

# 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.

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 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.<sup>1</sup> In the US, an estimated 6.9 million older adults lived with ADRD in 2023, with projections doubling by 2060.<sup>2</sup> ADRD is the fifth leading cause of death among older US residents, with an estimated cost of \$360 billion related to ADRD in 2023.<sup>2</sup> 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.<sup>3-5</sup> 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.<sup>6</sup>

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)<sup>7</sup> due to their additional cardiovascular, kidney, and weight loss benefits.<sup>8-10</sup> Recent studies have suggested that GLP-1RAs and SGLT2is may also mitigate ADRD pathophysiology,<sup>11,12</sup> with population-based studies indicating a potential association between their use and reduced ADRD risk.<sup>13-15</sup> 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.

## 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](#).<sup>16,17</sup> 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.<sup>18</sup> 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

## 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.

and dispensed medications), procedures, vital signs, and laboratory results.<sup>19</sup> 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],  $\alpha$ -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.<sup>20</sup> 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)<sup>21</sup> and an increased risk of all-cause dementia.<sup>22,23</sup>

### 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.<sup>24</sup> 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<sup>25,26</sup> 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<sub>1c</sub> 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.<sup>27</sup> 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.<sup>28</sup> 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<sub>1c</sub> and BMI, we used multiple imputation by chained equation.<sup>29</sup> 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.<sup>30</sup>

### 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<sup>31</sup>; 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

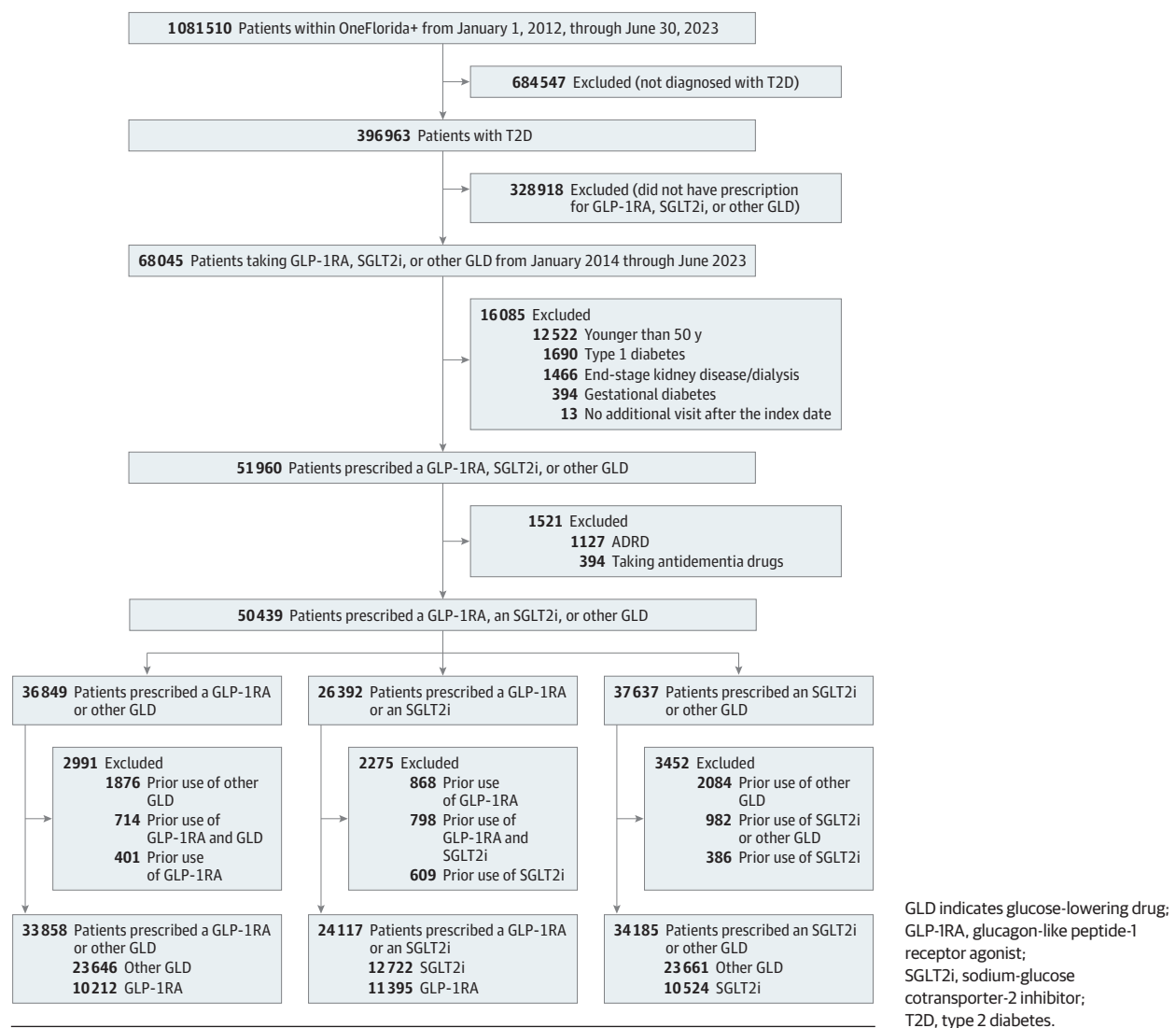
### Study Population

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



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. (%) <sup>a</sup>			SGLT2i vs other GLD cohort, No. (%) <sup>a</sup>			GLP-1RA vs SGLT2i cohort, No. (%) <sup>b</sup>		
	GLP-1RA (n = 10 212)	Other GLD (n = 23 646)	SMD Before IPTW	SGLT2i (n = 10 524)	Other GLD (n = 23 661)	SMD Before IPTW	GLP-1RA (n = 11 395)	SGLT2i (n = 12 722)	SMD Before IPTW
Age, mean (SD), y	62.3 (8.0)	66.2 (9.5)	-0.451	64.8 (9.0)	66.2 (9.6)	-0.152	62.5 (8.1)	64.9 (9.0)	-0.282
Race and ethnicity									
Hispanic	1346 (13.2)	3258 (13.8)	0.094	1791 (17.0)	3675 (15.5)	0.060	1934 (17.0)	2259 (17.8)	0.069
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 <sup>b</sup>	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	4862 (46.2)	12 002 (50.7)	-0.091	6692 (58.7)	5778 (45.4)	0.269
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	759 (7.2)	1549 (6.5)	0.103	802 (7.0)	871 (6.8)	0.128
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 <sup>c</sup>	566 (5.5)	1996 (8.4)		649 (6.2)	1974 (8.3)		423 (3.7)	562 (4.4)	
Median family income, \$ <sup>d</sup>									
≤40 000	5067 (49.6)	10 127 (42.8)	0.158	4512 (42.9)	10 110 (42.7)	0.053	5444 (47.8)	5471 (43.0)	0.102
>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), % <sup>d</sup>									
≤15	4155 (40.7)	9695 (41.0)	-0.006	4451 (42.3)	9844 (41.6)	0.014	4715 (41.4)	5271 (41.4)	-0.001
>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	8632 (82.0)	11 037 (46.6)	0.795	8217 (72.1)	10 123 (79.6)	-0.175
Health care professional specialty									
Primary care/internal medicine	6607 (64.7)	15 949 (67.4)	0.346	6548 (62.2)	15 919 (67.3)	0.151	7393 (64.9)	8094 (63.6)	0.284
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 <sup>e</sup>	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	2675 (25.4)	7988 (33.8)	0.244	2619 (23.0)	3223 (25.3)	0.070
>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. (%) <sup>a</sup>			SGLT2i vs other GLD cohort, No. (%) <sup>a</sup>			GLP-1RA vs SGLT2i cohort, No. (%) <sup>b</sup>		
	GLP-1RA (n = 10 212)	Other GLD (n = 23 646)	SMD Before IPTW	SGLT2i (n = 10 524)	Other GLD (n = 23 661)	SMD Before IPTW	GLP-1RA (n = 11 395)	SGLT2i (n = 12 722)	SMD Before IPTW
<b>Diabetes complications</b>									
Diabetic retinopathy	572 (5.6)	894 (3.8)	0.086	-0.011	486 (4.6)	0.040	-0.008	634 (5.6)	591 (4.6)
Diabetic neuropathy	1345 (13.2)	2559 (10.8)	0.072	-0.006	1456 (13.8)	0.091	0.006	1487 (13.0)	1724 (13.6)
Peripheral vascular disease	713 (7.0)	2005 (8.5)	-0.056	0.003	1565 (14.9)	0.202	-0.011	784 (6.9)	1779 (14.0)
Hypoglycemia	110 (1.1)	163 (0.7)	0.042	-0.003	101 (1.0)	0.030	-0.003	136 (1.2)	120 (0.9)
Hyperglycemic emergency	162 (1.6)	447 (1.9)	-0.023	0.004	151 (1.4)	-0.036	-0.018	180 (1.6)	181 (1.4)
<b>Comorbidities</b>									
Ever smoking	65 (0.6)	562 (2.4)	-0.143	-0.017	184 (1.7)	-0.044	-0.010	69 (0.6)	219 (1.7)
Mild cognitive impairment	48 (0.5)	137 (0.6)	-0.015	0	65 (0.6)	0.005	0.012	53 (0.5)	78 (0.6)
Parkinson disease	39 (0.4)	137 (0.6)	-0.029	-0.026	50 (0.5)	-0.014	-0.009	39 (0.3)	56 (0.4)
Cardiovascular disease	1976 (19.3)	6073 (25.7)	-0.152	0.006	3801 (36.1)	0.229	-0.037	2147 (18.8)	4395 (34.5)
Atrial fibrillation	653 (6.4)	2094 (8.9)	-0.093	-0.008	1559 (14.8)	0.186	-0.022	699 (6.1)	1751 (13.8)
Heart failure	799 (7.8)	2163 (9.1)	-0.048	0.014	2778 (26.4)	0.467	-0.015	816 (7.2)	3036 (23.9)
Cerebrovascular disease	578 (5.7)	1930 (8.2)	-0.099	-0.001	946 (9.0)	0.031	-0.014	643 (5.6)	1108 (8.7)
Hyperlipidemia	6423 (62.9)	13 720 (58.0)	0.100	0.033	7198 (68.4)	0.219	0.036	7199 (63.2)	8710 (68.5)
Traumatic brain injury	45 (0.4)	166 (0.7)	-0.035	0.017	53 (0.5)	-0.026	0.013	53 (0.5)	54 (0.4)
Epilepsy/seizures	92 (0.9)	288 (1.2)	-0.031	-0.002	128 (1.2)	0.001	0.006	93 (0.8)	137 (1.1)
Posttraumatic stress disorder	78 (0.8)	138 (0.6)	0.022	-0.002	99 (0.9)	0.041	-0.001	86 (0.8)	108 (0.8)
Bipolar disorder	125 (1.2)	310 (1.3)	-0.008	0.012	150 (1.4)	0.009	0.012	144 (1.3)	173 (1.4)
Depression	1358 (13.3)	2457 (10.4)	0.090	0.003	1232 (11.7)	0.041	0.033	1495 (13.1)	1436 (11.3)
Anxiety	1415 (13.9)	2422 (10.2)	0.111	0.017	1471 (14.0)	0.115	0.010	1525 (13.4)	1688 (13.3)
Hypertension	7440 (72.9)	17 227 (72.9)	0	0.005	8330 (79.2)	0.151	0.014	8330 (73.1)	10 001 (78.6)
Chronic obstructive pulmonary disease	701 (6.9)	2002 (8.5)	-0.060	0.014	1125 (10.7)	0.076	-0.008	773 (6.8)	1280 (10.1)
Chronic kidney disease	1225 (12.0)	3469 (14.7)	-0.079	0.009	2105 (20.0)	0.142	-0.033	1425 (12.5)	2439 (19.2)
Asthma	895 (8.8)	1665 (7.0)	0.064	0.019	823 (7.8)	0.029	-0.002	996 (8.7)	982 (7.7)
Anemia	1555 (15.2)	4643 (19.6)	-0.116	0.008	2296 (21.8)	0.055	-0.026	1750 (15.4)	2660 (20.9)
Sleeping disorder	2713 (26.6)	4359 (18.4)	0.196	0.027	2877 (27.3)	0.214	0.026	2922 (25.6)	3287 (25.8)
Hearing impairment	404 (4.0)	841 (3.6)	0.021	-0.007	400 (3.8)	0.014	0.004	457 (4.0)	470 (3.7)
Alcohol use disorder	138 (1.4)	531 (2.2)	-0.067	0.012	273 (2.6)	0.024	-0.017	151 (1.3)	303 (2.4)
Obesity	3536 (34.6)	4411 (18.7)	0.395	0.017	5939 (56.4)	0.132	0.040	3821 (33.5)	3589 (28.2)
Pancreatitis	64 (0.6)	183 (0.8)	-0.018	0.019	117 (1.1)	0.036	-0.003	69 (0.6)	142 (1.1)
MASLD	672 (6.6)	1036 (4.4)	0.097	0.006	654 (6.2)	0.083	0	731 (6.4)	751 (5.9)
Thyroid disease	1820 (17.8)	3560 (15.1)	0.075	0.002	1745 (16.6)	0.040	0.013	1987 (17.4)	2068 (16.3)
Cancer	985 (9.6)	3005 (12.7)	-0.097	0.002	1171 (11.1)	-0.047	-0.009	1130 (9.9)	1412 (11.1)

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

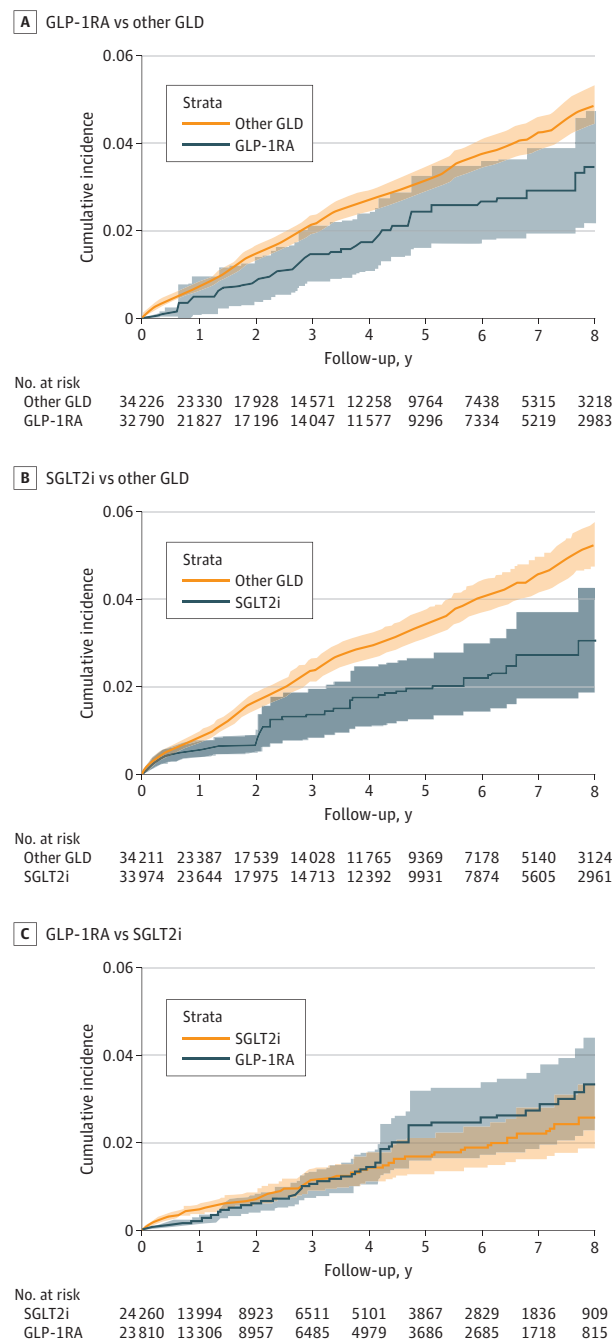
This population-based cohort study using a target trial emulation approach found that the use of GLP-1RAs and SGLT2is was associated with a lower risk of ADRD compared with other second-line GLDs among people with T2D. Specifically, GLP-1RA use was associated with a 33% lower risk of ADRD, while SGLT2i 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<sup>13-15,32,33</sup> and meta-analyses<sup>34,35</sup> 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 non-users in people with T2D.<sup>34</sup> Another meta-analysis showed an improvement in cognitive function scores with SGLT2i use, particularly among populations with mild cognitive impairment or ADRD.<sup>35</sup> 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,<sup>36,37</sup> improve insulin signaling in the brain,<sup>38</sup> and promote neurogenesis.<sup>39</sup> These agents may also enhance synaptic plasticity and reduce amyloid- $\beta$  and tau pathology, which are hallmarks of AD.<sup>40,41</sup> Similarly, SGLT2is may exert neuroprotection through improved cerebral blood flow, reduced oxidative stress, and enhanced mitochondrial function.<sup>42-44</sup> Furthermore, both GLP-1RAs and SGLT2is have been associated with improved metabolic control and vascular outcomes,<sup>10,45,46</sup> which may contribute to better cognitive outcomes given the strong link between vascular health and cognitive function.<sup>47</sup> 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 AD/DRD risk, while weight loss may increase risk.<sup>48,49</sup> Both GLP-1RAs and SGLT2is reduce body weight, with GLP-1RAs having greater effects,<sup>50</sup> potentially contributing to the opposing trends. The underlying explanations for the varying associations between GLP-1RAs and AD/DRD 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 AD/DRD. This finding is particularly intriguing given the existing research on semaglutide's neuroprotective properties.<sup>51,52</sup> 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.<sup>53</sup> 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 AD/DRD should be interpreted with caution given the relatively short duration of follow-up (mean, 1.95-3.76 years). The development of AD/DRD is a protracted process that typically unfolds over several years, and the pathological changes associated with AD/DRD often begin long before clinical symptoms manifest.<sup>54</sup> 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 AD/DRD progression,<sup>55,56</sup> GLP-1RAs, and SGLT2is may effectively manage diabetes and improve other AD/DRD 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 AD/DRD 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 AD, longer follow-up would be ideal to assess the durability of the observed association. Third, the study relied on diagnosis codes to identify AD cases, which may introduce misclassifications. The CCW claims-based algorithm for AD was used, but its performance in electronic health records within OneFlorida+ remains unclear. To capture all possible AD 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 AD 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 AD 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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**Concept and design:** Tang, Donahoo, DeKosky, Guo. **Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Tang.

**Critical review of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Tang, Lee.

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**Administrative, technical, or material support:** DeKosky, Lee, Kotecha, Bian, Guo.

**Supervision:** Donahoo, Svensson, Bian, Guo.

**Other - expertise in Alzheimer disease to aid in the writing of the manuscript:** DeKosky.

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