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GLP-1 receptor agonists versus Sitagliptin and incident Alzheimer's disease in type 2 diabetes: A propensity score-matched TriNetX cohort study

Meet P. Kachhadia[1], Piyush Puri[2], Usmaan Topiwala[3], Parth Pambhar[4], Akshara Dhami[4], Juber D. Shaikh[5], Gurnoor Gill1, Samarth Shah[6], Jay Patel[7] & Harshal A. Sanghvi[8,*]

[1]Department of Neurology, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA; [2]Department of Internal Medicine, Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals/Queens, New York, NY, USA; [3]Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India; [4]Prime Healthcare, IL, USA; [5]Department of Neurology, Henry Ford Hospital, Detroit, MI, USA; [6]Department of Technology and Clinical Trials, Advanced Research LLC, FL, USA; [7]Department of Biomedical Engineering, Florida Atlantic University, Boca Raton, FL, USA; [8]Department of Information Technology and Operations Management, College of Business, Florida Atlantic University, Boca Raton, FL, USA; *Corresponding author

Affiliation URLs:

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Author contact:
Meet P. Kachhadia - E-mail: mkachhadia@health.fau.edu
Piyush Puri - E-mail: piyush.puri@mssm.edu
Usmaan Topiwala - E-mail: usmaantopiwala@gmail.com
Parth Pambhar - E-mail: parthpambhar@gmail.com
Akshara Dhami - E-mail: akidhami24@gmail.com
Juber D. Shaikh - E-mail: jubershaikh703@yahoo.com
Gurnoor Gill - E-mail: ggill2023@health.fau.edu
Samarth Shah - E-mail: samarthshah341@gmail.com
Jay Patel - E-mail: jay16501@gmail.com
Harshal A. Sanghvi - E-mail: hsanghvi2020@fau.edu

Abstract:
Type 2 diabetes mellitus (T2DM) raises Alzheimer's disease (AD) risk and GLP-1 receptor agonists (GLP-1 RAs) show neuroprotective signals, yet head-to-head comparisons against sitagliptin are limited. Using the TriNetX US Collaborative Network, we propensity score-matched T2DM patients prescribed GLP-1 RAs versus sitagliptin (198,976 per cohort) for incident AD and a broad dementia composite. Incident AD occurred in 0.51% versus 1.80% (hazard ratio 0.452; 95% CI 0.421-0.486; P < 0.001). The dementia composite occurred in 3.03% versus 8.58% (hazard ratio 0.553; 95% CI 0.536-0.570; P < 0.001). Thus, data shows that given substantial follow-up imbalance and a non-standard multi-agent exposure definition, these associations are hypothesis-generating rather than evidence of causal neuroprotection.

Keywords: GLP-1 receptor agonists (GLP-1 RAs), Alzheimer's disease (AD), type 2 diabetes mellitus (T2DM), dementia, sitagliptin, propensity score matching, TriNetX

Background:
Alzheimer's disease (AD) is the leading cause of dementia and affects an estimated 7.2 million Americans aged 65 years and older **[1]**. Type 2 diabetes mellitus (T2DM) is an independent risk factor for AD **[2, 3]**, with shared mechanisms that include cerebral insulin resistance, neuroinflammation, amyloid-beta deposition and cerebrovascular injury **[3]**. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce amyloid-beta accumulation and neuroinflammation and restore synaptic plasticity in preclinical models **[4, 5]**. GLP-1 receptors are expressed in hippocampal and cortical regions **[6]**. Observational and emulated-trial data report lower dementia risk among GLP-1 RA users than among users of DPP-4 inhibitors **[7, 8]** and a meta-analysis of randomized trials reported an odds ratio of 0.55 for dementia with GLP-1 RAs **[9]**. Direct comparisons between GLP-1 RAs and DPP-4 inhibitors, a related incretin-based class that raises endogenous GLP-1, remain limited **[7, 10, 11 and 12]**. Therefore, it is of interest to report the incident AD and broad dementia among GLP-1 RA versus sitagliptin users with T2DM after propensity score matching, using the TriNetX US Collaborative Network.

Materials and Methods:

Study design and data source:
This retrospective cohort study used the TriNetX US Collaborative Network, a HIPAA-compliant federated platform of de-identified electronic health records from 66 US healthcare organizations **[10, 11]**. The analysis was performed on April 12, 2026. Because only aggregate de-identified data were queried through the federated network, the study met criteria for non-human-subjects research and informed consent was not required.

Study population, exposure and outcomes:
Cohort 1 comprised adults with T2DM (ICD-10 E11) prescribed semaglutide (RxNorm 1991302) and at least one additional GLP-1 RA among liraglutide (475968), dulaglutide (1551291), or exenatide (60548). This multi-agent requirement was intended to capture sustained, intensive class exposure; we note explicitly that simultaneous prescription of two GLP-1 RAs is not a guideline-endorsed regimen and does not reflect routine practice (see Limitations). Cohort 2 comprised adults with T2DM prescribed sitagliptin (RxNorm 593411). The index event was the first qualifying prescription. A continuous minimum exposure period was not enforced and a disease-onset lag was not applied; outcome observation began one day after the index date, a

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window discussed as a limitation. The primary outcome was incident AD (ICD-10 G30); the secondary outcome was a broad dementia composite (G30 + G31 + F03).

Propensity score matching and statistical analysis:

One-to-one nearest-neighbor propensity score matching was performed on demographic variables (age at index, sex, race and ethnicity), 10 comorbidities (hypertension I10, dyslipidemia E78, obesity E66, ischemic heart disease I25, heart failure I50, atrial fibrillation I48, sleep apnea G47.3, chronic kidney disease N18, depression F32, cerebral infarction I63) and 6 laboratory or anthropometric parameters (HbA1c, LDL cholesterol, blood urea nitrogen, creatinine, body mass index, systolic blood pressure). Duration of diabetes, alcohol use and menopausal status were not available as discrete matching covariates and are addressed as residual confounders in the Limitations. Balance was assessed by standardized mean differences (SMD), with SMD < 0.10 indicating adequate balance. Risk ratio, odds ratio, hazard ratio (Cox proportional hazards) and Kaplan-Meier survival with log-rank testing were computed within the TriNetX analytics platform. The proportional hazards assumption was evaluated with the Grambsch-Therneau test. All-cause death during follow-up was not modeled as a competing risk; this is noted as a limitation.

Table 1: Baseline characteristics after 1:1 propensity score matching (n = 198,976 per cohort). SMD, standardized mean difference

Variable	GLP-1 RA n	GLP-1 RA %	Sitagliptin n	Sitagliptin %	SMD
Hypertension (I10)	149,853	75.3	150,097	75.4	0.003
Dyslipidemia (E78)	147,853	74.3	149,313	75	0.017
Obesity (E66)	119,785	60.2	119,641	60.1	0.001
Ischemic heart disease (I25)	42,295	21.3	41,918	21.1	0.005
Heart failure (I50)	24,162	12.1	23,634	11.9	0.008
Atrial fibrillation (I48)	16,613	8.3	16,089	8.1	0.01
Sleep apnea (G47.3)	57,718	29	57,108	28.7	0.007
Chronic kidney disease (N18)	35,243	17.7	34,883	17.5	0.005
Depression (F32)	53,273	26.8	52,202	26.2	0.012
Cerebral infarction (I63)	10,613	5.3	10,333	5.2	0.006

Table 2: Primary outcome: incident Alzheimer's disease (ICD-10 G30) after propensity score matching

Measure	Value
Patients per cohort	198,976 (each arm)
AD, GLP-1 RA, n (%)	1,024 (0.51%)
AD, sitagliptin, n (%)	3,590 (1.80%)
KM survival (GLP-1 RA vs sitagliptin)	96.63% vs 94.13%
Risk ratio (95% CI)	0.285 (0.266-0.306)
Odds ratio (95% CI)	0.282 (0.263-0.302)
Hazard ratio (95% CI)	0.452 (0.421-0.486); P < 0.001
Log-rank test	χ^2 = 490.808; P < 0.001

Table 3: Secondary outcome: broad dementia composite (G30 + G31 + F03) after propensity score matching

Measure	Value
Patients per cohort	198,976 (each arm)
Dementia, GLP-1 RA, n (%)	6,036 (3.03%)
Dementia, sitagliptin, n (%)	17,074 (8.58%)
KM survival (GLP-1 RA vs sitagliptin)	88.57% vs 72.90%
Hazard ratio (95% CI)	0.553 (0.536-0.570); P < 0.001
Log-rank test	χ^2 = 1,486.073; P < 0.001

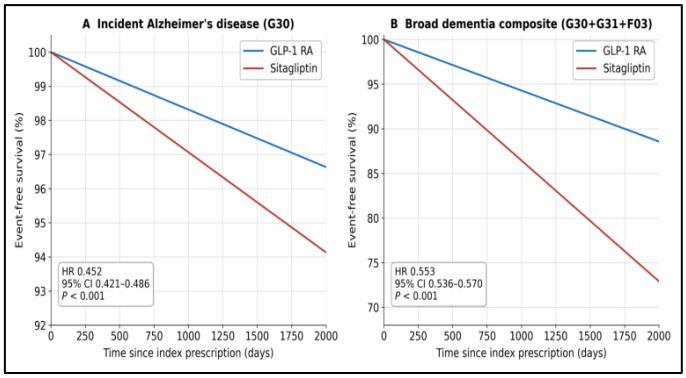

Figure 1: Kaplan-Meier survival curves for incident Alzheimer's disease and the broad dementia composite

Results and Discussion:

Before matching, Cohort 1 included 220,789 patients and Cohort 2 included 632,306 patients, with baseline imbalances (obesity 64.1% vs 25.2%; mean BMI 36.9 vs 32.4 kg/m²; sleep apnea 34.3% vs 12.9%). After 1:1 matching, 198,976 patients remained per cohort, with most covariates well balanced **(Table 1)**; residual imbalance persisted in BMI (SMD 0.209) and HbA1c (SMD 0.099). Mean follow-up was 1,078 ± 724 days in the GLP-1 RA cohort and 1,931 ± 1,419 days in the sitagliptin cohort. This difference, attributable in part to the longer market availability of sitagliptin, was substantial and is treated as a primary threat to validity in the Discussion. For the primary outcome, incident AD occurred in 1,024 patients (0.51%) in the GLP-1 RA group versus 3,590 (1.80%) in the sitagliptin group (hazard ratio 0.452; 95% CI 0.421-0.486; P < 0.001; Kaplan-Meier survival 96.63% vs 94.13%; log-rank χ^2 = 490.808; P < 0.001) **(Table 2, Figure 1)**. For the broad dementia composite, events occurred in 6,036 patients (3.03%) versus 17,074 (8.58%) (hazard ratio 0.553; 95% CI 0.536-0.570; P < 0.001; Kaplan-Meier survival 88.57% vs 72.90%; log-rank χ^2 = 1,486.073; P < 0.001) **(Table 3, Figure 1)**. In this matched cohort, GLP-1 RA use was associated with a lower hazard of incident AD (HR 0.452) and broad dementia (HR 0.553) than sitagliptin **[7, 12]**. The intended methodological contribution was a comparison against an incretin-based DPP-4i rather than non-users, sulfonylureas, or insulin **[7]**. These associations are directional only; the design features discussed below preclude any causal or near-causal interpretation. The observed effect sizes are larger than prior estimates. An emulated target trial in Sweden reported a hazard ratio of 0.77 for dementia with GLP-1 RAs versus DPP-4 inhibitors **[7]** and a TriNetX study in CKD reported a hazard ratio of 0.76 for AD

using a single-agent, new-user design with a dementia-free lookback and an onset lag **[12]** and a target trial emulation in older adults reported a hazard ratio of 0.76 for dementia versus DPP-4 inhibitors with external validation in TriNetX **[14]**. However, the same emulation and a separate metformin-anchored TriNetX cohort found no reduction in dementia risk for GLP-1 RAs versus SGLT2 inhibitors (hazard ratios 1.53 and 1.01, respectively), indicating that the apparent neuroprotection is specific to the incretin-based comparator rather than a class-independent effect **[14, 15]**. The larger effect here is most plausibly explained by the non-standard multi-agent exposure requirement and the unequal follow-up rather than by a stronger biological effect; the convergence of our composite estimate (0.553) with the randomized-trial odds ratio of 0.55 **[9]** is noted but should not be over-interpreted given these design differences. Mechanistically, DPP-4 inhibitors raise endogenous GLP-1 modestly, whereas GLP-1 RAs achieve higher receptor occupancy and semaglutide can engage central GLP-1 receptors **[6]**. Preclinical data describe effects on amyloid-beta clearance and neuroinflammation **[4, 5]**. We emphasize that these are preclinical and pharmacological observations and do not by themselves establish a clinical neuroprotective effect. The EVOKE and EVOKE+ phase 3 trials enrolled 3,808 patients with amyloid-confirmed symptomatic AD and found no benefit of oral semaglutide on CDR-SB at week 104 **[13]**. Our cohort comprised T2DM patients without a recorded AD diagnosis, so the contrast is consistent with a prevention-versus-treatment distinction; however, because we did not exclude prevalent or prodromal disease, this interpretation is tentative.

Limitations:
Several limitations materially constrain interpretation. First, the exposure required concurrent prescription of two GLP-1 RAs. This is not supported by any treatment guideline, does not represent real-world practice, raises safety concerns including additive risks of medullary thyroid carcinoma and pancreatitis and selects for an adherent, intensively treated population; the resulting estimates are therefore not generalizable to standard single-agent therapy. Second, mean follow-up differed nearly two-fold between cohorts (1,078 vs 1,931 days). Because AD incidence accumulates with age and observation time, the longer sitagliptin follow-up could inflate the apparent protective association independent of any drug effect; a design restricted to comparable exposure windows would be required to address this. Third, no minimum continuous exposure (for example, ≥ 6 months) was enforced, no washout was applied, patients with pre-existing or prodromal AD were not excluded and outcome observation began one day after index. Capturing outcomes immediately after index risks counting prevalent rather than incident disease. Fourth, the proportional hazards assumption was violated, so reported hazard ratios represent time-averaged rather than constant effects. Fifth, all-cause death was not handled as a competing risk, which can bias time-to-event estimates for an age-related outcome. Sixth, residual confounding by APOE genotype, cognitive reserve, physical activity, socioeconomic status, diabetes duration, alcohol use and menopausal status cannot be excluded and outcomes relied on ICD-10 coding subject to misclassification. Finally, generalizability is limited to the US organizations in the TriNetX network.

Conclusion:
Propensity score-matched T2DM cohort, GLP-1 RA use was associated with lower hazards of incident AD and dementia than sitagliptin. Given the dual-agent exposure, marked follow-up imbalance and proportional hazards violation, these findings are hypothesis-generating only. Thus, adequately designed new-user, active-comparator studies with matched follow-up and ultimately prevention trials, are needed before any clinical inference can be drawn.

Abbreviations:
AD: Alzheimer's disease; BMI: body mass index; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; CKD: chronic kidney disease; DPP-4i: dipeptidyl peptidase-4 inhibitor; EHR: electronic health record; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA1c: hemoglobin A1c; HR: hazard ratio; ICD-10: International Classification of Diseases, Tenth Revision; KM: Kaplan-Meier; LDL: low-density lipoprotein; OR: odds ratio; SMD: standardized mean difference; T2DM: type 2 diabetes mellitus

Declarations:
Acknowledgments: None.

Funding:
None

Conflicts of interest: The authors declare no conflicts of interest.

Ethics approval and informed consent:
This study queried de-identified, aggregate data through the TriNetX federated network and was classified as non-human-subjects research; informed consent was not applicable. The authors acknowledge that the multi-agent exposure definition raises ethical considerations and would merit prospective ethical review in any interventional extension of this work.

Use of artificial intelligence:
Large language model tools were used to assist with drafting and formatting of this manuscript. All content, data interpretation and references were reviewed and verified by the authors, who take full responsibility for the accuracy and integrity of the work.

Author contributions:
MPK: conceptualization, data acquisition, writing – original draft. PP: methodology, statistical analysis, writing – review and editing. UT: data acquisition, writing – review and editing. JDS: critical revision. AD: data acquisition. GG: data acquisition. SS: data analysis. JP: data analysis. HAS: conceptualization, supervision and corresponding author. All authors approved the final manuscript.

Data availability:
Data were accessed through the TriNetX US Collaborative Network (https://trinetx.com). Access requires a data use agreement with TriNetX; the authors cannot share patient-level data.

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