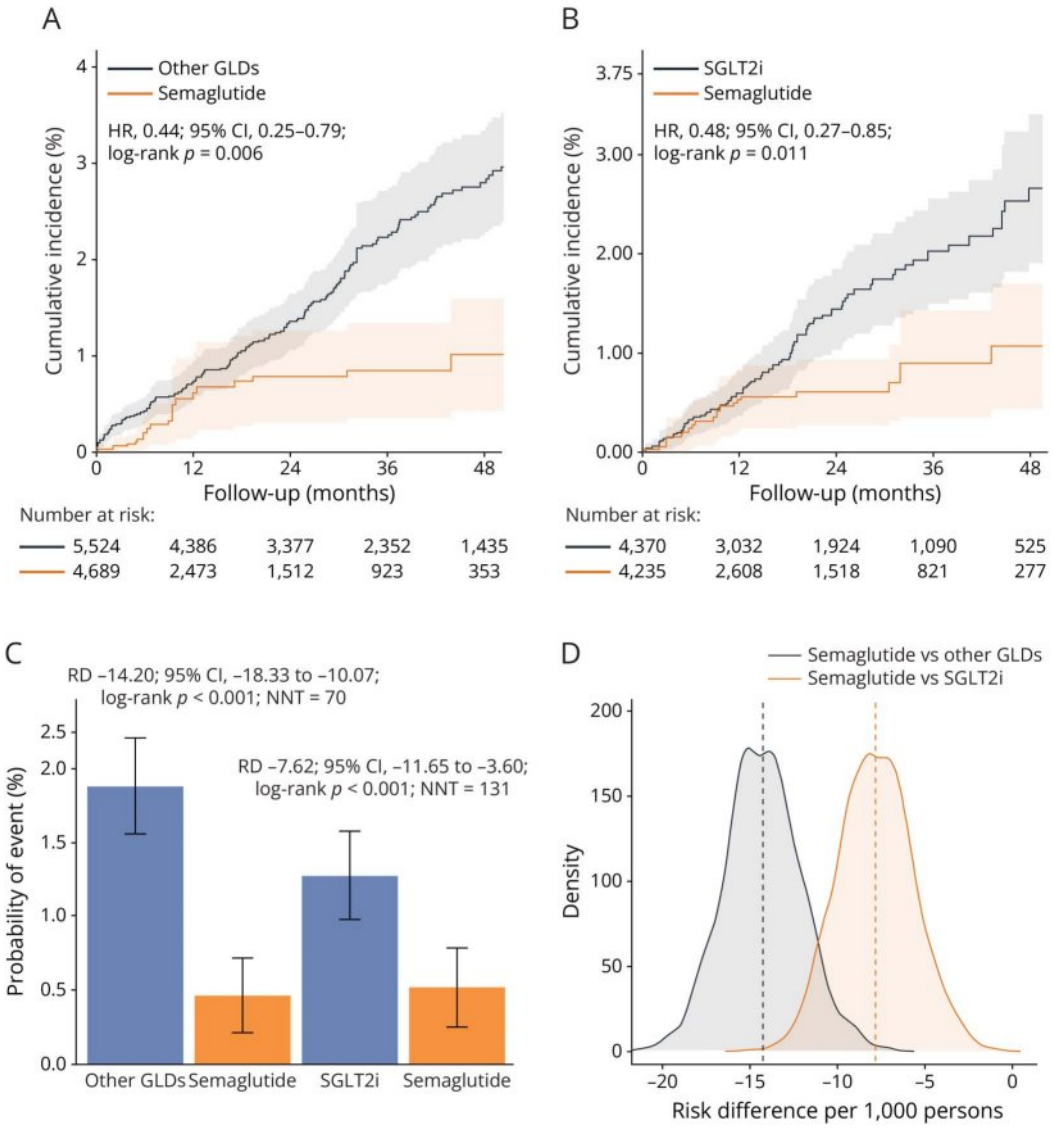
Continued

Table 1 Unweighted Baseline Characteristics of Patients With Type 2 Diabetes in the Adult-Onset Seizure Occurrence Analysis for Semaglutide vs Comparator Groups *(continued)*

Characteristics	Semaglutide vs other GLDs (n = 10,213)				Semaglutide vs SGLT2i (n = 8,605)			
			SMD[a]				SMD[a]	
	Semaglutide (n = 2,586)	Other GLDs (n = 7,627)	Before IPTW	After IPTW	Semaglutide (n = 2,814)	SGLT2i (n = 5,791)	Before IPTW	After IPTW
Renal disease[e]			0.064	0.002			0.191	0.010
Mild to moderate, n (%)	328 (12.7)	1,000 (13.1)			353 (12.5)	1,147 (19.8)		
Severe n (%)	41 (1.6)	183 (2.4)			48 (1.7)	91 (1.6)		
Malignancy			0.093	0.046			0.083	0.038
Nonmetastatic, n (%)	198 (7.7)	634 (8.3)			218 (7.7)	561 (9.7)		
Metastatic, n (%)	≤20 (0.8)	107 (1.5)			≤20 (0.7)	60 (1.1)		
HIV/AIDS, n (%)	29 (1.1)	94 (1.2)	0.007	0.002	35 (1.2)	95 (1.6)	0.034	0.002
Medications								
Anticoagulants, n (%)	210 (8.1)	576 (7.6)	0.018	0.004	218 (7.7)	799 (13.8)	0.198	0.045
Antiplatelet agents, n (%)	128 (4.9)	436 (5.7)	0.030	0.005	134 (4.8)	561 (9.7)	0.190	0.018
RAAS inhibitors, n (%)	1,328 (51.4)	4,008 (52.6)	0.025	0.033	1,482 (52.7)	3,518 (60.7)	0.160	0.001
Beta-blockers, n (%)	812 (31.4)	2,386 (31.3)	0.001	0.018	859 (30.5)	2,419 (41.8)	0.234	0.022
Calcium channel blockers, n (%)	614 (23.7)	1,861 (24.4)	0.014	0.007	656 (23.3)	1,624 (28.0)	0.105	0.005
Diuretics, n (%)	784 (30.3)	2,026 (26.6)	0.084	0.021	824 (29.3)	2,067 (35.7)	0.137	0.028
Mineralocorticoid receptor antagonists, n (%)	171 (6.6)	314 (4.1)	0.107	0.004	144 (5.1)	620 (10.7)	0.203	0.068
Other antihypertension agents, n (%)	117 (4.6)	439 (5.8)	0.043	0.015	102 (3.7)	565 (9.9)	0.061	0.008
Statin, n (%)	1,463 (56.6)	4,424 (58.0)	0.033	0.016	1,620 (57.6)	3,951 (68.2)	0.224	0.011
Ezetimibe, n (%)	87 (3.4)	140 (1.8)	0.097	0.020	83 (2.9)	237 (4.1)	0.062	0.008
Biguanides, n (%)	1,495 (57.8)	4,608 (60.4)	0.044	0.018	1,631 (58.0)	3,540 (61.1)	0.058	0.014
Insulin, n (%)	904 (35.0)	2,325 (30.5)	0.103	0.024	937 (33.3)	2,247 (38.8)	0.117	0.029
Sulfonylurea, n (%)	0 (0.0)	4,379 (57.4)	—	—	438 (15.6)	1,341 (23.2)	0.195	0.019
DPP4i, n (%)	0 (0.0)	2,403 (31.5)	—	—	236 (8.4)	773 (13.3)	0.161	0.019
Thiazolidinediones, n (%)	0 (0.0)	942 (12.4)	—	—	76 (2.7)	237 (4.1)	0.078	0.001
SGLT2i, n (%)	456 (17.6)	652 (8.5)	0.277	0.076	0 (0.0)	5,791 (100.0)	—	—
Semaglutide, n (%)	2,586 (100.0)	0 (0.0)	—	—	2,814 (100.0)	0 (0.0)	—	—
Other GLP-1RAs, n (%)	587 (22.7)	599 (7.9)	0.428	0.044	608 (21.6)	1,016 (17.5)	0.103	0.043

Abbreviations: BMI = body mass index; COVID = coronavirus disease 2019; DPP4i = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; GLD = glucose-lowering drug; GLP-1RAs = glucagon-like peptide-1 receptor agonists; IPTW = inverse probability of treatment weighting; RAAS = renin-angiotensin-aldosterone system; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SMD = standardized mean difference.
In accordance with the *All of Us* Data and Statistics Dissemination Policy, participant counts of 1–20 were suppressed to protect privacy.
[a] Absolute values are shown.
[b] Includes Asian American, Middle Eastern/North African, Native Hawaiian/Pacific Islander, American Indian/Alaska Native.
[c] Patients who declined to provide a response.
[d] Liver disease; mild: chronic hepatitis (or cirrhosis without complications); moderate to severe: conditions with clinical decompensation, including esophageal varices, hepatic failure, and hepatorenal syndrome according to modified Charlson Comorbidity Index.
[e] Renal disease; mild to moderate: stage 1–4 kidney disease (eGFR >15 mL/min/1.73 m^2); severe: stage 5 kidney disease (GFR <15 mL/min/1.73 m^2) and end-stage renal disease according to modified Charlson Comorbidity Index.

Figure 2 Comparative Effectiveness of Semaglutide on Adult-Onset Seizure Risk



(A and B) IPTW-adjusted cumulative incidence curves comparing semaglutide with other GLDs and with SGLT2i over the study period. (C) TMLE-adjusted risk differences per 1,000 persons estimates between treatment groups. (D) Bootstrap distributions of TMLE risk differences across 1,000 iterations. Note that the median risk differences observed in the bootstrap distributions (D) may differ slightly from the primary TMLE point estimates shown in (C). GLD = glucose-lowering drug; HbA1c = hemoglobin A1c; IPTW = inverse probability of treatment weighting; NNT = number needed to treat; RD = risk difference; SGLT2i = sodium-glucose cotransporter-2 inhibitors; TMLE = targeted maximum likelihood estimation.

semaglutide vs SGLT2i comparison, the HRs ranged from 0.41 to 0.50 (eTable 10). We also computed *E*-values to quantify the strength of unmeasured confounding that would be required to fully explain the observed associations. The *E*-value was 3.97 for semaglutide vs other GLDs and 3.59 for semaglutide vs SGLT2i (eTable 11).

The Protective Effect on Adult-Onset Seizure of Semaglutide Was Independent of HbA1c and BMI Mediation

To explore potential mechanisms, we conducted mediation analyses to evaluate the roles of HbA1c and BMI within each treatment comparison. To accommodate the longitudinal time to event structure, we used the Vansteelandt framework for survival mediation[26] and defined the mediators as mean HbA1c and mean BMI during the first year after the index date.

First, we confirmed that semaglutide significantly improved glycemic control and reduced BMI compared with other GLDs and SGLT2i, consistent with prior reports (eTable 12 and 13).[10,11] In the causal mediation analyses, HbA1c and BMI accounted for a minimal proportion of the association with adult-onset seizure over 48 months of follow-up (HbA1c: 2.4% vs other GLDs; 6.5% vs SGLT2i, BMI: 0% vs other GLDs; 0.7% vs SGLT2i), implying a protective mechanism largely independent of glycemic control and BMI reduction (eTable 14 and 15). Counterfactual cumulative-incidence analyses yielded consistent results: When the

Table 2 Protective Effect of Semaglutide on Adult-Onset Seizure Compared with Other GLDs or SGLT2i

	Semaglutide vs other GLDs		Semaglutide vs SGLT2i	
	Semaglutide	**Other GLDs**	**Semaglutide**	**SGLT2i**
Nonweighted cohort				
No. of events/no. of patients at risk	17/2,586	153/7,627	18/2,814	75/5,791
Follow-up years, mean (SD)	1.55 (1.21)	2.80 (1.66)	1.61 (1.24)	1.98 (1.46)
Unadjusted HR	0.56 (0.34 to 0.92), $p = 0.023$	1 (reference)	0.59 (0.35 to 0.99), $p = 0.047$	1 (reference)
IPTW-weighted cohort				
No. of events/no. of patients at risk	24/4,689	104/5,524	23/4,235	56/4,370
Follow-up years, mean (SD)	1.56 (1.38)	2.65 (1.63)	1.69 (1.30)	2.00 (1.44)
Incidence rate per 1,000 person-years (95% CI)	3.34 (2.01 to 4.66)	7.10 (5.73 to 8.46)	3.17 (1.87 to 4.47)	6.42 (4.74 to 8.11)
Rate difference per 1,000 person-years (95% CI)	−3.76 (−5.66 to −1.86)		−3.26 (−5.38 to −1.13)	
4-y cumulative incidence, % (95% CI)	1.01 (0.42 to 1.59)	2.79 (2.25 to 3.34)	1.07 (0.43 to 1.70)	2.53 (1.82 to 3.24)
4-y risk difference, % (95% CI)	−1.78 (−2.58 to −0.98)		−1.46 (−2.41 to −0.51)	
Weighted HR (95% CI)	0.44 (0.25 to 0.79), $p = 0.006$	1 (reference)	0.48 (0.27 to 0.85), $p = 0.011$	1 (reference)
TMLE analysis				
Risk ratio (95% CI)	0.25 (0.14 to 0.44), $p < 0.001$	1 (reference)	0.41 (0.23 to 0.71), $p = 0.002$	1 (reference)
Risk difference per 1,000 persons (95% CI)	−14.20 (−18.33 to −10.07), $p < 0.001$		−7.62 (−11.65 to −3.60), $p < 0.001$	
Number needed to treat	70		131	

Abbreviations: GLD = glucose-lowering drug; HR = hazard ratio; IPTW = inverse probability of treatment weighting; SGLT2i = sodium-glucose cotransporter 2 inhibitors; TMLE = targeted maximum likelihood estimation.

HbA1c and BMI pathways were set to a no-mediation scenario, the resulting incidence curves of adult-onset seizure nearly superimposed on the original curve throughout follow-up, indicating minimal mediation by HbA1c and BMI (Figure 3; eFigure 8).

This study provides Class II evidence that semaglutide use was associated with a lower risk of adult-onset seizures compared with other GLDs and SGLT2is.

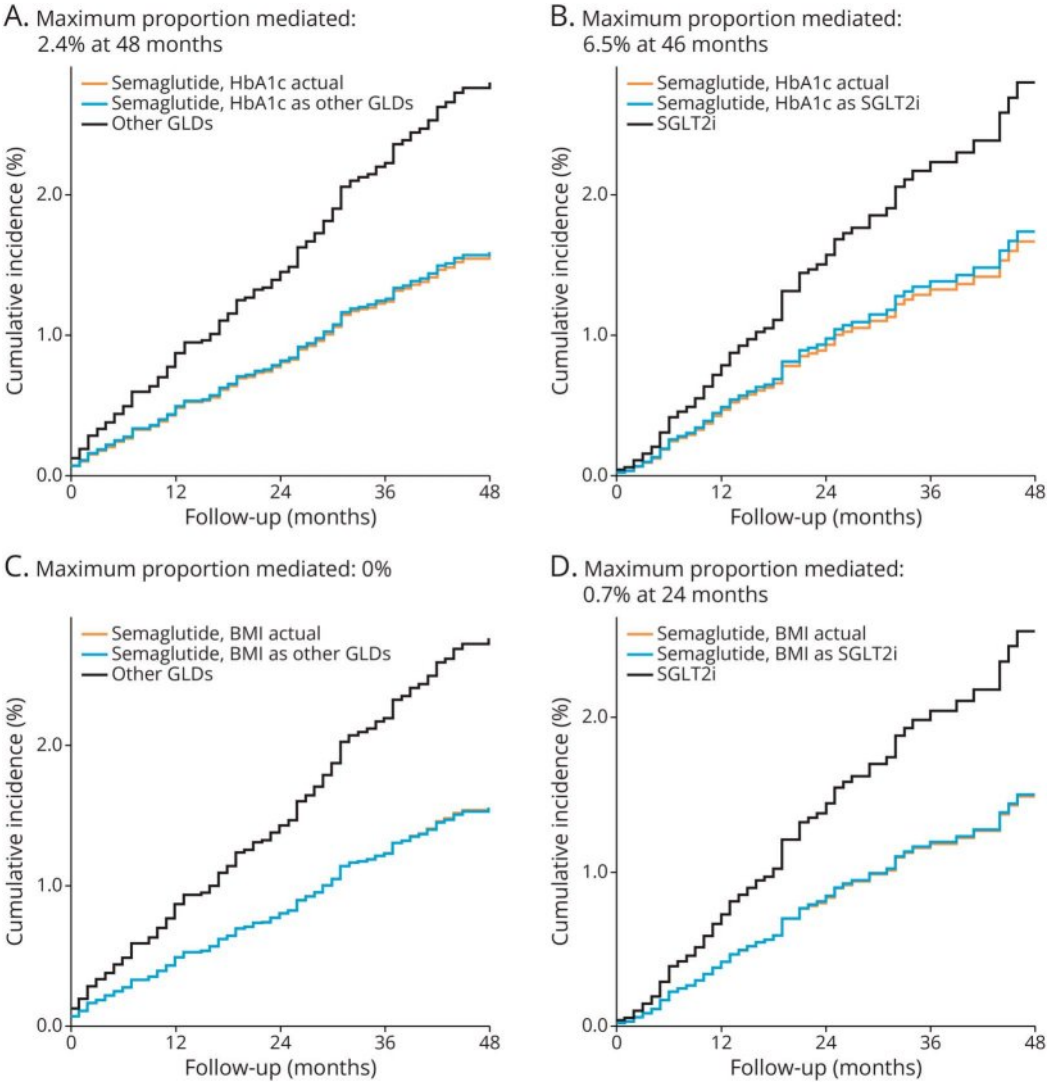
Discussion

In this population-based target trial emulation, semaglutide use was associated with a lower risk of incident adult-onset seizure compared with SGLT2i and other GLDs in adults with type 2 diabetes. The association was consistent across complementary causal inference approaches, including IPTW and TMLE, and longitudinal mediation analyses indicated that changes in HbA1c and BMI contributed only minimally to the observed association. In the secondary outcome analysis, the association was more pronounced for late-onset seizure.

Our primary outcome was incident adult-onset seizure identified using diagnosis codes, a broader endpoint than the conventional epilepsy definition of at least 2 unprovoked seizures[28]; therefore, it may include single seizures and potentially provoked events. Within this broader outcome framework, semaglutide initiation was associated with a lower risk of adult-onset seizure. Sensitivity analyses using stricter epilepsy-oriented definitions, including the G40-only definition and the recurrent-seizure definition, showed estimates in the same direction, suggesting that semaglutide may be associated not only with lower seizure risk but also with lower epilepsy risk.

The seizure-protective association observed with semaglutide suggests attenuation of acquired brain insults that accumulate with age. Evidence from studies of cerebrovascular and neurodegenerative disorders indicates benefits that extend beyond metabolic control and microvascular protection.[10,14,15,29,30] In our mediation analysis, changes in HbA1c and BMI accounted for little of the association, consistent with a recent analysis from the SELECT trial.[31] This pattern points to mechanisms distinct from those implicated in metabolic dysfunction-associated steatohepatitis or chronic kidney disease, in which metabolic drivers mediate a larger share.[32,33] The more pronounced association in late-onset seizure further supports the possibility that semaglutide limits age-related brain insults and thereby lowers the risk of adult-onset seizure.

Figure 3 Mediation Analysis of HbA1c and BMI in the Association Between Semaglutide and Adult-Onset Seizure Risk



Counterfactual mediation models assessing the proportion of the association between semaglutide use and epilepsy risk explained by glycemic control (HbA1c) and BMI over 48 months of follow-up. (A) HbA1c mediation comparing semaglutide with other GLDs. (B) HbA1c mediation comparing semaglutide with SGLT2i. (C) BMI mediation comparing semaglutide with other GLDs. (D) BMI mediation comparing semaglutide with SGLT2i. BMI = body mass index; GLD = glucose-lowering drug; HbA1c = hemoglobin A1c; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

In addition, semaglutide may exert direct antiepileptogenic effects by modulating neuroinflammatory pathways. Diverse etiologies of adult-onset seizure disorder often converge on neuroinflammation,[34-36] consistent with current concepts of epileptogenesis.[37] This is well illustrated in autoimmune encephalitis cohorts, including LGI1-antibody encephalitis,[38] and in status epilepticus,[39,40] where responsiveness to immunotherapies has been reported. Although GLP-1RAs broadly possess anti-inflammatory properties beyond metabolic benefit,[41,42] and experimental models have demonstrated anti-epileptogenic effects,[43] seizure risk reduction in our analyses was observed with semaglutide but not with other GLP-1RAs, suggesting a drug-specific rather than class-wide mechanism.

Semaglutide's distinct pharmacology may underlie this specificity.[41] Semaglutide's reversible albumin binding prolongs half-life and enables sustained receptor engagement,[44] potentially enhancing cumulative immunomodulatory signaling. In contrast to several GLP-1RAs that are structurally distinct from human GLP-1 or covalently linked to large proteins with limited blood–brain barrier penetration,[45,46] semaglutide can partially access the CNS.[47] Because epileptogenesis is largely mediated by microglial and astrocytic inflammatory signaling,[48] central exposure may be critical. Consistent with this, semaglutide produces substantial reductions in systemic inflammatory markers[49] and suppresses microglial activation in preclinical models,[50] supporting indirect neuroimmune modulation rather than direct anti-seizure activity.[43] Dose and formulation data in *All of Us* were unavailable, precluding dose-specific comparisons, and given marked heterogeneity in GLP-1RA structure and blood–brain barrier penetrance, the observed association may reflect semaglutide-specific neuropharmacology

rather than a class effect. Given semaglutide's emerging role in other neurodegenerative disorders,[15,30] delineating these specific neuropharmacologic drivers is a priority.

These findings should be interpreted with caution. Our study is a target trial emulation and did not directly measure biological mechanisms. Accordingly, although a direct antiseizure action of semaglutide is unlikely given its mechanism of action, we cannot fully exclude this possibility as an explanation for the observed reduction in the incidence of adult-onset seizure. For the mediation analysis, estimates are obtained under the standard identifying assumptions for natural direct and indirect effects. Our implementation included treatment and the baseline mediator value, without additional adjustment for other baseline covariates. Thus, the mediation results should be interpreted as an assumption-based decomposition of the observed association, rather than as effects of a feasible intervention that directly manipulates HbA1c or BMI.

Follow-up was shorter in semaglutide users than in comparator groups. Because semaglutide was approved on December 5, 2017, treatment initiation was concentrated in later calendar years, creating temporal imbalance and overlap with pre–COVID-19 vs post–COVID-19 periods. The pandemic may have affected health care utilization, treatment-seeking behavior, prescribing patterns, and seizure ascertainment.[51] We addressed this with exact calendar-year matching, a pre-COVID restricted analysis (2018–2019), and a minimum 2-year follow-up restriction, but residual confounding cannot be fully excluded. Longer follow-up is needed to assess durability of the association.

The modest number of outcome events also limits precision, particularly for subgroup and interaction analyses. The observed effect size for semaglutide (HR 0.44) is relatively large and may be partly influenced by low event counts and residual confounding. However, we performed additional sensitivity analyses to evaluate the robustness of our findings despite the limited event counts. Leave-one-out influence analyses demonstrated that excluding any single event case did not substantially alter the HR estimates, suggesting that the observed associations are not driven by a small number of influential cases. Furthermore, *E*-value calculations indicated that an unmeasured confounder would need to have a relatively strong association with both treatment and outcome to fully explain away the observed protective effect of semaglutide. These findings provide reassurance regarding the stability and reliability of our main results. Nevertheless, these results are best interpreted as hypothesis-generating rather than practice-changing, pending confirmation in larger randomized clinical trials.

In this population-based target trial emulation, semaglutide initiation was associated with a lower incidence of adult-onset seizure than active glucose-lowering comparators, a pattern not fully accounted for by glycemic or weight changes. Despite the inherent limitations of observational research that preclude definitive causal conclusions, these findings carry clinical relevance in a field where preventive options remain scarce. Confirmation through larger prospective and randomized studies with longer follow-up, alongside mechanistic investigations and trials in established epilepsy, will be essential to establish whether GLP-1 receptor agonism represents a viable preventive or disease-modifying strategy for adult-onset seizure and related neurologic disorders.

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Author Contributions

Y. Eun: 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. S. Bong: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. H.Y. Koh: analysis or interpretation of data. R.K. Trousdale: study concept or design; drafting/revision of the manuscript for content; analysis or interpretation of data. Y.M. Cho: analysis or interpretation of data. Y. Jang: 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. S.-T. Lee: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data.

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