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GLP-1RA and SGLT2i Medications for Type 2 Diabetes and Alzheimer Disease and Related Dementias

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IMPORTANCE The association between glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) and risk of Alzheimer disease and related dementias (ADRD) remains to be confirmed.

OBJECTIVE To assess the risk of ADRD associated with GLP-1RAs and SGLT2is in people with type 2 diabetes (T2D).

DESIGN, SETTING, AND PARTICIPANTS This target trial emulation study used electronic health record data from OneFlorida+ Clinical Research Consortium from January 2014 to June 2023. Patients were 50 years or older with T2D and no prior diagnosis of ADRD or antidementia treatment. Among the 396 963 eligible patients with T2D, 33 858 were included in the GLP-1RA vs other glucose-lowering drug (GLD) cohort, 34 185 in the SGLT2i vs other GLD cohort, and 24 117 in the GLP-1RA vs SGLT2i cohort.

EXPOSURES Initiation of treatment with a GLP-1RA, SGLT2i, or other second-line GLD.

MAIN OUTCOMES AND MEASURES ADRD was identified using clinical diagnosis codes. Hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazard regression models with inverse probability of treatment weighting (IPTW) to adjust for potential confounders.

RESULTS This study included 33 858 patients in the GLP-1RA vs other GLD cohort (mean age, 65 years; 53.1% female), 34 185 patients in the SGLT2i vs other GLD cohort (mean age, 65.8 years; 49.3% female), and 24 117 patients in the GLP-1RA vs SGLT2i cohort (mean age, 63.8 years; 51.7% female). In IPTW-weighted cohorts, the incidence rate of ADRD was lower in GLP-1RA initiators compared with other GLD initiators (rate difference [RD], −2.26 per 1000 person-years [95% CI, −2.88 to −1.64]), yielding an HR of 0.67 (95% CI, 0.47-0.96). SGLT2i initiators had a lower incidence than other GLD initiators (RD, −3.05 per 1000 person-years [95% CI, −3.68 to −2.42]), yielding an HR of 0.57 (95% CI, 0.43-0.75). There was no difference between GLP-1RAs and SGLT2is, with an RD of −0.09 per 1000 person-years (95% CI, −0.80 to 0.63) and an HR of 0.97 (95% CI, 0.72-1.32).

CONCLUSION AND RELEVANCE In people with T2D, both GLP-1RAs and SGLT2is were statistically significantly associated with decreased risk of ADRD compared with other GLDs, and no difference was observed between both drugs.

Editorial

Supplemental content

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Alzheimer disease and related dementias (ADRD), including Alzheimer disease (AD), characterized by a progressive decline in cognitive function, has emerged as a major global health challenge.[1] In the US, an estimated 6.9 million older adults lived with ADRD in 2023, with projections doubling by 2060.[2] ADRD is the fifth leading cause of death among older US residents, with an estimated cost of $360 billion related to ADRD in 2023.[2] Despite recent US Food and Drug Administration approvals of disease-modifying treatments for AD (eg, aducanumab, lecanemab, and donanemab), their efficacy and risks remain controversial.[3-5] Therefore, identifying alternative strategies to mitigate ADRD risk is crucial. Drug repurposing, the strategy of finding novel applications for existing drugs, presents an attractive approach to expedite the discovery of new treatments for ADRD.[6]

Newer glucose-lowering drugs (GLDs), particularly glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is), have gained prominence in the management of type 2 diabetes (T2D)[7] due to their additional cardiovascular, kidney, and weight loss benefits.[8-10] Recent studies have suggested that GLP-1RAs and SGLT2is may also mitigate ADRD pathophysiology,[11,12] with population-based studies indicating a potential association between their use and reduced ADRD risk.[13-15] However, their associations remain to be confirmed. To address this critical question and provide more definitive evidence, a population-based cohort study using a target trial emulation approach to assess the association between GLP-1RA and SGLT2i use and ADRD risk was conducted.

Key Points

Question What are the associations of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) with risk of Alzheimer disease and related dementias (ADRD) in people with type 2 diabetes (T2D)?

Findings In this target trial emulation study of people with T2D, both GLP-1RAs and SGLT2is were associated with a lower risk of ADRD than other second-line glucose-lowering drugs and there was no significant difference between GLP-1RAs and SGLT2is. The results were consistent across various sensitivity and subgroup analyses.

Meaning The results from this study support the neuroprotections of GLP-1RAs and SGLT2is, suggesting their possible role in ADRD prevention strategies in people with T2D.

Methods

Study Design

This retrospective, population-based cohort study emulated a target trial to assess the risk of ADRD among people with T2D, comparing those initiating an SGLT2i, GLP-1RA, or other second-line GLD. We followed the framework of target trial emulation, with key components outlined in eTable 1 in Supplement 1.[16,17] The University of Florida Institutional Review Board approved the study with a waiver of informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Data Source

This study used data from the OneFlorida+ Data Trust, a comprehensive health care data repository managed by the OneFlorida+ Clinical Research Consortium.[18] The OneFlorida+ Data Trust integrates longitudinal electronic health records linked with the National Death Index from multiple health care partners from Florida (~17 million patient records covering all 67 Florida counties), Georgia, and Alabama. As of 2023, it includes data on more than 21 million individuals, covering approximately 86% of Florida's population. The repository encompasses both inpatient and outpatient settings, providing a wide range of patient information, including demographics, diagnoses, medications (including both prescribed and dispensed medications), procedures, vital signs, and laboratory results.[19] Data are refreshed quarterly and adhere to the PCORnet Common Data Model, ensuring data quality and compatibility with national research networks. The Data Trust's broad coverage of diverse populations, including all age groups and racial and ethnic groups, enhances its generalizability for population health research.

Study Population

This study included eligible patients 50 years or older who initiated treatment with a GLP-1RA, SGLT2i, or other second-line GLD (sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 inhibitor [DPP4i], α-glucosidase inhibitor, or meglitinide) in OneFlorida+ between January 1, 2014 (the first SGLT2i was approved in 2013), and June 30, 2023. The treatment initiation date (index) was the date of the first prescription for a GLP-1RA, SGLT2i, or other second-line GLD, defined as without a previous prescription for either drug in the previous year. Additionally, the patients had to have a diagnosis of T2D before or on the index date. Patients with T2D were identified using at least 1 diagnosis code for T2D (eTable 2 in Supplement 1). One validation study conducted within PCORnet (including OneFlorida+) showed a high positive predictive value of 96.4% when using an inpatient or outpatient diagnosis code in combination with GLD use.[20] The eligibility criteria are included in eTable 1 in Supplement 1.

Treatments Under Comparison

In this study, we conducted the following 3 comparisons: (1) GLP-1RA initiators vs other second-line GLD initiators, (2) SGLT2i initiators vs other second-line GLD initiators, and (3) GLP-1RA initiators vs SGLT2i initiators. Details of drugs of interest are included in eTable 3 in Supplement 1. Insulin was excluded from the comparison due to its association with a longer duration of diabetes (a serious condition)[21] and an increased risk of all-cause dementia.[22,23]

Outcome Measures

The study end point was ADRD, including AD, as well as other forms of dementia, such as vascular dementia, frontotemporal dementia, and Lewy body dementia. To identify ADRD

cases, the study used the Chronic Conditions Data Warehouse (CCW) chronic condition algorithms.[24] The *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) diagnosis codes used for ADRD identification are detailed in eTable 2 in Supplement 1.

Study Follow-Up

This study followed an intention-to-treat approach so individuals remained in their initially assigned treatment group regardless of the discontinuation of the prescribed treatment (eFigure 1 in Supplement 1). Patients were followed up from treatment initiation until outcome onset, death, or end of the study (June 30, 2023), whichever occurred first.

Baseline Covariates

The baseline covariates were selected based on previous research findings[25,26] and clinical experience (eTable 4 in Supplement 1). We included demographic characteristics, socioeconomic factors, health care utilization, diabetes complications, and other comorbidities (occurring within the previous 2 years and classified as present if patient had at least 1 diagnosis code), as well as medication use (collected within the previous year and classified as yes/no). Additionally, the most recent HbA_{1c} and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) values within the previous year were collected. Obesity was classified based on either the presence of at least 1 obesity diagnosis code or a baseline BMI of 30 or greater.

Statistical Analysis

To account for the nonrandom allocation of patients receiving treatments in each comparison, we applied a standard inverse probability of treatment weighting (IPTW), aiming to maintain statistical power and precision, especially when dealing with rare outcomes.[27] The IPTW was derived from propensity scores, which were calculated from a multivariable logistic regression model that included baseline covariates. We used standardized mean difference (SMD) to assess the balance of confounders between groups before and after IPTW. The baseline covariates were considered negligible differences between groups if the SMD was less than 0.1.[28] We estimated the incidence of ADRD for each group and calculated the rate difference (RD) between groups. Additionally, we generated adjusted Kaplan-Meier curves to visualize the progression of ADRD over time and used a Cox proportional hazard model to estimate adjusted hazard ratios (HRs) with a 95% CI for ADRD.

Missing Data and Unmeasured Confounders

To address the presence of missing values in HbA_{1c} and BMI, we used multiple imputation by chained equation.[29] To determine the potential influence of unmeasured confounders on the observed treatment outcome association, we calculated the E-value, which is an alternative approach to sensitivity analyses for unmeasured confounding in observational studies that avoids making assumptions.[30]

Subgroup and Sensitivity Analyses

To investigate potential treatment association modification, we conducted the following subgroup analyses: (1) age (<65 or ≥65 years), (2) sex (female or male), (3) race and ethnicity (Hispanic, non-Hispanic Black, or non-Hispanic White), (4) obesity at baseline (yes or no), (5) metformin use at baseline (yes or no), (6) insulin use at baseline (yes or no), and (7) molecular structure of GLP-1RA (exenatide, dulaglutide, liraglutide, or semaglutide) or SGLT2i (canagliflozin, dapagliflozin, or empagliflozin).

To test the robustness of our findings, we performed the following sensitivity analyses: (1) using a 1:1 propensity score-matched Cox model; (2) excluding individuals with mild cognitive impairment at baseline; (3) excluding individuals with Parkinson disease at baseline; (4) excluding patients with a diagnosis of ADRD within 6 months after the index date given the potential lag period for a diagnosis of ADRD; (5) addressing the competing risk of death by using a Cox proportional hazards model with the Fine and Gray method[31]; and (6) using a per-protocol analysis, censoring patients when they discontinued, switched, or initiated another study medication. All analyses were performed using SAS version 9.4 (SAS Institute). *P* values were 2-sided and a *P* value of less than .05 was considered statistically significant.

Results

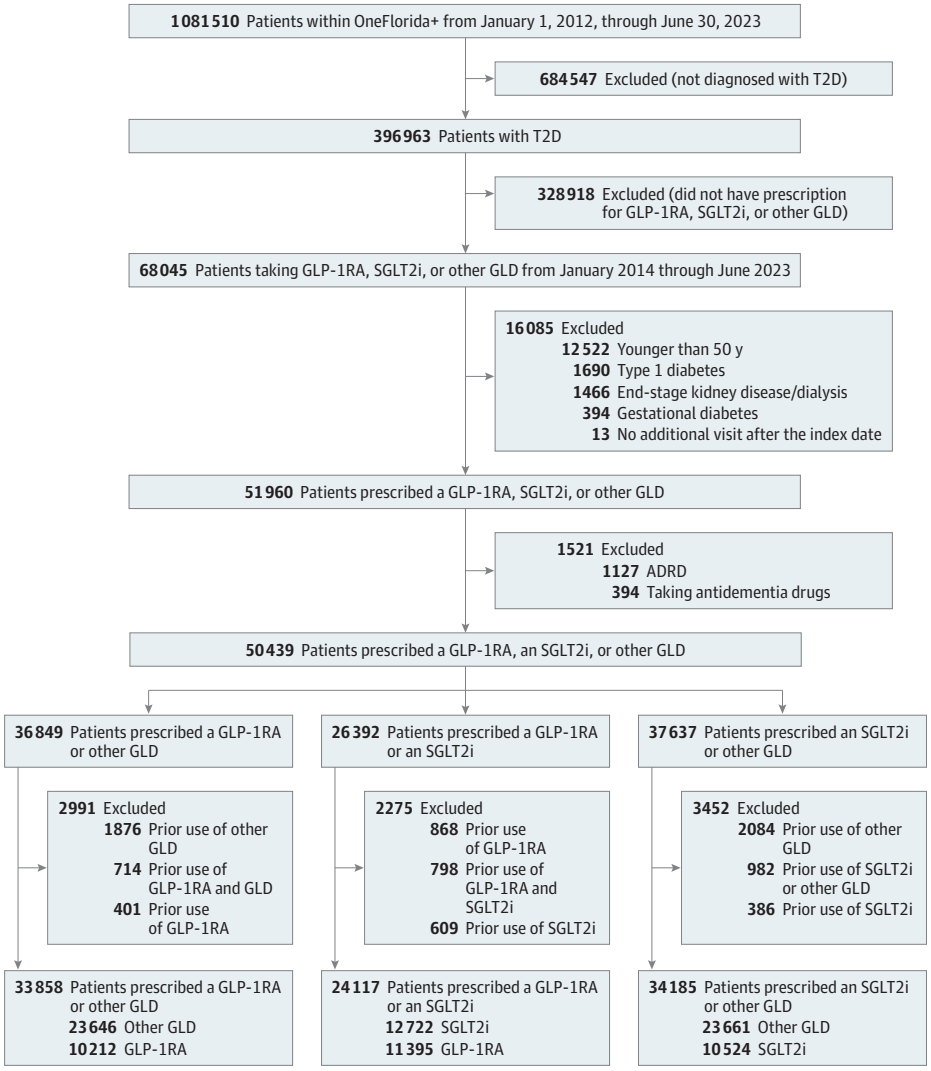
Study Population

The flowchart of patient selection based on the inclusion and exclusion criteria is presented in **Figure 1**. We included 33 858 patients with T2D in the GLP-1RA (n = 10 212) vs other GLD (n = 23 646) cohort, 34 185 patients in the SGLT2i (n = 10 524) vs other GLD (n = 23 661) cohort, and 24 117 patients in the GLP-1RA (n = 11 395) vs SGLT2i (n = 12 722) cohort. The baseline characteristics of the 3 study cohorts are presented in **Table 1** (eTable 5 in Supplement 1). The frequency of individual GLP-1RAs and SGLT2is used in each study cohort is detailed in eTable 6 in Supplement 1.

GLP-1RA vs Other GLD Cohort

GLP-1RA initiators were generally younger (62.3 vs 66.2 years) and had a higher percentage of females (58.8% vs 50.7%) with a higher mean baseline BMI (33.8 vs 30.7) compared with other GLD initiators. Additionally, they were more likely to use SGLT2is (3.6% vs 1.3%). After applying IPTW, all baseline covariates were well balanced, with SMDs less than 0.1. During follow-up, 75 ADRD cases were identified among GLP-1RA users (mean follow-up, 2.22 years) compared with 639 cases among other GLD users (mean follow-up, 3.74 years). The crude HR was 0.44 (95% CI, 0.34-0.55) (**Table 2**). In the IPTW-weighted cohort, incidence rates were 4.35 and 6.60 per 1000 person-years for the GLP-1RA and other GLD groups, respectively, yielding an RD of −2.26 (95% CI, −2.88 to −1.64) per 1000 person-years. GLP-1RA use was statistically significantly associated with a decreased risk of ADRD, with an adjusted HR of 0.67 (95% CI, 0.47-0.96). The adjusted Kaplan-Meier plot shows the cumulative incidence of ADRD (**Figure 2**). The re-

Figure 1. Flowchart of Patient Selection



GLD indicates glucose-lowering drug; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.

sults were consistent across sensitivity analyses (eFigure 2 in Supplement 1). Subgroup analyses revealed no potential association modification between GLP-1RAs and risk of ADRD (all *P* values >.05) (eFigure 3 in Supplement 1).

SGLT2i vs Other GLD Cohort

SGLT2i initiators were younger (64.8 vs 66.2 years) and more likely to use GLP-1RAs (5.9% vs 1.4%) with a higher mean baseline BMI (31.6 vs 30.7) compared with other GLD initiators. After applying IPTW, all baseline covariates achieved balance, with SMDs less than 0.1. During follow-up, 101 ADRD cases were identified among SGLT2i users (mean follow-up, 1.95 years) compared with 642 cases among other GLD users (mean follow-up, 3.76 years) (Table 2). The crude HR was 0.62 (95% CI, 0.50-0.76). In the IPTW-weighted cohort, incidence rates were 4.19 and 7.23 per 1000 person-years for the SGLT2i and other GLD groups, respectively, yielding an RD of −3.05 (95% CI, −3.68 to −2.42) per 1000 person-years. SGLT2i use was statistically significantly associated with a decreased risk of ADRD, with an adjusted HR of 0.57 (95% CI, 0.43-0.75). The IPTW-adjusted Kaplan-Meier plot shows the cumulative incidence of ADRD (Figure 2). The findings were consistent across all sensitivity analyses (eFigure 2 in Supplement 1) and subgroup analyses (*P* value >.05) (eFigure 3 in Supplement 1).

GLP-1RA vs SGLT2i Cohort

GLP-1RA initiators were younger (62.5 vs 64.9 years) and had a higher percentage of females (58.7% vs 45.4%) with a higher BMI at baseline (33.9 vs 31.5) compared with SGLT2i initiators. After applying IPTW, all baseline covariates achieved balance, with SMDs less than 0.1. During follow-up, 90 ADRD cases were identified among GLP-1RA users (mean follow-up, 2.39 years) compared with 130 cases among SGLT2i users (mean follow-up, 2.07 years) (Table 2). The crude HR was 0.68 (95% CI, 0.52-0.88). In the IPTW-weighted cohort, incidence rates were 3.65 and 3.74 per 1000 person-years for the GLP-1RA and SGLT2i groups, respectively, yielding an RD of −0.09 (95% CI, −0.80 to 0.63). There was no significant difference

Table 1. Selected Baseline Characteristics of Patients With Type 2 Diabetes Within the 3 Study Cohorts

Characteristic	GLP-1RA vs other GLD cohort, No. (%)[a]		SMD		SGLT2i vs other GLD cohort, No. (%)[a]		SMD		GLP-1RA vs SGLT2i cohort, No. (%)[a]		SMD	
	GLP-1RA (n = 10 212)	Other GLD (n = 23 646)	Before IPTW	After IPTW	SGLT2i (n = 10 524)	Other GLD (n = 23 661)	Before IPTW	After IPTW	GLP-1RA (n = 11 395)	SGLT2i (n = 12 722)	Before IPTW	After IPTW
Age, mean (SD), y	62.3 (8.0)	66.2 (9.5)	−0.451	−0.020	64.8 (9.0)	66.2 (9.6)	−0.152	−0.038	62.5 (8.1)	64.9 (9.0)	−0.282	−0.006
Race and ethnicity												
Hispanic	1346 (13.2)	3258 (13.8)	0.094	0.054	1791 (17.0)	3675 (15.5)	0.060	0.031	1934 (17.0)	2259 (17.8)	0.069	0
Non-Hispanic Black	2964 (29.0)	6583 (27.8)			2834 (26.9)	6566 (27.8)			3280 (28.8)	3347 (26.3)		
Non-Hispanic White	4096 (40.1)	10 108 (42.7)			4526 (43.0)	10 137 (42.8)			4678 (41.1)	5420 (42.6)		
Other[b]	1806 (17.7)	3697 (15.6)			1373 (13.0)	3283 (13.9)			1503 (13.2)	1696 (13.3)		
Sex												
Female	6003 (58.8)	11 981 (50.7)	0.164	−0.009	4862 (46.2)	12 002 (50.7)	−0.091	0.022	6692 (58.7)	5778 (45.4)	0.269	0.004
Male	4209 (41.2)	11 665 (49.3)			5662 (53.8)	11 659 (49.3)			4703 (41.3)	6944 (54.6)		
Insurance coverage												
Medicaid	701 (6.9)	1554 (6.6)	0.240	0.042	759 (7.2)	1549 (6.5)	0.103	0.069	802 (7.0)	871 (6.8)	0.128	0
Medicare	4048 (39.6)	11 412 (48.3)			4804 (45.6)	11 465 (48.5)			4631 (40.6)	5840 (45.9)		
Private	4897 (48.0)	8684 (36.7)			4312 (41.0)	8673 (36.7)			5539 (48.6)	5449 (42.8)		
Other/unknown[c]	566 (5.5)	1996 (8.4)			649 (6.2)	1974 (8.3)			423 (3.7)	562 (4.4)		
Median family income, $[d]												
≤40 000	5067 (49.6)	10 127 (42.8)	0.158	0.024	4512 (42.9)	10 110 (42.7)	0.053	0.045	5444 (47.8)	5471 (43.0)	0.102	0.027
>40 000 to ≤60 000	2356 (23.1)	6752 (28.6)			2853 (27.1)	6746 (28.5)			2734 (24.0)	3410 (26.8)		
>60 000	2789 (27.3)	6767 (28.6)			3159 (30.0)	6805 (28.8)			3217 (28.2)	3841 (30.2)		
Educational attainment (bachelor's degree and above), %[d]												
≤15	4155 (40.7)	9695 (41.0)	−0.006	−0.007	4451 (42.3)	9844 (41.6)	0.014	−0.006	4715 (41.4)	5271 (41.4)	−0.001	−0.003
>15	6057 (59.3)	13 951 (59.0)			6073 (57.7)	13 817 (58.4)			6680 (58.6)	7451 (58.6)		
Enrollment during COVID-19 period (2020–2023)	7669 (75.1)	11 075 (46.8)	0.605	0.026	8632 (82.0)	11 037 (46.6)	0.795	−0.002	8217 (72.1)	10 123 (79.6)	−0.175	−0.018
Health care professional specialty												
Primary care/internal medicine	6607 (64.7)	15 949 (67.4)	0.346	0.031	6548 (62.2)	15 919 (67.3)	0.151	0.095	7393 (64.9)	8094 (63.6)	0.284	0.031
Nurse practitioner/physician assistant	1735 (17.0)	3118 (13.2)			1412 (13.4)	3152 (13.3)			1983 (17.4)	1751 (13.8)		
Endocrinology	1013 (9.9)	1041 (4.4)			689 (6.5)	1051 (4.4)			1127 (9.9)	785 (6.2)		
Other[e]	857 (8.4)	3538 (15.0)			1875 (17.8)	3539 (15.0)			892 (7.8)	2092 (16.4)		
Health care encounters at baseline, No.												
≤5	2483 (24.3)	7988 (33.8)	0.230	0.025	2675 (25.4)	7988 (33.8)	0.244	0.043	2619 (23.0)	3223 (25.3)	0.070	0.025
>5 to ≤20	3419 (33.5)	7285 (30.8)			3049 (29.0)	7282 (30.8)			3699 (32.5)	3736 (29.4)		
>20	4310 (42.2)	8373 (35.4)			4800 (45.6)	8391 (35.5)			5077 (44.6)	5763 (45.3)		

(continued)

Table 1. Selected Baseline Characteristics of Patients With Type 2 Diabetes Within the 3 Study Cohorts (continued)

Characteristic	GLP-1RA vs other GLD cohort, No. (%)[a]		SMD		SGLT2i vs other GLD cohort, No. (%)[a]		SMD		GLP-1RA vs SGLT2i cohort, No. (%)[a]		SMD	
	GLP-1RA (n = 10 212)	Other GLD (n = 23 646)	Before IPTW	After IPTW	SGLT2i (n = 10 524)	Other GLD (n = 23 661)	Before IPTW	After IPTW	GLP-1RA (n = 11 395)	SGLT2i (n = 12 722)	Before IPTW	After IPTW
Diabetes complications												
Diabetic retinopathy	572 (5.6)	894 (3.8)	0.086	−0.011	486 (4.6)	904 (3.8)	0.040	−0.008	634 (5.6)	591 (4.6)	0.042	0.005
Diabetic neuropathy	1345 (13.2)	2559 (10.8)	0.072	−0.006	1456 (13.8)	2568 (10.9)	0.091	0.006	1487 (13.0)	1724 (13.6)	−0.015	0.002
Peripheral vascular disease	713 (7.0)	2005 (8.5)	−0.056	0.003	1565 (14.9)	1993 (8.4)	0.202	−0.011	784 (6.9)	1779 (14.0)	−0.234	−0.015
Hypoglycemia	110 (1.1)	163 (0.7)	0.042	−0.003	101 (1.0)	164 (0.7)	0.030	−0.003	136 (1.2)	120 (0.9)	0.024	−0.001
Hyperglycemic emergency	162 (1.6)	447 (1.9)	−0.023	0.004	151 (1.4)	447 (1.9)	−0.036	−0.018	180 (1.6)	181 (1.4)	0.013	0.001
Comorbidities												
Ever smoking	65 (0.6)	562 (2.4)	−0.143	−0.017	184 (1.7)	562 (2.4)	−0.044	−0.010	69 (0.6)	219 (1.7)	−0.104	−0.004
Mild cognitive impairment	48 (0.5)	137 (0.6)	−0.015	0	65 (0.6)	138 (0.6)	0.005	0.012	53 (0.5)	78 (0.6)	0.070	0.025
Parkinson disease	39 (0.4)	137 (0.6)	−0.029	−0.026	50 (0.5)	137 (0.6)	−0.014	−0.009	39 (0.3)	56 (0.4)	−0.016	0.001
Cardiovascular disease	1976 (19.3)	6073 (25.7)	−0.152	0.006	3801 (36.1)	6061 (25.6)	0.229	−0.037	2147 (18.8)	4395 (34.5)	−0.361	−0.011
Atrial fibrillation	653 (6.4)	2094 (8.9)	−0.093	−0.008	1559 (14.8)	2090 (8.8)	0.186	−0.022	699 (6.1)	1751 (13.8)	−0.257	−0.017
Heart failure	799 (7.8)	2163 (9.1)	−0.048	0.014	2778 (26.4)	2140 (9.0)	0.467	−0.015	816 (7.2)	3036 (23.9)	−0.474	−0.028
Cerebrovascular disease	578 (5.7)	1930 (8.2)	−0.099	−0.001	946 (9.0)	1925 (8.1)	0.031	−0.014	643 (5.6)	1108 (8.7)	−0.119	−0.002
Hyperlipidemia	6423 (62.9)	13 720 (58.0)	0.100	0.033	7198 (68.4)	13 701 (57.9)	0.219	0.036	7199 (63.2)	8710 (68.5)	−0.112	−0.003
Traumatic brain injury	45 (0.4)	166 (0.7)	−0.035	0.017	53 (0.5)	166 (0.7)	−0.026	0.013	53 (0.5)	54 (0.4)	0.006	0.002
Epilepsy/seizures	92 (0.9)	288 (1.2)	−0.031	−0.002	128 (1.2)	285 (1.2)	0.001	0.006	93 (0.8)	137 (1.1)	−0.027	−0.003
Posttraumatic stress disorder	78 (0.8)	138 (0.6)	0.022	−0.002	99 (0.9)	138 (0.6)	0.041	−0.001	86 (0.8)	108 (0.8)	−0.011	−0.005
Bipolar disorder	125 (1.2)	310 (1.3)	−0.008	0.012	150 (1.4)	312 (1.3)	0.009	0.012	144 (1.3)	173 (1.4)	−0.008	0.005
Depression	1358 (13.3)	2457 (10.4)	0.090	0.003	1232 (11.7)	2464 (10.4)	0.041	0.033	1495 (13.1)	1436 (11.3)	0.056	−0.001
Anxiety	1415 (13.9)	2422 (10.2)	0.111	0.017	1471 (14.0)	2425 (10.2)	0.115	0.010	1525 (13.4)	1688 (13.3)	0.003	−0.008
Hypertension	7440 (72.9)	17 227 (72.9)	0	0.005	8330 (79.2)	17 205 (72.7)	0.151	0.014	8330 (73.1)	10 001 (78.6)	−0.129	−0.005
Chronic obstructive pulmonary disease	701 (6.9)	2002 (8.5)	−0.060	0.014	1125 (10.7)	1999 (8.4)	0.076	−0.008	773 (6.8)	1280 (10.1)	−0.118	−0.008
Chronic kidney disease	1225 (12.0)	3469 (14.7)	−0.079	0.009	2105 (20.0)	3461 (14.6)	0.142	−0.033	1425 (12.5)	2439 (19.2)	−0.183	−0.001
Asthma	895 (8.8)	1665 (7.0)	0.064	0.019	823 (7.8)	1670 (7.1)	0.029	−0.002	996 (8.7)	982 (7.7)	0.037	−0.001
Anemia	1555 (15.2)	4643 (19.6)	−0.116	0.008	2296 (21.8)	4633 (19.6)	0.055	−0.026	1750 (15.4)	2660 (20.9)	−0.144	−0.003
Sleeping disorder	2713 (26.6)	4359 (18.4)	0.196	0.027	2877 (27.3)	4355 (18.4)	0.214	0.026	2922 (25.6)	3287 (25.8)	−0.004	−0.003
Hearing impairment	404 (4.0)	841 (3.6)	0.021	−0.007	400 (3.8)	837 (3.5)	0.014	0.004	457 (4.0)	470 (3.7)	0.016	0.002
Alcohol use disorder	138 (1.4)	531 (2.2)	−0.067	0.012	273 (2.6)	527 (2.2)	0.024	−0.017	151 (1.3)	303 (2.4)	−0.078	−0.001
Obesity	3536 (34.6)	4411 (18.7)	0.395	0.017	5939 (56.4)	11 794 (49.8)	0.132	0.040	3821 (33.5)	3589 (28.2)	0.295	0
Pancreatitis	64 (0.6)	183 (0.8)	−0.018	0.019	117 (1.1)	182 (0.8)	0.036	−0.003	69 (0.6)	142 (1.1)	−0.055	0.006
MASLD	672 (6.6)	1036 (4.4)	0.097	0.006	654 (6.2)	1030 (4.4)	0.083	0	731 (6.4)	751 (5.9)	0.021	0.003
Thyroid disease	1820 (17.8)	3560 (15.1)	0.075	0.002	1745 (16.6)	3575 (15.1)	0.040	0.013	1987 (17.4)	2068 (16.3)	0.032	−0.002
Cancer	985 (9.6)	3005 (12.7)	−0.097	0.002	1171 (11.1)	2994 (12.7)	−0.047	−0.009	1130 (9.9)	1412 (11.1)	−0.039	−0.001

(continued)

Table 1. Selected Baseline Characteristics of Patients With Type 2 Diabetes Within the 3 Study Cohorts (continued)

Characteristic	GLP-1RA vs other GLD cohort, No. (%)[a]				SGLT2i vs other GLD cohort, No. (%)[a]				GLP-1RA vs SGLT2i cohort, No. (%)[a]			
	GLP-1RA (n = 10 212)	Other GLD (n = 23 646)	SMD Before IPTW	SMD After IPTW	SGLT2i (n = 10 524)	Other GLD (n = 23 661)	SMD Before IPTW	SMD After IPTW	GLP-1RA (n = 11 395)	SGLT2i (n = 12 722)	SMD Before IPTW	SMD After IPTW
Medications												
ACEIs	2351 (23.0)	6996 (29.6)	−0.150	0.003	2476 (23.5)	6987 (29.5)	−0.136	−0.024	2884 (25.3)	3320 (26.1)	−0.018	0.007
β-Blockers	2238 (21.9)	6841 (28.9)	−0.162	−0.003	3713 (35.3)	6823 (28.8)	0.138	−0.065	2634 (23.1)	4438 (34.9)	−0.262	−0.014
Calcium channel blockers	2309 (22.6)	6454 (27.3)	−0.108	−0.006	2420 (23.0)	6456 (27.3)	−0.099	−0.041	2723 (23.9)	3085 (24.2)	−0.008	0.005
Diuretics	2954 (28.9)	7198 (30.4)	−0.033	0.006	4071 (38.7)	7184 (30.4)	0.176	−0.053	3485 (30.6)	4845 (38.1)	−0.158	−0.016
Angiotensin receptor blockers	2336 (22.9)	5101 (21.6)	0.031	0.001	3180 (30.2)	5090 (21.5)	0.200	−0.015	2725 (23.9)	3857 (30.3)	−0.144	−0.020
Statins	4897 (48.0)	12 070 (51.0)	−0.062	0.003	5793 (55.0)	12 053 (50.9)	0.082	−0.037	5805 (50.9)	7315 (57.5)	−0.132	−0.001
NSAIDS	2107 (20.6)	4544 (19.2)	0.036	0.002	1823 (17.3)	4541 (19.2)	−0.048	0.030	2483 (21.8)	2307 (18.1)	0.092	0.005
Proton pump inhibitors	1985 (19.4)	6019 (25.5)	−0.145	−0.007	2568 (24.4)	6022 (25.5)	−0.024	−0.047	2364 (20.7)	3113 (24.5)	−0.089	−0.008
Antidepressants	1409 (13.8)	2811 (11.9)	0.057	−0.010	1254 (11.9)	2821 (11.9)	0	−0.004	1619 (14.2)	1508 (11.9)	0.070	0.003
Antipsychotics	386 (3.8)	1387 (5.9)	−0.098	−0.015	494 (4.7)	1382 (5.8)	−0.051	−0.017	431 (3.8)	571 (4.5)	−0.036	−0.003
Anti-Parkinson agents	643 (6.3)	1971 (8.3)	−0.078	−0.016	797 (7.6)	1965 (8.3)	−0.027	−0.045	724 (6.4)	901 (7.1)	−0.029	−0.008
Benzodiazepines	1400 (13.7)	4463 (18.9)	−0.140	−0.022	1862 (17.7)	4454 (18.8)	−0.029	−0.054	1562 (13.7)	2160 (17.0)	−0.091	−0.020
Oral steroids	2719 (26.6)	6559 (27.7)	−0.025	−0.022	2949 (28.0)	6561 (27.7)	0.007	−0.028	3173 (27.8)	3564 (28.0)	−0.004	−0.001
Opioids	2166 (21.2)	7598 (32.1)	−0.249	−0.015	2821 (26.8)	7595 (32.1)	−0.116	−0.057	2486 (21.8)	3314 (26.0)	−0.099	−0.010
Aspirin	1179 (11.5)	5002 (21.2)	−0.262	−0.014	2451 (23.3)	4994 (21.1)	0.053	−0.071	1403 (12.3)	2843 (22.3)	−0.268	−0.016
Insulin	3538 (34.6)	7930 (33.5)	0.023	−0.014	3802 (36.1)	7989 (33.8)	0.050	−0.050	3932 (34.5)	4276 (33.6)	0.019	−0.007
Metformin	4110 (40.2)	10 855 (45.9)	−0.115	0.006	3932 (37.4)	10 845 (45.8)	−0.173	0.025	4956 (43.5)	5363 (42.2)	0.027	0.020
SGLT2is	368 (3.6)	319 (1.3)	0.146	−0.003								
GLP-1RAs					619 (5.9)	334 (1.4)	0.240	−0.023				
Other GLDs									1586 (13.9)	1855 (14.6)	−0.019	0.017
Baseline HbA_{1c}, %[f]	7.8 (1.6)	7.7 (1.5)	0.045	0.025	7.7 (1.5)	7.7 (1.4)	−0.002	0.004	7.9 (1.6)	7.8 (1.6)	0.064	0.018
Baseline BMI[f]	33.8 (6.8)	30.7 (6.4)	0.457	0.004	31.6 (6.5)	30.7 (6.3)	0.144	0.004	33.9 (6.9)	31.5 (6.7)	0.361	0.002

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GLD, glucose-lowering drug; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; IPTW, inverse probability of treatment weighting; MASLD, metabolic dysfunction-associated steatotic liver disease; NSAIDS, nonsteroidal anti-inflammatory drugs; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMD, standardized mean difference.

[a] Unless otherwise indicated.

[b] Includes American Indian or Alaska Native, Asian American, Native Hawaiian or Other Pacific islander, or unknown.

[c] Includes no payment and others.

[d] Zip code levels.

[e] Includes cardiology and others.

[f] After imputation.

Table 2. Risk of Alzheimer Disease and Related Dementias Within 3 Study Cohorts

	GLP-1RA vs other GLD cohort		SGLT2i vs other GLD cohort		GLP-1RA vs SGLT2i cohort	
	GLP-1RA	Other GLD	SGLT2i	Other GLD	GLP-1RA	SGLT2i
Unweighted cohort						
No. of events/ No. of patients at risk	75/10 212	639/23 646	101/10 524	642/23 661	90/11 395	130/12 722
Follow-up, mean (SD), y	2.22 (2.30)	3.74 (3.48)	1.95 (2.04)	3.76 (2.91)	2.39 (2.41)	2.07 (2.14)
Crude HR (95% CI)	0.44 (0.34 to 0.55)	1 (reference)	0.62 (0.50 to 0.76)	1 (reference)	0.68 (0.52 to 0.88)	1 (reference)
IPTW-weighted cohort						
No. of events/ No. of patients at risk	465/32 790	736/34 226	472/33 974	789/34 211	200/23 810	210/24 260
Follow-up, mean (SD), y	3.26 (5.07)	3.26 (3.38)	3.32 (5.06)	3.19 (3.35)	2.30 (3.25)	2.32 (3.24)
Incidence rate per 1000 person-years	4.35 (3.96 to 4.76)	6.60 (6.14 to 7.10)	4.19 (3.82 to 4.58)	7.23 (6.73 to 7.75)	3.65 (3.16 to 4.19)	3.74 (3.25 to 4.28)
Rate difference per 1000 person-years	−2.26 (−2.88 to −1.64)	0 (reference)	−3.05 (−3.68 to −2.42)	0 (reference)	−0.09 (−0.80 to 0.63)	0 (reference)
Adjusted HR (95% CI)	0.67 (0.47 to 0.96)	1 (reference)	0.57 (0.43 to 0.75)	1 (reference)	0.97 (0.72 to 1.32)	1 (reference)

Abbreviations: GLD, glucose-lowering drug; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IPTW, inverse probability of treatment weighting; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

between GLP-1RAs and SGLT2is in risk of ADRD, with an adjusted HR of 0.97 (95% CI, 0.72-1.32). The IPTW-adjusted Kaplan-Meier plot shows the cumulative incidence of ADRD (Figure 2). The findings were consistent across all sensitivity analyses (eFigure 2 in Supplement 1). No significant association modification was observed in the subgroup analyses, although opposing trends were observed for obesity (P = .09) and metformin (P = .05) (eFigure 3 in Supplement 1). It is intriguing to find that among individual GLP-1RAs, semaglutide was statistically significantly associated with a decreased risk of ADRD compared with SGLT2is (HR, 0.54 [95% CI, 0.31-0.94]).

E-Value

The E-value for GLP-1RAs vs other GLDs was 2.35, and for SGLT2is vs other GLDs, 2.9. To negate the observed association of GLP-1RAs with ADRD risk, an unmeasured confounder would need to have an HR of at least 2.35 with both the treatment and the outcome. Similarly, for SGLT2is, an unmeasured confounder would need an HR of at least 2.90.

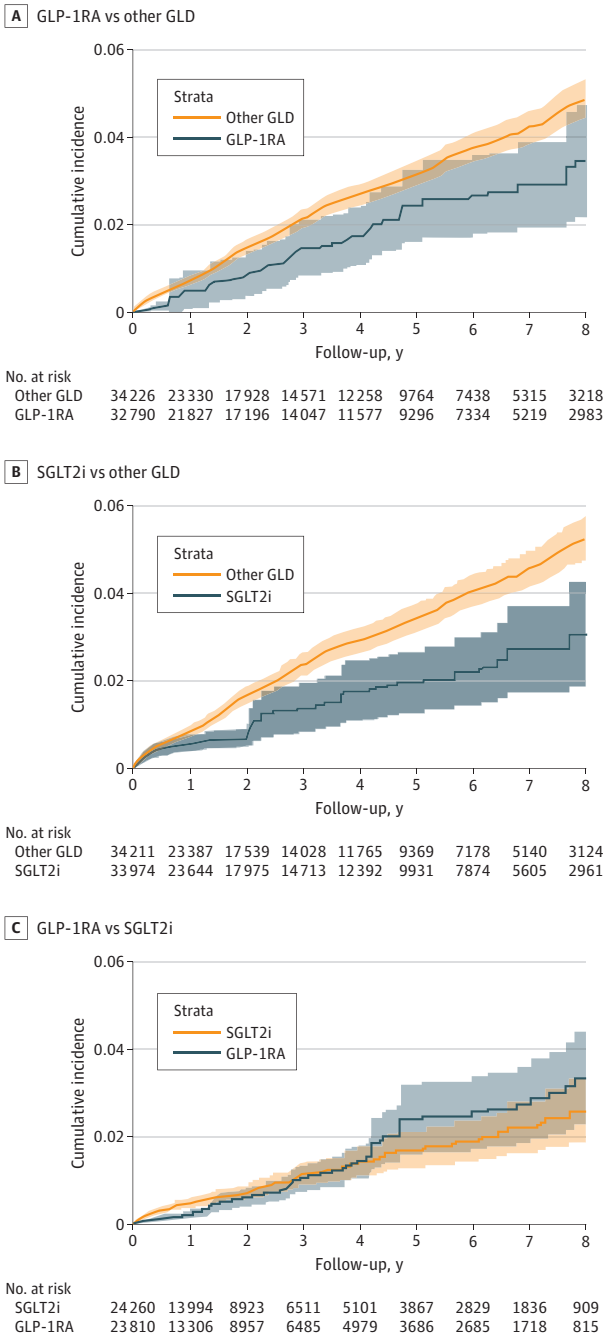
Discussion

This population-based cohort study using a target trial emulation approach found that the use of GLP-1RAs and SGLT2is was associated with a lower risk of ADRD compared with other second-line GLDs among people with T2D. Specifically, GLP-1RA use was associated with a 33% lower risk of ADRD, while SGLT2i use was associated with a 43% lower risk compared with other GLDs. However, when directly compared, there was no significant difference in ADRD risk between GLP-1RA and SGLT2i users. The findings were consistent across sensitivity and subgroup analyses, further strengthening the reliability of the results. Moreover, no significant association modifications were identified in the subgroup analyses.

Study findings are consistent with and extend previous observational studies[13-15,32,33] and meta-analyses[34,35] suggesting a potential protective role of GLP-1RAs and SGLT2is in reducing risk of ADRD in people with T2D. Previous meta-analysis of observational studies reported that both GLP-1RA and SGLT2i users had a lower risk of ADRD compared with nonusers in people with T2D.[34] Another meta-analysis showed an improvement in cognitive function scores with SGLT2i use, particularly among populations with mild cognitive impairment or ADRD.[35] The present target trial emulation study, using a more rigorous methodological approach and robust adjustment for confounding factors, strengthens the evidence supporting the potential neuroprotections of these medications. Although the underlying mechanisms remain unknown, several mechanisms may be proposed. GLP-1RAs have been shown to reduce neuroinflammation,[36,37] improve insulin signaling in the brain,[38] and promote neurogenesis.[39] These agents may also enhance synaptic plasticity and reduce amyloid-β and tau pathology, which are hallmarks of AD.[40,41] Similarly, SGLT2is may exert neuroprotection through improved cerebral blood flow, reduced oxidative stress, and enhanced mitochondrial function.[42-44] Furthermore, both GLP-1RAs and SGLT2is have been associated with improved metabolic control and vascular outcomes,[10,45,46] which may contribute to better cognitive outcomes given the strong link between vascular health and cognitive function.[47] The similar pathways through which these drug classes act may help explain no significant difference between GLP-1RA and SGLT2i users in reducing ADRD risk.

The consistency of the findings across various sensitivity and subgroup analyses strengthens the robustness of the results. The lack of significant association modification by age, sex, race and ethnicity, obesity status, or use of metformin or insulin suggests that the potential neuroprotection of GLP-1RAs and SGLT2is may be applicable across diverse patient populations. However, the study observed some opposing

Figure 2. Inverse Probability of Treatment Weighting (IPTW)–Adjusted Cumulative Incidence of Alzheimer Disease and Related Dementias Within the 3 Study Cohorts



GLD indicates glucose-lowering drug; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

trends when comparing GLP-1RAs with SGLT2is in subgroups defined by age (<65 vs ≥65 years), obesity status, and metformin use. These findings, although not statistically significant, hint at the possibility of personalized treatment approaches in diabetes management. For instance, the opposing direction in obesity subgroups might be partially explained by the differential effects of GLP-1RAs and SGLT2is on body weight. Late-life obesity has been associated with decreased ADRD risk, while weight loss may increase risk.[48,49] Both GLP-1RAs and SGLT2is reduce body weight, with GLP-1RAs having greater effects,[50] potentially contributing to the opposing trends. The underlying explanations for the varying associations between GLP-1RAs and ADRD risk compared with SGLT2is in age and metformin use subgroups warrant further investigation. It is important to emphasize that these subgroup analyses were exploratory, and the observed trends did not reach statistical significance. Therefore, these findings should be interpreted cautiously and considered hypothesis-generating rather than definitive. Among the GLP-1RAs, semaglutide seems to be promising in reducing the risk of ADRD. This finding is particularly intriguing given the existing research on semaglutide's neuroprotective properties.[51,52] Currently, 2 placebo-controlled phase 3 trials (EVOKE [NCT04777396] and EVOKE Plus [NCT04777409]) have been initiated to study the efficacy of oral semaglutide (14 mg) in patients with early AD.[53] The results from these trials will provide crucial insights into the potential cognitive benefits of semaglutide.

The potential benefits of GLP-1RAs and SGLT2is on the risk of ADRD should be interpreted with caution given the relatively short duration of follow-up (mean, 1.95-3.76 years). The development of ADRD is a protracted process that typically unfolds over several years, and the pathological changes associated with ADRD often begin long before clinical symptoms manifest.[54] The observed immediate neuroprotections of GLP-1RAs and SGLT2is could be explained by the following: (1) the higher prevalence of mild cognitive impairment among patients with T2D, which accelerates ADRD progression,[55,56] GLP-1RAs, and SGLT2is may effectively manage diabetes and improve other ADRD risk factors (eg, cardiovascular disease and cerebrovascular disease), potentially accounting for their immediate neuroprotections; and (2) GLP-1RA and SGLT2i users tended to be younger than other GLD users in this study, despite it being balanced in the weighted cohort. This age discrepancy could contribute to the observed neuroprotection, as younger individuals generally have a lower baseline ADRD risk, potentially overestimating the protective association. Thus, future studies with longer follow-up periods are warranted to confirm these findings and assess the durability of the observed associations.

Strengths and Limitations

This study's strengths include the target trial emulation approach, adjustment for numerous baseline covariates, and consistent results across multiple sensitivity and subgroup analyses. However, several limitations warrant consideration. First, despite extensive covariate adjustment, the observational nature of this study precluded the complete elimination of residual confounding. Unmeasured confounders, such as duration and severity of T2D, socioeconomic factors, and cognitive status, may influence the observed associations. To mitigate the potential influence of duration and severity of T2D, the study adjusted for insulin use at baseline, a proxy for the severity of diabetes, and conducted subgroup analyses to further explore potential confounding factors. To account for

socioeconomic factors, the study incorporated health insurance, median family income, and educational attainment in the IPTW. Furthermore, the relatively high E-values suggest robustness to potential unmeasured confounding. Despite these efforts, some degree of residual confounding may persist, particularly regarding factors such as cognitive status, which were unavailable in this study. Second, the relatively short follow-up period, especially for GLP-1RA and SGLT2i users, represents another major limitation. As these are newer GLDs, the available follow-up time is inherently constrained. Given the protracted development of ADRD, longer follow-up would be ideal to assess the durability of the observed association. Third, the study relied on diagnosis codes to identify ADRD cases, which may introduce misclassifications. The CCW claims-based algorithm for ADRD was used, but its performance in electronic health records within OneFlorida+ remains unclear. To capture all possible ADRD cases, at least 1 diagnosis code was used, but this approach may lead to false positives.

Conclusions

Study findings suggest that the use of GLP-1RAs and SGLT2is is associated with a lower risk of ADRD compared with other second-line GLDs in patients with T2D. These results support the potential neuroprotections of GLP-1RAs and SGLT2is and highlight their possible role in ADRD prevention strategies. The comparable association between GLP-1RAs and SGLT2is provides flexibility in treatment choices while potentially offering cognitive benefits. However, further research, particularly randomized controlled trials, is necessary to validate study findings and assess their applicability to other populations.

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