Received: 29 July 2024 | Revised: 10 September 2024 | Accepted: 12 September 2024

DOI: 10.1002/alz.14313

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US

William Wang[1] | **QuangQiu Wang**[2] | **Xin Qi**[3] | **Mark Gurney**[2] | **George Perry**[2,4] | **Nora D. Volkow**[5] | **Pamela B. Davis**[6] | **David C. Kaelber**[7] | **Rong Xu**[2]

[1]Center for Science, Health, and Society, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[2]Center for Artificial Intelligence in Drug Discovery, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[3]Department of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[4]Department of Neuroscience, Development and Regenerative Biology, College of Sciences, The University of Texas at San Antonio, San Antonio, Texas, USA

[5]National Institute on Drug Abuse, National Institutes of Health, Maryland, USA

[6]Center for Community Health Integration, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[7]Center for Clinical Informatics Research and Education, The MetroHealth System, Ohio, USA

Correspondence
Rong Xu, Center for Artificial Intelligence in Drug Discovery, Case Western Reserve University School of Medicine, Sears Tower T304 10900 Euclid Avenue, Cleveland, OH 44106-7288, USA.
Email: rxx@case.edu

Funding information
National Institute on Aging, Grant/Award Number: AG057557 AG061388 AG062272 AG076649; National Center for Advancing Translational Sciences, Grant/Award Number: TR004528

Abstract

INTRODUCTION: Emerging preclinical evidence suggests that semaglutide, a glucagon-like peptide receptor agonist (GLP-1RA) for type 2 diabetes mellitus (T2DM) and obesity, protects against neurodegeneration and neuroinflammation. However, real-world evidence for its ability to protect against Alzheimer's disease (AD) is lacking.

METHODS: We conducted emulation target trials based on a nationwide database of electronic health records (EHRs) of 116 million US patients. Seven target trials were emulated among 1,094,761 eligible patients with T2DM who had no prior AD diagnosis by comparing semaglutide with seven other antidiabetic medications. First-ever diagnosis of AD occurred within a 3-year follow-up period and was examined using Cox proportional hazards and Kaplan–Meier survival analyses.

RESULTS: Semaglutide was associated with significantly reduced risk for first-time AD diagnosis, most strongly compared with insulin (hazard ratio [HR], 0.33 [95% CI: 0.21 to 0.51]) and most weakly compared with other GLP-1RAs (HR, 0.59 [95% CI: 0.37 to 0.95]). Similar results were seen across obesity status, gender, and age groups.

DISCUSSION: These findings support further studies to assess semaglutide's potential in preventing AD.

HIGHLIGHTS:

- Semaglutide was associated with 40% to 70% reduced risks of first-time AD diagnosis in T2DM patients compared to other antidiabetic medications, including other GLP-1RAs.
- Semaglutide was associated with significantly lower AD-related medication prescriptions.
- Similar reductions were seen across obesity status, gender, and age groups.
- Our findings provide real-world evidence supporting the potential clinical benefits of semaglutide in mitigating AD initiation and development in patients with T2DM.

- These findings support further clinical trials to assess semaglutide's potential in delaying or preventing AD.

KEYWORDS
Alzheimer's disease, emulation target trial, patient electronic health records, prevention, real-world data, semaglutide, type 2 diabetes

1 | BACKGROUND

An estimated 6.9 million Americans aged 65 and older will be living with Alzheimer's disease (AD) in 2024, a number that is projected to increase to 13.8 million by 2060.[1] AD has no cure, and about 40% of cases are linked to modifiable risk factors.[2] Given its growing prevalence, profound societal and economic impact, and absence of a cure, targeting these modifiable risk factors is crucial to prevent or delay AD and related dementia.[3,4]

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), was approved by the US Food and Drug Administration (FDA) for type 2 diabetes mellitus (T2DM) in 2017 and for weight loss in 2021. Both T2DM and obesity are significant modifiable risk factors for AD.[2] Furthermore, semaglutide has demonstrated benefits in managing various other health conditions such as cardiovascular factors, alcohol use, smoking, and depression,[5–9] many of which are also linked to AD risk.[2] Given its ability to target these risk factors, we hypothesize that semaglutide may reduce the risk of developing AD in high-risk patients.

Two placebo-controlled trials are currently assessing semaglutide's neuroprotective effects in early AD,[10,11] alongside a study on its impact on the immune system in AD patients.[12] However, there are no clinical trials investigating whether semaglutide can delay or prevent the onset of AD. In this study, we conducted an emulation target trial using real-world electronic health records (EHRs) of T2DM patients without prior AD diagnosis. Our aim was to determine whether semaglutide is associated with a reduced risk for first-time diagnoses of AD in a high-risk population, stratified by gender, age groups, and obesity status.

2 | METHODS

2.1 | Specification of the target trials

2.1.1 | Study overview

We compared the new use of semaglutide with the new use of other antidiabetic medications on first-time diagnoses of AD using a target trial emulation framework.[13,14] We assessed six T2DM patient populations without prior AD diagnosis: all patients, older patients (≥60), women, men, patients with obesity, and patients without obesity. Table S1 lists key protocol components. For each population, we specified seven target trials separately comparing semaglutide with insulins, metformin, dipeptidyl-peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter-2 inhibitors (SGLT2i), sulfonylureas (SUs), thiazolidinediones (TZDs), and other GLP-1RAs (albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide). The target trials are specified as follows.

2.1.2 | Eligibility criteria

Eligibility criteria for all target trials included patients with T2DM who had medical encounters between December 2017 and May 2021, had no use of any antidiabetic medications within the past 6 months ("new user"), and were diagnosed with at least one condition among semaglutide's prescription guidelines (eg, obesity, hypertension, hypercholesterolemia, heart diseases, stroke, or A1C ≥8.5%).[15] Exclusions included a history of AD, co-prescription of semaglutide and comparison medications, and certain medical conditions (pancreatitis, type 1 diabetes, thyroid cancer, gastroparesis) based on contraindications, warnings, and limited use information for semaglutide.[15] Additional criteria for subpopulations were as follows:

- Older patients: age ≥60 (age based on time of medication prescription)
- Women/men: gender-based inclusion
- Patients with obesity: recent medical encounters for obesity diagnosis within past 2 years
- Patients without obesity: excluded if they had a recent medical encounter for obesity diagnosis within past 2 years (Table S2)

2.1.3 | Treatment strategies

In each of the seven target trials, the treatment strategies were the initiation of semaglutide use at baseline (index event) or the initiation of comparison antidiabetic medication use at baseline (index event), but not both. For all treatment strategies, initiation of use is defined as the first prescription for the drug, consistent with an intention-to-treat design. The treatment strategy is assigned at baseline, regardless of medication use adherence, medication switch, or add-on.

2.1.4 | Study outcomes

The main outcome is a first-time diagnosis of AD (International Classification of Diseases, 10th revision [ICD-10] code G30 for "Alzheimer's

disease") as documented in patient EHRs. AD-related medication prescriptions (donepezil, rivastigmine, galantamine, memantine, aducanumab, lecanemab) were used as a secondary outcome. Two non-AD-specific healthcare measures were used for sensitivity analyses: overall medical encounters and outpatient medical encounters. Each outcome was analyzed separately (no multiple comparisons nor competing outcomes). Each eligible patient was followed from the index event until the occurrence of the outcome, death, loss to follow-up, or 3 years after the index event, whichever occurred first.

2.1.5 | Analysis approach

The causal estimates of interest represent the intention-to-treat effect of being assigned to the treatment strategies. Cumulative incidences were estimated using the Kaplan–Meier survival analysis in patients who were propensity-score matched (1:1 using nearest-neighbor greedy matching with a caliper of 0.25 times the standard deviation) for baseline covariates. Cox proportional hazards analyses were used to compare rates of time to events daily during the follow-up time after the index event. Hazard ratios (HRs) and 95% CIs were calculated. All models are adjusted for confounders at baseline by propensity-score-matching baseline covariates.

2.2 | Emulation of target trials

We explicitly emulated the target trials described previously using data and built-in analytic functions on the TriNetX Analytics platform. TriNetX is a global, federated, health research network providing access to deidentified and aggregated EHRs from approximately 113 million patients in 64 large healthcare organizations covering diverse geographic regions, age, race and ethnicity, income and insurance groups, and clinical settings.[16] This study analyzed deidentified and population-based EHR data within the TriNetX Analytics platform. The built-in analytics within the TriNetX Analytic platform analyzed patient-level data; however, only population-level results are reported to users. TriNetX data are HIPAA (Health Insurance Portability and Accountability Act) de-identified and access to protected health information is not allowed. Therefore, there is no risk for protected health information disclosure, and Institutional Review Board review was not required. The TriNetX platform has been successfully used in retrospective cohort studies for AD[17–19] and to evaluate associations of semaglutide with suicidal ideation,[20] cannabis use,[21] alcohol use,[7] and smoking[8] and for associations of GLP-1RAs with cancer risks.[22–24]

Available data elements of EHRs include extensive information on demographics, diagnoses, medications, procedures, laboratory tests, visits, and socioeconomic and lifestyle information. All covariates are either binary, categorical, or continuous but essentially guaranteed to exist (more details of TriNetX are in the Supplementary Material).

Each component of the target trial was emulated using EHRs from the TriNetX Analytics platform (more details of target trial emulation components are in Tables S1 to S4 and Figure S1). Patients were classified into drug treatment groups – semaglutide versus other antidiabetic medications (insulins, metformin, DPP-4i, SGLT2i, SU, TZDs, and other GLP-1RAs) – based on the first prescription in the study period (December 2017 to May 2021), which was the baseline or index event. The study period of December 2017 to May 2021 was chosen because semaglutide was approved as Ozempic to treat T2DM in December 2017 and before it was approved as Wegovy for weight loss in June 2023. Eligibility criteria and more than 50 baseline covariates were evaluated at baseline. The semaglutide group and each of the seven comparison treatment groups were separately propensity-score matched for covariates at the baseline to emulate randomization. After propensity-score matching, the semaglutide group and its corresponding comparison group were balanced.

2.2.1 | Statistical analysis

The data were collected and analyzed on June 24, 2024 within the TriNetX Analytics platform. All of the statistical analyses in this study, including propensity-score matching, Kaplan–Meier survival analysis, and Cox proportional hazards analysis, were done using built-in functions within the TriNetX Analytics platform that are implemented using Survival 3.2-3 in R version 4.0.2 and libraries and utilities for data science and statistics in Python version 3.7 and Java version 11.0.16.

RESEARCH IN CONTEXT

- **Systematic review**: The authors reviewed the literature using PubMed sources. Emerging evidence suggests semaglutide, a glucagon-like peptide receptor agonist (GLP-1RA) for type 2 diabetes mellitus (T2DM) and obesity, may have neuroprotective and anti-inflammatory effects. However, real-world evidence on its role in delaying or preventing Alzheimer's disease (AD) is lacking. The relevant references are appropriately cited.
- **Interpretation**: Our findings show that semaglutide was linked to lower risks of first-time AD diagnosis in T2DM patients compared to other antidiabetic medications, including other GLP-1RAs. These findings support further clinical trials to assess semaglutide's potential in delaying or preventing AD.
- **Future directions**: Future research should explore its effects in mild cognitive impairment, other dementias, and neurodegenerative diseases, as well as investigate other GLP-1RAs like tirzepitide and combination therapies with other antidiabetic medications. Additional preclinical and clinical studies are necessary to understand the mechanisms and establish causal effects through randomized trials.

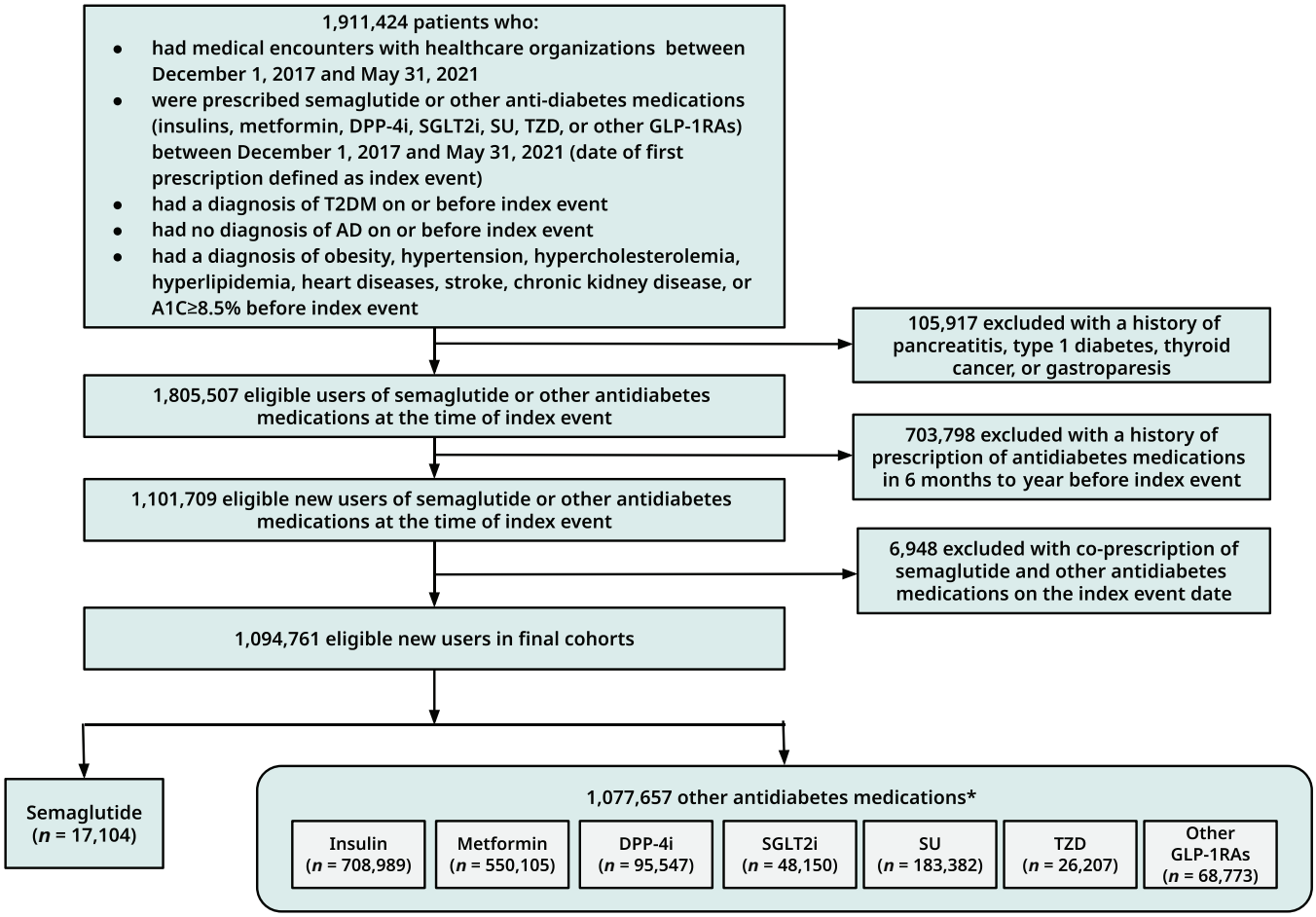


FIGURE 1 Study flow diagram. DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TUD, tobacco use disorder; TZD, thiazolidinedione. * The combined total of patients (n = 1,077,657) is not a sum of the patients from each of the seven comparison antidiabetic medication cohorts because a patient could be prescribed more than one antidiabetic medication during the study period, though there was no overlap between semaglutide and comparison medications groups. Other GLP-1RAs included albiglutide (0.5%), dulaglutide (60.6%), exenatide (10.6%), liraglutide (35.2%), and lixisenatide (2.1%).

Details of clinical codes for eligibility criteria, treatment strategies, outcomes, and baseline covariates are in Table S4.

3 | RESULTS

3.1 | Study populations

Figure 1 is a flow chart of the cohort composition. The study included 1,094,761 new users of antidiabetic medications, including 17,104 new users of semaglutide and 1,077,657 new users of other antidiabetic medications. Semaglutide was separately compared with each of the seven antidiabetic medication classes in patients with T2DM. Before propensity-score matching, the insulin and semaglutide groups differed by age, sex, ethnicity, diagnosis of obesity, some cardiovascular conditions, and AD-related risk factors and by overall medical encounters including outpatient visits. After propensity-score matching, comparison groups were balanced (Table 1).

3.2 | Associations of semaglutide and first-time diagnosis of AD in patients with T2DM

Patients with T2DM who were prescribed semaglutide had a significantly decreased risk of receiving a first-time diagnosis of AD during a 3-year follow-up compared with those prescribed other antidiabetic medications, with a HR of 0.33 (0.21 to 0.51) compared with insulins and 0.59 (0.37 to 0.95) compared with other GLP-1RAs (Figure 2A). Among older adults aged ≥60 years at the index event (average 67.9 ± 5.79), the overall 3-year risk of first-time diagnosis of AD was twice as high as in the general population (average 58.1 ± 12.1): 0.33% versus 0.16%. Nonetheless, a similar decrease in first-time diagnoses of AD was observed for semaglutide (Figure S2).

The 3-year cumulative incidence curves comparing semaglutide with each of the seven antidiabetic medications are shown in Figure 2B. The average follow-up times for semaglutide versus each comparison group are as follows: insulin (973.4 ± 101.3 vs 847.2 ± 190.0

TABLE 1 Characteristics of semaglutide group and insulin group before and after propensity-score matching.

	Before propensity-score matching			After propensity-score matching		
	Semaglutide	Insulin	SMD	Semaglutide	Insulin	SMD
Total number	17,104	708,989		17,087	17,087	
Age at index event (years, mean ± SD)	58.1 ± 12.1	64.9 ± 14.1	0.52[a]	58.1 ± 12.1	58.0 ± 14.8	0.03
Sex (%)						
Female	52.0	44.6	0.15[a]	52.0	53.1	0.02
Male	40.4	51.2	0.22[a]	40.4	39.8	0.01
Unknown	7.6	4.2	0.15[a]	7.6	7.1	0.02
Ethnicity (%)						
Hispanic/Latinx	5.8	9.4	0.13[a]	5.8	5.8	<0.001
Not Hispanic/Latinx	68.9	64.4	0.09	68.9	70.5	0.04
Unknown	25.3	26.2	0.02	25.2	23.6	0.04
Race (%)						
American Indian or Alaska Native	0.2	0.3	0.01	0.2	0.2	0.001
Asian	3.4	4.1	0.04	3.3	3.1	0.01
Black	14.9	18.4	0.09	14.9	15.3	0.009
Native Hawaiian or other Pacific Islander	0.9	0.8	0.007	0.9	0.9	<0.001
White	63.3	60.4	0.06	63.3	64.1	0.02
Unknown	14.4	12.7	0.05	14.4	13.5	0.03
Adverse socioeconomic determinants of health (%)	3.0	2.4	0.03	3.0	3.1	0.005
Problems related to lifestyle (%)	6.5	4.6	0.08	6.5	6.5	0.002
Type 2 diabetes mellitus (**T2DM) complications (%)**						
T2DM with hyperglycemia	38.1	23.9	0.31[a]	38.0	38.2	0.004
T2DMwith kidney complications	15.3	17.5	0.06	15.3	15.2	0.001
T2DMwith ophthalmic complications	7.8	6.3	0.06	7.8	7.7	0.004
T2DMwith neurological complications	17.1	13.8	0.09	17.1	17.2	0.004
T2DMwith circulatory complications	6.7	6.2	0.02	6.7	6.8	0.006
T2DMwith other specified complications	43.6	28.8	0.31[a]	43.6	43.7	0.003
T2DMwith unspecified complications	14.4	7.4	0.23[a]	14.4	14.4	<0.001
Pre-existing medical conditions, procedures, and medications (%)						
Morbid (severe) obesity due to excess calories	32.2	11.1	0.53[a]	32.1	31.4	0.01
Obesity, unspecified	42.6	18.0	0.56[a]	42.5	42.6	0.001
Alcohol-related disorders	1.9	3.8	0.12[a]	1.9	1.8	0.003
Tobacco use disorder	11.3	13.6	0.07	11.3	11.4	0.006
Depression	23.5	14.6	0.23[a]	23.4	23.4	<0.001
Conductive and sensorineural hearing loss	5.0	2.9	0.11[a]	5.0	4.9	0.004
Other and unspecified hearing loss	5.3	3.8	0.08	5.3	5.3	0.002
Sleep disorders	38.1	18.2	0.45[a]	38.1	37.7	0.007
Down syndrome	0.1	0.0	0.009	0.1	0.1	<0.001
Viral infections	6.2	4.0	0.10[a]	6.2	6.3	0.005

(Continues)

TABLE 1 (Continued)

	Before propensity-score matching			After propensity-score matching		
	Semaglutide	Insulin	SMD	Semaglutide	Insulin	SMD
COVID-19	1.5	1.9	0.03	1.5	1.5	0.004
Unspecified dementia	0.3	2.9	0.20[a]	0.3	0.3	0.001
Vascular dementia	0.1	0.6	0.09	0.1	0.1	0.002
Mild cognitive impairment	0.7	0.8	0.02	0.7	0.6	0.003
Hypertension	77.3	65.8	0.26*	77.3	78.8	0.04
Disorders of lipoprotein metabolism and other lipidemias	75.0	50.7	0.52[a]	74.9	76.1	0.03
Ischemic heart diseases	21.8	28.7	0.16[a]	21.8	22.2	0.01
Other forms of heart disease	28.6	37.2	0.19[a]	28.6	29.3	0.02
Cerebrovascular diseases	9.1	14.6	0.17[a]	9.1	9.3	0.009
Stroke	1.7	2.2	0.04	1.7	1.6	0.004
Diseases of arteries, arterioles, and capillaries	12.6	15.7	0.09	12.6	13.0	0.01
Metabolic syndrome and other insulin resistance	4.6	0.9	0.22[a]	4.5	4.1	0.02
Bariatric surgery	3.8	1.0	0.19[a]	3.8	3.5	0.02
Donepezil	0.3	1.0	0.08	0.3	0.4	0.009
Rivastigmine	0.1	0.1	0.02	0.1	0.1	<0.001
Galantamine	0.1	0.0	0.02	0.1	0.1	<0.001
Memantine	0.3	0.5	0.04	0.3	0.3	<0.001
Aspirin	33.8	30.7	0.07	33.8	34.4	0.01
Non-steroidal anti-inflammatory analgesics	21.6	12.4	0.25[a]	21.6	21.5	0.003
Overall medical visits	98.2	86.6	0.45[a]	98.2	98.6	0.03
Outpatient medical visits	88.7	70.1	0.47[a]	88.7	89.3	0.02

Note: Shown are groups before and after propensity-score matching for the listed variables. The status of variables was based on the presence of related clinical codes any time up to 1 day before the index event (first prescription of semaglutide or insulin during the period from December 2017 to May 2021).
Abbreviations: SD, standard deviation; SMD, standardized mean differences.
[a]SMD greater than 0.1, a threshold indicating cohort imbalance. Adverse socioeconomic determinants of health included housing and economic circumstances, upbringing, education, physical environment, and social environment. Problems with lifestyle included tobacco use, lack of physical exercise, inappropriate diet and eating habits, and others.

days), metformin (973.4 ± 101.4 vs 921.4 ± 144.2 days), DPP-4i (970.1 ± 103.7 vs 893.1 ± 160.4 days), SGLT2i (969.0 ± 104.3 vs 896.4 ± 157.2 days), SU (971.6 ± 102.5 vs 892.9 ± 162.9 days), TZD (955.8 ± 113.4 vs 868.4 ± 176.0 days), and other GLP-1RAs (973.1 ± 101.5 vs 933.3 ± 133.8 days). The separation between the curves begins within the first 30 days and continues to diverge, indicating the potential sustained benefits of semaglutide in delaying or slowing AD development.

3.3 | Associations of semaglutide and first-time diagnosis of AD in patients with T2DM by gender

After propensity-score matching, there were 8881 women in each of the balanced semaglutide versus insulin groups (average age 56.8 years) and 6895 men in each of the balanced semaglutide versus insulin groups (average age 59.5 years). The characteristics of the semaglutide and insulin groups for women and for men before and after propensity-score matching are presented in Tables S5 and S6. Semaglutide was associated with decreased risk for first-time diagnosis of AD in women with a HR of 0.22 compared with insulins and a HR of 0.53 compared with other GLP-1RAs (Figure 3A). Similar trends were observed in men, though the associations were weaker than in women, but with overlapping confidence intervals (Figure 3B).

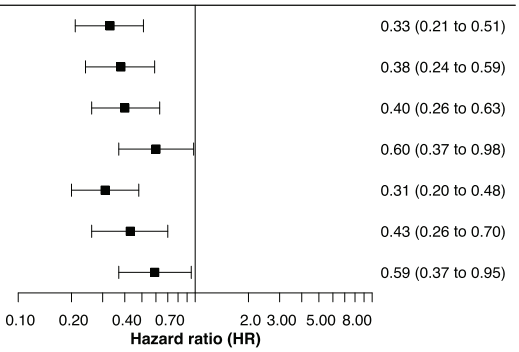
3.4 | Associations of semaglutide and first-time diagnoses of AD in patients with T2DM, with and without obesity

Among the subpopulation of patients with obesity (who had a recent medical encounter for obesity diagnosis in the past 2 years), semaglu-

(A)

Risk of first–time diagnosis of Alzheimer's disease in patients with type 2 diabetes (comparison between matched semaglutide vs other antidiabetes medications groups)

Size/Group	Exposure group	Comparison group	Exposure Group Cases (overall risk)	Comparison Group Cases (overall risk)	HR (95% CI)
17,087	Semaglutide	Insulin	27 (0.16%)	73 (0.43%)	0.33 (0.21 to 0.51)
17,080	Semaglutide	Metformin	27 (0.16%)	68 (0.40%)	0.38 (0.24 to 0.59)
15,878	Semaglutide	DPP–4i	27 (0.17%)	62 (0.39%)	0.40 (0.26 to 0.63)
15,288	Semaglutide	SGLT2i	26 (0.17%)	40 (0.26%)	0.60 (0.37 to 0.98)
16,503	Semaglutide	SU	27 (0.16%)	80 (0.49%)	0.31 (0.20 to 0.48)
10,847	Semaglutide	TZD	24 (0.22%)	51 (0.47%)	0.43 (0.26 to 0.70)
17,029	Semaglutide	Other GLP–1RAs	27 (0.16%)	44 (0.26%)	0.59 (0.37 to 0.95)



(B)

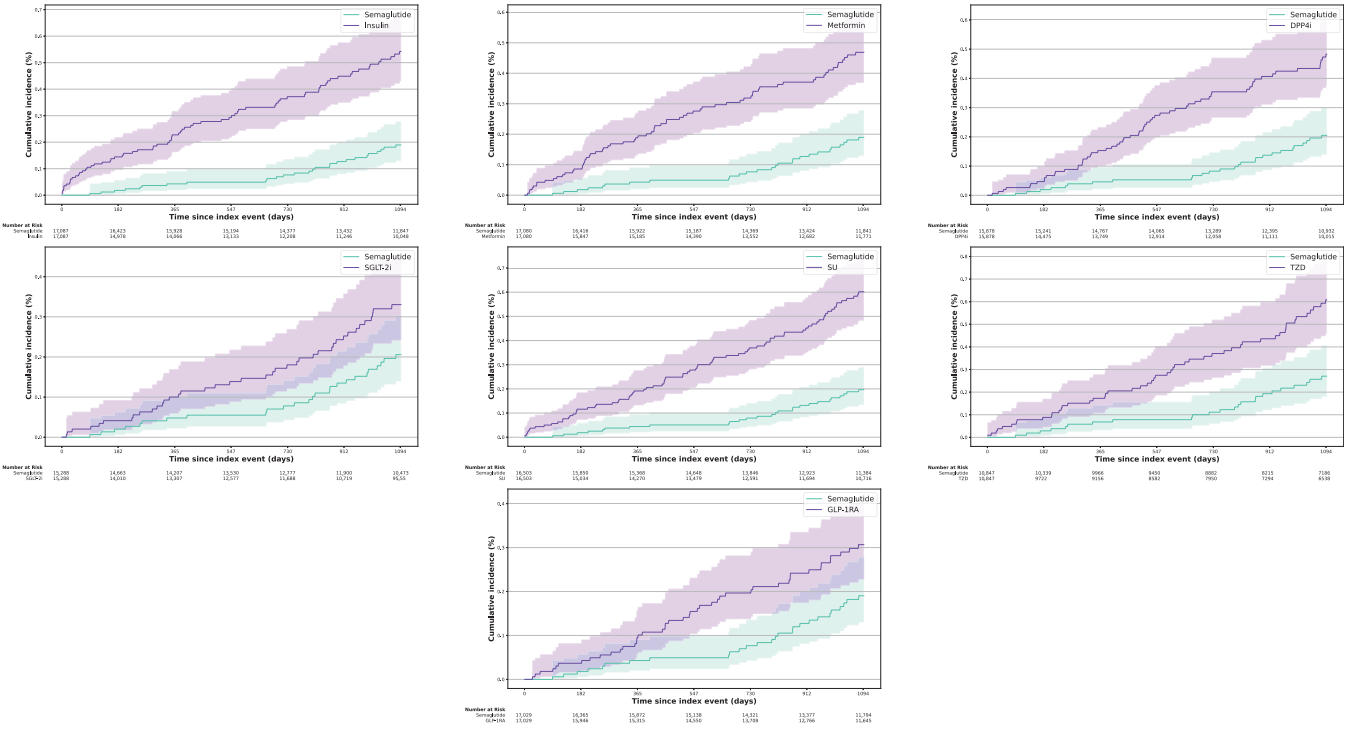


FIGURE 2 (A) Comparison of first-time diagnosis of AD between propensity-score-matched semaglutide versus other antidiabetic medications groups in patients with T2DM and (B) cumulative AD incidences for the seven comparisons between propensity-score-matched semaglutide versus other antidiabetic medication groups. The exposure and comparison groups were propensity-score matched for variables listed in Table 1, and the status of variables was based on the presence of related clinical codes any time up to 1 day before the index event (the first prescription of semaglutide vs comparison medication classes from December 2017 to May 2021). Outcomes were followed for 3 years after the index event for both matched exposure and comparison groups. Individuals in the matched groups were followed from the index event until the occurrence of the outcome, death, or loss to follow-up or 3 years after the index event, whichever occurred first. Hazard rates were calculated using a Cox proportional hazards model with censoring applied. Overall risk = number of patients with outcomes during follow-up time window/number of patients in cohort at beginning of time window. DPP-4i, dipeptidyl-peptidase-4 inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitors; SU, sulfonylureas; TZD, thiazolidinediones. Other GLP-1RAs included albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.

tide was associated with decreased risk of first-time diagnosis of AD compared to other antidiabetic medication groups, with a HR of 0.29 compared with insulin and a HR of 0.59 compared with other GLP-1RAs (Figure 4). Similar results were observed in patients without a recent medical encounter with an obesity diagnosis (Figure 4). The characteristics of the semaglutide versus insulin groups for T2DM patients with and without obesity before and after propensity-score matching are presented in Tables S7 and S8.

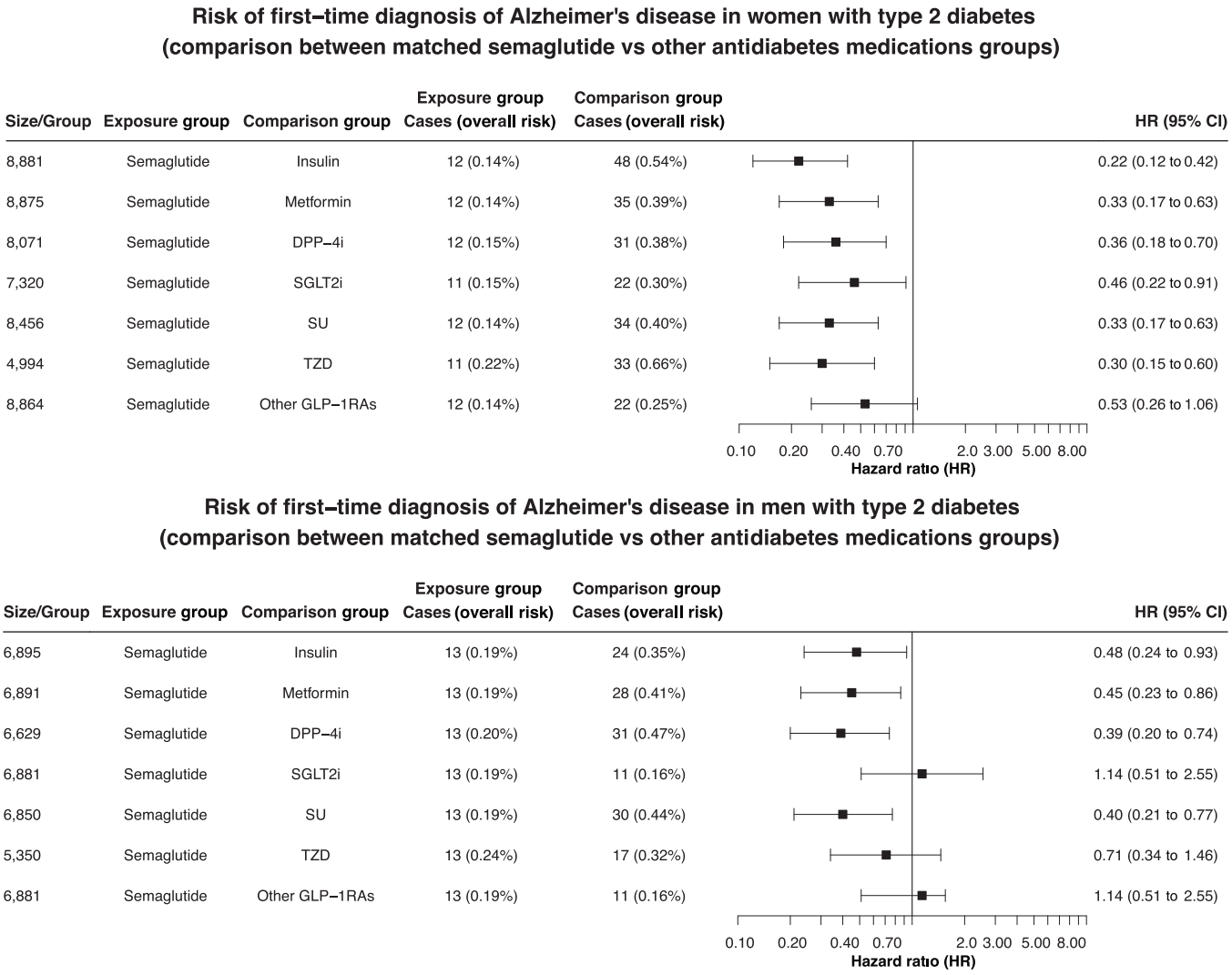


FIGURE 3 Comparison of AD incidence (first-time diagnosis) between propensity-score-matched semaglutide versus other antidiabetic medications groups in women with T2DM and in men with T2DM. AD, Alzheimer's disease; T2DM, type 2 diabetes mellitus.

3.5 | Associations of semaglutide and AD-related medication prescriptions in patients with T2DM

We examined AD-related medication prescriptions (donepezil, rivastigmine, galantamine, memantine, aducanumab, and lecanemab) as an alternative outcome in patients with T2DM who had no prior diagnosis of AD. Semaglutide was associated with a decreased risk of AD-related medication prescriptions compared with other antidiabetic medications in patients with T2DM, with and without obesity (Figure S3), consistent with the main finding based on a first-time diagnosis of AD.

3.6 | Sensitivity analysis

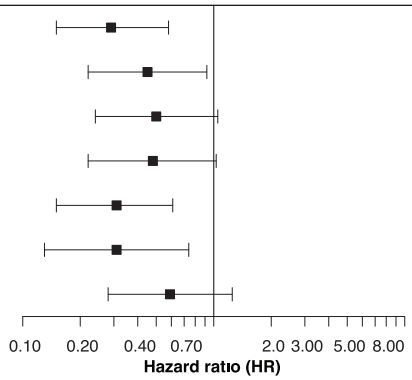
As a sensitivity analysis of potential differences in overall healthcare utilization, we compared both the overall and outpatient medical encounters between the matched groups. The semaglutide group did not differ substantially from the comparison groups in overall or outpatient medical encounters, though most of the comparisons were statistically significant, with a HR from 0.87 to 1.14, during a 3-year follow-up (Figure S4).

4 | DISCUSSION

In our study of real-world populations with T2DM, a high-risk group for AD, semaglutide showed a lower risk of first-time AD diagnosis or AD-related medication prescriptions compared to insulin, other non-insulin/non-GLP-1RAs, and other GLP-1RAs. These results were similar for older patients, both genders, and those with and without obesity. Cumulative incidence curves began to diverge within 30 days and continued to separate thereafter, indicating semaglutide's potential to delay or slow AD development with sustained effects.

Risk of first–time diagnosis of Alzheimer's disease in patients with type 2 diabetes (with obesity) (comparison between matched semaglutide vs other antidiabetes medications groups)

Size/Group	Exposure group	Comparison group	Exposure group Cases (overall risk)	Comparison group Cases (overall risk)	HR (95% CI)
9,533	Semaglutide	Insulin	11 (0.12%)	33 (0.35%)	0.29 (0.15 to 0.58)
9,530	Semaglutide	Metformin	11 (0.12%)	23 (0.24%)	0.45 (0.22 to 0.92)
8,224	Semaglutide	DPP–4i	11 (0.13%)	20 (0.24%)	0.50 (0.24 to 1.05)
7,649	Semaglutide	SGLT2i	<10 (<0.13%)	19 (0.25%)	0.48 (0.22 to 1.03)
8,867	Semaglutide	SU	11 (0.12%)	33 (0.37%)	0.31 (0.15 to 0.61)
4,256	Semaglutide	TZD	<10 (<0.24%)	20 (0.47%)	0.31 (0.13 to 0.74)
9,448	Semaglutide	Other GLP–1RAs	11 (0.12%)	18 (0.19%)	0.59 (0.28 to 1.25)



Risk of first–time diagnosis of Alzheimer's disease in patients with type 2 diabetes (without obesity) (comparison between matched semaglutide vs other antidiabetes medications groups)

Size/Group	Exposure group	Comparison group	Exposure group Cases (overall risk)	Comparison group Cases (overall risk)	HR (95% CI)
7,544	Semaglutide	Insulin	16 (0.21%)	44 (0.58%)	0.32 (0.18 to 0.57)
7,548	Semaglutide	Metformin	16 (0.21%)	38 (0.50%)	0.41 (0.23 to 0.73)
7,507	Semaglutide	DPP–4i	16 (0.21%)	32 (0.43%)	0.47 (0.26 to 0.86)
7,539	Semaglutide	SGLT2i	16 (0.21%)	29 (0.39%)	0.54 (0.29 to 0.99)
7,532	Semaglutide	SU	16 (0.21%)	43 (0.57%)	0.35 (0.20 to 0.62)
6,422	Semaglutide	TZD	15 (0.23%)	43 (0.67%)	0.33 (0.18 to 0.59)
7,539	Semaglutide	Other GLP–1RAs	16 (0.21%)	29 (0.39%)	0.54 (0.29 to 0.99)

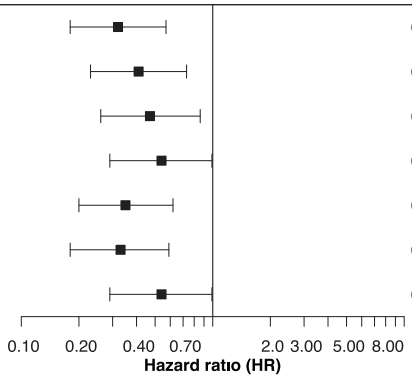


FIGURE 4 Comparison of first-time diagnosis of AD between propensity-score matched semaglutide versus other antidiabetic medication groups in patients with T2DM who had recent medical encounters for obesity diagnosis in the past 2 years and in those who did not. AD, Alzheimer's disease; T2DM, type 2 diabetes mellitus.

Our study findings align with recent evidence suggesting GLP-1RAs like semaglutide may protect cognitive function.[25,26] Preclinical research indicates semaglutide's potential in reducing Aβ-mediated neurotoxicity, enhancing autophagy, improving brain glucose uptake, and reducing Aβ plaques and tau tangles.[27,28] Clinical data, including studies with dulaglutide, show GLP-1RAs can reduce cognitive impairment in patients with T2DM.[29] Data pooled from three randomized, placebo-controlled trials and nationwide prescription registers from Demark showed that GLP-1RAs were associated with a 53% reduction in all-cause dementia in patients with T2DM.[30] Our large-scale study of 1,094,761 US patients with T2DM found semaglutide associated with a 40% to 70% decrease in first-time AD diagnoses, including a 40% reduction compared to other GLP-1RAs. Ongoing randomized trials are assessing semaglutide's therapeutic effects in early AD.[10,11] Our findings support conducting future prevention trials to determine semaglutide's ability to delay or slow down the onset of AD.

AD pathology is multifactorial and complex. GLP receptors are expressed in various organs, influencing multiple intracellular responses that could directly affect AD development or progression in the brain.[25] Insulin dysregulation affects key pathological features of AD.[31]

Antidiabetic medications have shown promise in improving cognition, Aβ clearance, tau phosphorylation, neurotransmitter turnover, synaptic loss, bioenergetics, vascular function, inflammation, and lipid metabolism in AD.[31–35] Our study shows that semaglutide significantly reduces first-time AD diagnoses compared to other antidiabetic medications, suggesting potential benefits beyond insulin resistance improvement. This is further supported by the data comparing semaglutide with SGLT2i. Indeed, SGLT2i reduces blood glucose independent of insulin sensitivity and secretion.[36] SGLT2i crosses the blood–brain barrier and has neuroprotective effects by reducing neuroinflammation, oxidative stress, mitochondrial dysfunction, and increasing brain-derived neurotrophic factor.[37] A recent large

population-based cohort study showed that SGLT2i was associated with a lower risk of dementia compared with DPP-4i.[38] Our study shows that semaglutide was associated with significantly lower AD first-time diagnosis compared with SGLT2i, with an effect more profound than that of DPP4i. These findings align with prior research suggesting semaglutide may offer neuroprotective effects via pathways like neuroinflammation and mitochondrial function beyond insulin resistance improvement.

While the underlying mechanisms of the observed association of semaglutide and reduced risk of AD are unknown, they could also reflect semaglutide's improvement of AD risk factors such as T2DM, obesity, cardiovascular diseases, smoking, alcohol drinking, and depression, among others. Semaglutide was shown to improve cardiovascular health in patients with T2DM or obesity.[5,6] We recently reported that semaglutide was associated with reduced risks for alcohol use disorders[7] and tobacco use disorders.[8] A large cohort study in the United States showed that GLP-1RAs including semaglutide were correlated with lower risk of depression and anxiety.[9] Findings from this study support the idea that semaglutide could help delay or prevent the onset of AD by mitigating these modifiable risk factors.

In addition, GLP-1RAs have been reported to influence many pathways associated with the progression of AD, including oxidative stress, mitochondrial dysfunction, altered glycation status, and inflammation.[39] GLP-1 receptors have been identified in neurons, astrocytes, and microglia, all of which have been implicated in the cascade of events that drive the pathology of AD. These receptors also exist on macrophages and on cells derived from the macrophage lineage such as microglia and astrocytes, where their activation can reduce secretion of pro-inflammatory cytokines and increase anti-inflammatory mediators.[40] A recent study showed that semaglutide reduces the severity of polymicrobial inflammation and neuroinflammation through central neuronal GLP-1 receptors.[41] However, it is not possible from our studies to implicate any of these in the delay or prevention of an AD diagnosis, though it seems likely that the mechanism involves more than vigorous blood sugar control, given our comparison of antidiabetic drugs and weight loss given our subgroup analysis by obesity status.

Almost two-thirds of AD cases are in women, and the underlying mechanisms remain unknown.[1] In our study, semaglutide was associated with a more profound decrease in first-time diagnoses of AD in women with a HR 0.22 (0.12 to 0.42) than in men with HR 0.48 (0.24 to 0.93), though the confidence intervals overlapped and sample sizes were limited. However, the characteristics of these two study populations differed, with women being younger than men (average age 56.8 vs 59.6 years) and having a higher prevalence of obesity and depression and a lower prevalence of cardiovascular diseases. This analysis demonstrates the importance of conducting separate analyses based on gender since the genders' different characteristics may inform targeted prevention efforts. Larger, longer-term studies are needed to confirm these differences and to understand what drives the potential differential effects.

Obesity is now recognized as a major modifiable risk factor for AD and related dementias in the United States.[42] Semaglutide was approved as Ozempic for treating T2DM in December 2017 and as Wegovy for weight loss in June 2021. Our study population comprised patients with T2DM prescribed semaglutide between December 2017 and May 2021, before its approval for weight loss. Due to sample size limitations and a shorter follow-up time, we did not include patients prescribed semaglutide as Wegovy for obesity. However, we conducted stratified analyses by obesity status among T2DM patients and found a consistent decrease in first-time AD diagnosis regardless of obesity status. These findings suggest that semaglutide may have beneficial effects on delaying the onset of AD through mechanisms beyond weight loss.[43] Further research is needed to investigate semaglutide's effects in patients with obesity, both with and without T2DM.

Our study had several limitations. First, retrospective observational studies using patient EHRs, like ours, inherently can suffer from overdiagnosis, underdiagnosis, and misdiagnosis, as well as unmeasured or uncontrolled confounders and biases, precluding causal inference. Second, our patient cohort was sourced from the TriNetX Analytics platform, necessitating validation of results in other EHR databases and analytics platforms. Third, due to semaglutide's recent approval for treating T2DM, our follow-up period was limited to 3 years. Though we observed a significant reduction in AD risk in a high-risk population with T2DM and also high comorbidity (43% obesity and 77% hypertension), future studies should explore longer follow-ups and different populations. Fourth, we used the ICD-10 diagnosis code for AD as the primary outcome and corroborated the findings using AD-related medication prescriptions. However, AD diagnosis is challenging, and the diagnostic criteria are usually not documented in EHRs, which could also be influenced by many factors, including socioeconomic factors and biomarker usage.[44] Nevertheless, both exposure and comparison groups were drawn from the same healthcare organizations and were propensity-score matched for more than 50 variables, including socioeconomic and lifestyle factors, so relative rates of first-time diagnosis of AD as measured by HR are likely valid. Fifth, due to sample size limitations, this study could not examine the potential therapeutic benefits of semaglutide in patients with AD. A recent randomized placebo-controlled clinical trial of 204 patients with mild AD showed that liraglutide, a first-generation GLP-1RA, slowed the reduction in whole cortical gray matter and frontal, temporal, and parietal lobe volume compared to placebo.[45] These findings suggest that semaglutide could offer a promising therapeutic approach to treating AD. Finally, EHRs in TriNetX lack data on medication adherence and explicit tracking of cognitive impairment. Limited genomics data, particularly APOE genotypes, prevented further analysis by allele status. Practice pattern variations among healthcare organizations and patient healthcare utilization could not explicitly be controlled, though sensitivity analyses indicated similar healthcare utilization between semaglutide and comparison groups, minimizing potential surveillance bias.

Our findings support further clinical evaluation of semaglutide's role in mitigating AD initiation and development in patients with T2DM. Future research should explore its effects in mild cognitive impairment, other dementias, and neurodegenerative diseases, as well as investigate other GLP-1RAs like tirzepitide and combination therapies with other antidiabetic medications. Additional preclinical and clinical stud-

ies are needed to shed light on the mechanisms of the potential benefits of semaglutide in preventing or delaying the onset of AD and establish causal effects through randomized trials.

AUTHOR CONTRIBUTIONS

Rong Xu conceived, supervised, and designed the study. William Wang performed the data analysis and created figures and tables. Rong Xu drafted the manuscript. All authors, including QuangQiu Wang, Xin Qi, Mark Gurney, George Perry, Nora D. Volkow, Pamela B. Davis, and David C. Kaelber, critically contributed to the results, interpretation, and manuscript preparation. We confirm the originality of the content. Rong Xu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENTS

We would like to acknowledge support from Dr. Nathan A. Berger (1940 to 2024) who contributed in important ways to the early conception of this study and had been the primary research mentor of William Wang since 2020. Rong Xu, Pamela B Davis, David C Kaelber received funding which went to Case Western Reserve University, from the National Institute on Aging (AG057557, AG061388, AG062272, AG076649) and the National Center for Advancing Translational Sciences (NCATS) (TR004528).

CONFLICT OF INTEREST STATEMENT

All authors declare no competing interests. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

This study used population-level aggregate and HIPAA de-identified data collected by the TriNetX platform ("US Collaborative Network") and available from TriNetX, LLC (https://trinetx.com/), but third-party restrictions apply to the availability of these data. The data were used under license for this study with restrictions that do not allow for the data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs may be incurred, and a data-sharing agreement may be necessary. Data specific to this study, including diagnosis codes and cohort characteristics in aggregated format, are included in the manuscript as tables, figures, and supplementary files. Data through the TriNetX platform is queried in real time, with results being returned typically in seconds to minutes. Data from the underlying electronic health records of participating healthcare organizations are refreshed in the TriNetX platform from daily to every couple of months depending on the healthcare organization.

CONSENT STATEMENT

This study did not involve human subjects, and consent was not necessary.

CODE AVAILABILITY

All the statistical analyses in this study, including propensity-score matching and Cox proportional hazards, used web-based built-in functions within the TriNetX Analytics platform that are implemented using Survival version 3.2-3 in R version 4.0.2 and libraries/utilities for data science and statistics in Python version 3.7 and Java version 11.0.16. Data and code to recreate findings in the study can be accessed at https://github.com/bill-pipi/semaglutide_AD

REFERENCES

1. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3708-3821.
2. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446.
3. Committee on the Public Health Dimensions of Cognitive Aging, Board on Health Sciences Policy, Institute of Medicine. *Cognitive Aging: Progress in Understanding and Opportunities for Action*. In Blazer DG, Yaffe K, Liverman CT, eds. National Academies Press (US); 2015.
4. World Health Organization. Risk reduction of cognitive decline and dementia: WHO guidelines. World Health Organization. Published January 1, 2019. Accessed June 29, 2024. https://www.who.int/publications/i/item/9789241550543
5. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
6. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
7. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population. *Nat Commun*. 2024;15(1):4548.
8. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with tobacco use disorder in patients with type 2 diabetes. target trial emulation using real-world data. *Ann Intern Med*. 2024;177(8):1016-1027. doi:10.7326/M23-2718
9. Anna Miller RN, Joyce B, Kersten Bartelt RN, Deckert J, Most GLP-1 medications correlated with a lower likelihood of anxiety and depression diagnoses. Accessed July 4, 2024. https://www.epicresearch.org/articles/most-glp-1-medications-correlated-with-a-lower-likelihood-of-anxiety-and-depression-diagnoses
10. Clinicaltrials.gov. A research study investigating semaglutide in people with early Alzheimer's disease (EVOKE). Accessed October 10, 2023. https://clinicaltrials.gov/study/NCT04777396
11. Clinicaltrials.gov. A randomised double-blind placebo-controlled clinical trial investigating the effect and safety of oral semaglutide in subjects with early Alzheimer´s disease (EVOKE Plus). Published June 6, 2024. Accessed June 27, 2024. https://www.clinicaltrials.gov/study/NCT04777409?cond=Alzheimer%20Disease&intr=semaglutide&rank=2
12. A randomised double-blind placebo-controlled clinical study investigating the effects of semaglutide S.C. once-weekly versus placebo on central and peripheral inflammation in participants with Alzheimer's disease. Published June 6, 2024. Accessed June 27, 2024. https://www.clinicaltrials.gov/study/NCT05891496?cond=Alzheimer%20Disease&intr=semaglutide&rank=1
13. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758-764.
14. Hernán MA, Wang W, Leaf DE. Target trial emulation: a framework for causal inference from observational data. *JAMA*. 2022;328(24):2446-2447.

15. Novo Nordisk. Ozempic prescribing information. Accessed June 27, 2024. https://www.ozempic.com/prescribing-information.html
16. TriNetX—The World's Largest, Living Ecosystem of Real-World Data and Evidence. TriNetX. Published August 26, 2021. Accessed January 16, 2024. https://trinetx.com/real-world-data/
17. Wang L, Davis PB, Volkow ND, Berger NA, Kaelber DC, Xu R. Association of COVID-19 with new-onset Alzheimer's disease. *J Alzheimers Dis*. 2022;89(2):411-414. doi:10.3233/JAD-220717
18. Gorenflo MP, Davis PB, Kendall EK, Olaker VR, Kaelber DC, Xu R. Association of aspirin use with reduced risk of developing Alzheimer's disease in elderly ischemic stroke patients: a retrospective cohort study. *J Alzheimers Dis*. 2023;91(2):697-704.
19. Wang L, Davis PB, Kaelber DC, Xu R. COVID-19 breakthrough infections and hospitalizations among vaccinated patients with dementia in the United States between December 2020 and August 2021. *Alzheimers Dement*. 2022;19(2):421-432. doi:10.1002/alz.12669
20. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nat Med*. 2024;30:168-176.
21. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a retrospective cohort study. *Mol Psychiatry*. 2024;29(8):2587-2598. doi:10.1038/s41380-024-02498-5
22. Wang L, Wang W, Kaelber DC, Xu R, Berger NA. GLP-1 receptor agonists and colorectal cancer risk in drug-naive patients with type 2 diabetes, with and without overweight/obesity. *JAMA Oncol*. 2023;10(2):256-258. doi:10.1001/jamaoncol.2023.5573
23. Wang L, Berger NA, Kaelber DC, Xu R. Association of GLP-1 receptor agonists and hepatocellular carcinoma incidence and hepatic decompensation in patients with type 2 diabetes. *Gastroenterology*. 2024;167(4):689-703. doi:10.1053/j.gastro.2024.04.029
24. Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-like peptide 1 receptor agonists and 13 obesity-associated cancers in patients with type 2 diabetes. *JAMA Network Open*. 2024;7(7):e2421305.
25. Hammoud R, Drucker DJ. Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1. *Nat Rev Endocrinol*. 2023;19(4):201-216.
26. Mahapatra MK, Karuppasamy M, Sahoo BM. Therapeutic potential of semaglutide, a newer GLP-1 receptor agonist, in abating obesity, non-alcoholic steatohepatitis and neurodegenerative diseases: a narrative review. *Pharm Res*. 2022;39(6):1233-1248.
27. Chang YF, Zhang D, Hu WM, Liu DX, Li L. Semaglutide-mediated protection against Aβ correlated with enhancement of autophagy and inhibition of apotosis. *J Clin Neurosci*. 2020;81:234-239.
28. Wang ZJ, Li XR, Chai SF, et al. Semaglutide ameliorates cognition and glucose metabolism dysfunction in the 3xTg mouse model of Alzheimer's disease via the GLP-1R/SIRT1/GLUT4 pathway. *Neuropharmacology*. 2023;240:109716.
29. Cukierman-Yaffe T, Gerstein HC, Colhoun HM, et al. Effect of dulaglutide on cognitive impairment in type 2 diabetes: an exploratory analysis of the REWIND trial. *Lancet Neurol*. 2020;19(7):582-590.
30. Nørgaard CH, Friedrich S, Hansen CT, et al. Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. *Alzheimers Dement*. 2022;8(1):e12268.
31. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. *Lancet Neurol*. 2020;19(9):758-766.
32. Michailidis M, Tata DA, Moraitou D, et al. Antidiabetic drugs in the treatment of Alzheimer's disease. *Int J Mol Sci*. 2022;23(9):4641.
33. Hsu CC, Wahlqvist ML, Lee MS, Tsai HN. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. *J Alzheimers Dis*. 2011;24(3):485-493.
34. Perry T, Haughey NJ, Mattson MP, Egan JM, Greig NH. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. *J Pharmacol Exp Ther*. 2002;302(3):881-888.
35. Angelopoulou E, Piperi C. DPP-4 inhibitors: a promising therapeutic approach against Alzheimer's disease. *Ann Transl Med*. 2018;6(12):255-255.
36. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. *Cardiovasc Diabetol*. 2020;19(1):98.
37. Pawlos A, Broncel M, Woźniak E, Gorzelak-Pabiś P. Neuroprotective effect of SGLT2 inhibitors. *Molecules*. 2021;26(23):7213.
38. Wu CY, Iskander C, Wang C, et al. Association of sodium–glucose cotransporter 2 inhibitors with time to dementia: a population-based cohort study. *Diabetes Care*. 2023;46(2):297-304.
39. Chen SD, Chuang YC, Lin TK, Yang JL. Alternative role of glucagon-like Peptide-1 receptor agonists in neurodegenerative diseases. *Eur J Pharmacol*. 2023;938(175439):175439.
40. Bendotti G, Montefusco L, Lunati ME, et al. The anti-inflammatory and immunological properties of GLP-1 receptor agonists. *Pharmacol Res*. 2022;182(106320):106320.
41. Wong CK, McLean BA, Baggio LL, et al. Central glucagon-like peptide 1 receptor activation inhibits Toll-like receptor agonist-induced inflammation. *Cell Metab*. 2024;36(1):130-143.e5.
42. Nianogo RA, Rosenwohl-Mack A, Yaffe K, Carrasco A, Hoffmann CM, Barnes DE. Risk factors associated with alzheimer disease and related dementias by sex and race and ethnicity in the US. *JAMA Neurol*. 2022;79(6):584-591.
43. Alharbi SH. Anti-inflammatory role of glucagon-like peptide 1 receptor agonists and its clinical implications. *Ther Adv Endocrinol Metab*. 2024;15:20420188231222367. doi:10.1177/20420188231222367
44. Kerwin D, Abdelnour C, Caramelli P, et al. Alzheimer's disease diagnosis and management: perspectives from around the world. *Alzheimers Dement*. 2022;14(1):e12334. doi:10.1002/dad2.12334
45. Edison P. Evaluation of Novel GLP-1 analogue in the treatment of Alzheimer's disease. In: *Alzheimer's Association International Conference*. ALZ; 2024. https://alz.confex.com/alz/2024/meetingapp.cgi/Paper/89799

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang W, Wang QQ, Qi X, et al. Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US. *Alzheimer's Dement*. 2024;1-12. https://doi.org/10.1002/alz.14313