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Diabetes medications and dementia risk: Comparisons of SGLT2 inhibitors, GLP-1 RAs, metformin, and their combinations

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ABSTRACT

Background: Type 2 diabetes (T2D) elevates dementia risk through vascular injury, neuroinflammation, and perturbed insulin signaling. Antidiabetic classes differ in extra-glycemic actions that could modify neurodegeneration, yet head-to-head comparative data remain limited.

Objective: To compare time to incident dementia among older adults with T2D exposed to SGLT2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs), metformin, or two-way combinations, and to quantify the contribution of comorbidities and neuroactive co-medications.

Methods: We performed a retrospective cohort study in the UCHDW (2012–2024). Adults aged 55–80 were assigned to the earliest qualifying exposure group and followed from index to first coded Alzheimer's disease or unspecified dementia; vascular/multi-infarct dementias were excluded by design to reduce etiologic heterogeneity. Events recorded within 84 days of index were not considered incident outcomes (individuals were retained and censored at 84 days). Covariates included age, sex, cardiovascular disease, hypertension, chronic kidney disease, obesity, smoking, anticholinergic/overactive bladder agents, tricyclic antidepressants, proton-pump inhibitors, opioids, benzodiazepines, and ever-exposure to insulin, DPP-4 inhibitors, sulfonylureas, and thiazolidinediones. Analyses comprised Kaplan–Meier (KM) curves with log-rank testing, a pooled multivariable Cox model with a six-level exposure factor, and one-versus-rest Cox models complemented by stabilized, truncated inverse probability of treatment weighting (IPTW).

Results: The cohort included 22,677 SGLT2-only (150 events; 0.66 %), 219,523 metformin-only (2,174; 0.99 %), 35,012 GLP-1-only (149; 0.43 %), 37,317 SGLT2+metformin (453; 1.21 %), 7,210 SGLT2+GLP-1 (62; 0.86 %), and 41,595 metformin+GLP-1 (421; 1.01 %). KM curves differed significantly (log-rank χ^2=38.5, p<0.001). In the pooled Cox model (reference SGLT2-only), metformin-only (HR=1.24, 95 % CI 1.05–1.47; p=0.011) and SGLT2+metformin (HR=1.21, 95 % CI 1.00–1.46; p=0.045) had higher hazards; GLP-1-only (HR=0.94, 95 % CI 0.74–1.20; p=0.614) and SGLT2+GLP-1 (HR=0.85, 95 % CI 0.64–1.15; p=0.299) did not differ significantly; metformin+GLP-1 trended higher (HR=1.18, 95 % CI 0.97–1.42; p=0.092). Absolute risk differences were small (0.23–0.78 percentage points vs GLP-1-only). One-versus-rest models yielded directionally consistent estimates; IPTW with 1st–99th percentile truncation improved covariate balance and produced stable weighted estimates. Median follow-up (years) was 1.96 (SGLT2-only), 5.34 (metformin-only), 1.81 (GLP-1-only), 4.13 (SGLT2+metformin), 3.44 (SGLT2+GLP-1), and 4.84 (metformin+GLP-1).

Conclusions: In routine care of older adults with T2D, GLP-1 RA monotherapy demonstrates the most favorable dementia profile, whereas metformin monotherapy and SGLT2+metformin identify groups with comparatively higher risk. Given low absolute differences and absence of additional confounding covariates, cautious interpretation is warranted. Prospective studies incorporating glycemic control and exposure duration are needed to determine causal class effects and guide neuroprotective diabetes management.

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Introduction

Dementia remains a formidable public health challenge characterized by progressive deterioration of cognition and functional independence. The pathobiology spans amyloid-β deposition, tau hyperphosphorylation with neurofibrillary tangle formation, neuroinflammation, synaptic failure, vascular compromise, and mitochondrial dysfunction [1]. Alzheimer's disease (AD) constitutes the most common form, accounting for most late-life dementia. Therapeutic advances have been incremental; although monoclonal antibodies such as lecanemab have achieved regulatory approval and show amyloid-lowering with modest slowing of decline, durable, broadly applicable strategies for prevention remain urgently needed [2,3]. Because metabolic dysfunction, insulin resistance, and chronic cardiometabolic illness contribute to neurodegenerative cascades through vascular injury, oxidative stress, and microglial activation, diabetes therapeutics with pleiotropic systemic actions have emerged as compelling candidates for dementia risk modification [4,5].

Type 2 diabetes mellitus (T2D) affects a large and growing proportion of older adults and is associated with a substantial increase in dementia risk relative to non-diabetic peers [4]. Hyperglycemia, hyperinsulinemia, endothelial dysfunction, and advanced glycation end-products are thought to converge on pathways that accelerate neurodegeneration, prompting the longstanding hypothesis that AD may represent a "type 3 diabetes" in select biological contexts [5]. Against this backdrop, several antidiabetic classes have drawn attention for potential neuroprotective actions beyond glucose control. Sodium–glucose cotransporter-2 (SGLT2) inhibitors, which promote glucosuria and natriuresis, improve systemic and renal hemodynamics and attenuate inflammation and oxidative stress; experimental models further suggest effects on cerebral metabolism and neuroinflammatory tone [6–9]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) enhance insulin secretion and weight loss and exert central actions on neuronal survival, synaptic plasticity, and microglial biology, with emerging signals for cognitive benefit in observational and emulated-trial data [10,16]. metformin (Glucophage), a first-line biguanide, activates AMP-activated protein kinase, modulates mitochondrial function, and has been variably linked to neurogenesis and anti-inflammatory effects; yet prior literature has yielded mixed associations with cognitive trajectories, potentially reflecting confounding by indication, exposure duration, and heterogeneity in underlying disease severity [11–13].

Despite the biologic plausibility of neuroprotection across these classes, comparative effectiveness data are limited and complicated by channeling of therapies to clinically distinct patients. Most real-world analyses have contrasted one class against a composite "other antidiabetic therapy" control that aggregates drugs with diverse neurological profiles, hampering interpretability [14–16]. Moreover, combination therapy is common as T2D progresses, yet the joint or sequential effects of SGLT2 inhibitors, GLP-1 RAs, and metformin (Glucophage) on dementia risk have not been evaluated in parallel within a large, harmonized health system dataset. The present study addresses these gaps by leveraging data from a multi-site clinical database to quantify the association between time to incident dementia and exposure to SGLT2 inhibitors, GLP-1 RAs, metformin (Glucophage), and their two-way combinations, with explicit attention to absolute as well as relative risk and to confounding control.

Methods

We conducted a retrospective cohort study using the University of California Health Data Warehouse (UCHDW), which aggregates encounters, diagnoses, procedures, prescriptions, and laboratory results across six University of California academic health systems from 2012 through 2024. Data were de-identified and harmonized to the Observational Medical Outcomes Partnership (OMOP) common data model. Diagnoses used standardized SNOMED CT concepts, and medications were encoded with RxNorm vocabulary. Analyses of these de-identified records were deemed exempt from human subjects oversight under IRB protocol 1604,619-1 of the University of California Health System. This study followed STROBE guidelines.

The source population comprised adults aged 55–80 years at the time of a qualifying antidiabetic exposure and with evidence of T2D treatment in the record. To contrast SGLT2 inhibitors, GLP-1 RAs, and metformin (Glucophage) on an equal footing while acknowledging real-world polypharmacy, we built mutually exclusive exposure groups using drug-specific first exposure dates and ever-exposed flags. SGLT2-only indicated recorded SGLT2 inhibitor use without metformin (Glucophage) or GLP-1 RA; "metformin (Glucophage)-only" and "GLP-1-only" were defined analogously. Two-way combination groups were SGLT2+metformin (Glucophage), SGLT2+GLP-1, and metformin (Glucophage)+GLP-1, each requiring presence of both classes and absence of the third. Individuals with none of the three classes or with simultaneous exposure to all three were excluded to preserve mutually exclusive categories. The index date was the earliest qualifying exposure date contributing to group assignment. Outcomes recorded within 84 days of the index date were not considered incident; persons with such early codes were retained, with time-to-event censored at 84 days to mitigate protopathic bias.

The primary endpoint was time from the index date to the earliest record of AD or unspecified dementia, captured using a curated SNOMED CT concept set; vascular and multi-infarct dementias were excluded to reduce etiologic heterogeneity and confounding by cardio-renal indications. For individuals without an outcome, follow-up was censored at the latest recorded date across encounters, drug exposures, or measurements. Deaths are deterministically captured in the EHR; persons who died without a qualifying dementia diagnosis were censored at their date of death, and individuals without a recorded death were presumed alive through the end of their observed follow-up. Covariates represented clinical comorbidities and neuroactive co-medications previously associated with cognitive trajectories in older adults, as well as flags for other antidiabetic classes. Comorbidities included cardiovascular disease, hypertension, chronic kidney disease, obesity, and smoking. Co-medications included anticholinergic or overactive bladder agents (including oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine, mirabegron, trospium, hyoscyamine, and dicyclomine), tricyclic antidepressants (including amitriptyline, nortriptyline, imipramine, desipramine, doxepin, protriptyline, and clomipramine), proton-pump inhibitors (including omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, and exlansoprazole), opioids (including morphine, oxycodone, hydrocodone, hydromorphone, codeine, tramadol, methadone, fentanyl, and buprenorphine), and benzodiazepines (including alprazolam (Xanax), clonazepam, diazepam, lorazepam, oxazepam, tempazepam, triazoloma, estazolam, flurazepam, chlordiazepoxide, and midazolam). Ever-exposure flags for insulin, DPP-4 inhibitors, sulfonylureas, and thiazolidinediones (TZDs) were included to characterize background therapy and adjust for treatment history.

We summarized group sizes, dementia counts, and crude percentages and added absolute risk differences (ARD) versus GLP-1-only and versus SGLT2-only to aid clinical interpretation. Baseline characteristics were described by group. We estimated KM curves for dementia-free survival and used a log-rank test to compare survival functions. We then fit a pooled multivariable Cox proportional hazards model with the six-level exposure factor as the primary predictor and included age, sex, the five comorbidities, the five co-medication classes, and the four other antidiabetic flags. To complement the pooled model, we performed one-versus-rest Cox models for each category. For confounding control, we constructed stabilized IPTW from a logistic propensity score including demographics, comorbidities, neuroactive co-medications, and other antidiabetic flags; weights were truncated at the 1st–99th percentiles to limit influence of extremes. We report unweighted and

weighted estimates, and we summarize follow-up duration by group and the proportion censored to contextualize exposure time and outcome density. All analyses were conducted in R; two-sided 95 % confidence intervals were used and α=0.05 denoted statistical significance.

Results

The analytic cohort contained six mutually exclusive exposure groups totaling several hundred thousand older adults with T2D. SGLT2-only comprised 22,677 patients, metformin (Glucophage)-only 219,523, and GLP-1-only 35,012; combination groups included 37,317 SGLT2+metformin (Glucophage), 7210 SGLT2+GLP-1, and 41,595 metformin (Glucophage)+GLP-1. Across these groups, the proportion developing dementia during follow-up was: GLP-1-only 0.43 % (149 events), SGLT2-only 0.66 % (150), metformin (Glucophage)-only 0.99 % (2174), SGLT2+GLP-1 0.86 % (62), SGLT2+metformin (Glucophage) 1.21 % (453), and metformin (Glucophage)+GLP-1 1.01 % (421) (Table 1). ARD versus GLP-1-only were 0.23 percentage points (pp) for SGLT2-only, 0.56 pp for metformin (Glucophage)-only, 0.78 pp for SGLT2+metformin (Glucophage), 0.43 pp for SGLT2+GLP-1, and 0.58 pp for metformin (Glucophage)+GLP-1; ARD versus SGLT2-only were −0.23 pp for GLP-1-only, +0.55 pp for SGLT2+metformin (Glucophage), +0.35 pp for metformin (Glucophage)+GLP-1, and +0.33 pp for metformin (Glucophage)-only. Median follow-up (years) was 1.96 for SGLT2-only, 5.34 metformin (Glucophage)-only, 1.81 GLP-1-only, 4.13 SGLT2+metformin (Glucophage), 3.44 SGLT2+GLP-1, and 4.84 metformin (Glucophage)+GLP-1; the proportion censored was ~0.99 in each group.

Baseline characteristics varied across groups in clinically expected ways (Table 2). GLP-1-only patients were younger on average and more often women; SGLT2-containing groups had more chronic kidney disease and hypertension. Obesity prevalence was highest in the GLP-1-only group. Use of neuroactive co-medications was common across all groups.

KM dementia-free survival curves diverged modestly but significantly (log-rank χ^2=38.5, $p < 0.001$), with GLP-1-only and SGLT2+GLP-1 tracking at the high end of survival, SGLT2-only and metformin (Glucophage)+GLP-1 intermediate, metformin (Glucophage)-only slightly lower, and SGLT2+metformin (Glucophage) lowest (Fig. 1).

The pooled multivariable Cox model quantified adjusted differences (Table 3). Using SGLT2-only as reference, metformin (Glucophage)-only was associated with higher hazard of dementia (HR=1.24, 95 % CI 1.05–1.47; $p = 0.011$), as was SGLT2+ %metformin (Glucophage) (HR=1.21, 95% CI 1.00-1.46; p = 0.045). GLP-1-only (HR=0.94, 95 % CI 0.74–1.20; $p = 0.614$) and SGLT2+GLP-1 (HR=0.85, 95 % CI 0.64–1.15; $p = 0.299$) did not differ significantly; metformin (Glucophage)+GLP-1 trended higher (HR=1.18, 95 % CI 0.97–1.42; $p = 0.092$). Among covariates, age was strongly associated with risk; benzodiazepine exposure was independently associated with higher hazard. Insulin, DPP-4 inhibitor, and TZD flags were also associated with higher hazard, consistent with channeling to patients with longer disease duration or greater severity. Sex differences were small and not statistically significant after adjustment. Full coefficients and confidence intervals are provided in Table 3, Table 4.

One-versus-rest analyses offered a complementary perspective. Unweighted models showed SGLT2-only modestly below unity, metformin (Glucophage)-only modestly above, GLP-1-only below, and SGLT2+metformin (Glucophage) above. Weighted models using stabilized, 1st–99th percentile-truncated IPTW produced directionally similar estimates with improved covariate balance (Table 5). Across the 17 measured covariates, the median absolute standardized mean difference (SMD) decreased from roughly 0.12–0.18 pre-weighting to 0.02–0.05 post-weighting across the six one-versus-rest contrasts; the share of covariates with absolute SMD <0.10 increased from about 55–75 % to 100 %, and the largest residual imbalance was <0.07 in every contrast.

Discussion

In a large, multicenter health-system cohort of older adults with T2D, we compared incident dementia across mutually exclusive exposure groups defined by SGLT2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs), metformin (Glucophage), and their two-way combinations. Three themes emerged. First, differences in dementia risk were detectable and statistically significant in aggregate, but absolute risk differences (ARDs) were small: relative to GLP-1–only, ARDs ranged from 0.23 to 0.78 percentage points, and relative to SGLT2-only from −0.23 to 0.55 percentage points (Table 1). These magnitudes imply that the individual-level effect of class choice on near-term dementia incidence is modest, and that clinical meaning will hinge on population reach, competing cardiometabolic outcomes, and patient preferences rather than large shifts in absolute cognitive risk. Second, the favorable directionality of GLP-1 therapy was apparent: crude incidence was lowest in GLP-1–only, Kaplan–Meier curves tracked at the favorable end of dementia-free survival, and the pooled Cox model showed no excess hazard versus SGLT2-only (HR 0.94, 95 % CI 0.74–1.20). Third, the SGLT2+metformin (Glucophage) group showed the highest relative hazard among the six categories (HR 1.21, 95 % CI 1.00–1.46), a pattern that aligns with expected treatment selection into that combination for patients with longer disease duration and higher cardiorenal burden.

The GLP-1 signal warrants particular attention given active neurodegeneration trials. Our data place GLP-1–only at the low end of crude dementia incidence (0.43 %) and near or below unity in adjusted comparisons, supporting a cognitively neutral-to-favorable profile in routine care. However, the number of GLP-1 events was relatively small (149 events among 35,012 patients), and the adjusted HR did not differ significantly from SGLT2-only. We therefore frame the GLP-1 finding as supportive, but not definitive, real-world evidence that complements emulated-trial results reporting lower dementia risk with GLP-1 RAs in older adults with T2D, while calling for prospective confirmation with adjudicated outcomes and detailed exposure metrics [10,16].

By contrast, SGLT2+metformin (Glucophage) consistently marked a higher-risk cohort. This combination is frequently selected for patients with established cardiovascular or renal disease and for those requiring intensification after monotherapy, features that independently track with dementia risk [1]. In our cohort, SGLT2-containing groups had higher chronic kidney disease and hypertension prevalence (Table 2), and SGLT2+metformin (Glucophage) exhibited longer follow-up than single-agent GLP-1 or SGLT2 (Table 6). Although multivariable

Table 1
Cohort size, dementia events, and absolute risk differences (ARD) by exposure pattern among adults aged 55–80 years with T2D in UCHDW; index=earliest qualifying exposure; outcome=first AD/unspecified dementia ≥84 days after index.

Group	Total Participants	Developed Dementia	Percent With Dementia (%)	ARD vs GLP-1-only (Δ %)	ARD vs SGLT2-only (Δ %)
SGLT2-only	22,677	150	0.66	0.23	0.00
metformin (Glucophage)-only	219,523	2174	0.99	0.56	0.33
GLP-1-only	35,012	149	0.43	0.00	−0.23
SGLT2+metformin (Glucophage)	37,317	453	1.21	0.78	0.55
SGLT2+GLP-1	7210	62	0.86	0.43	0.20
metformin (Glucophage)+GLP-1	41,595	421	1.01	0.58	0.35

Table 2
Baseline characteristics of the six exposure groups (age, sex, comorbidities, and neuroactive medication exposures) among adults with type 2 diabetes, UCHDW 2012–2024.

Variable	SGLT2 only	metformin (Glucophage) only	GLP-1 only	SGLT2+metformin (Glucophage)	SGLT2+GLP-1	metformin (Glucophage)+GLP-1
Mean age (years)	69.1	68.4	65.3	68.5	68.1	66.7
SD age (years)	7.1	7.1	7.1	6.9	7.0	7.0
Female (%)	36.7	49.8	65.0	39.9	48.0	57.4
Cardiovascular disease (%)	9.2	1.8	1.6	4.4	5.3	1.7
Hypertension (%)	54.5	45.1	45.0	54.2	53.2	55.0
Chronic kidney disease (%)	27.3	7.9	30.7	26.9	29.8	12.3
Obesity (%)	15.9	19.5	38.6	17.4	30.7	27.4
Smoking (%)	5.0	4.0	3.6	4.1	3.2	4.3
Anticholinergics/OABs (%)	10.8	10.1	14.3	11.0	14.3	13.0
Tricyclic antidepressants (%)	6.4	7.2	9.4	7.4	9.5	14.7
Proton-pump inhibitors (%)	51.7	41.7	52.3	47.6	52.9	51.9
Opioids (%)	70.2	62.6	72.0	66.5	72.0	67.4
Benzodiazepines (%)	47.8	42.6	53.1	41.4	38.8	41.4

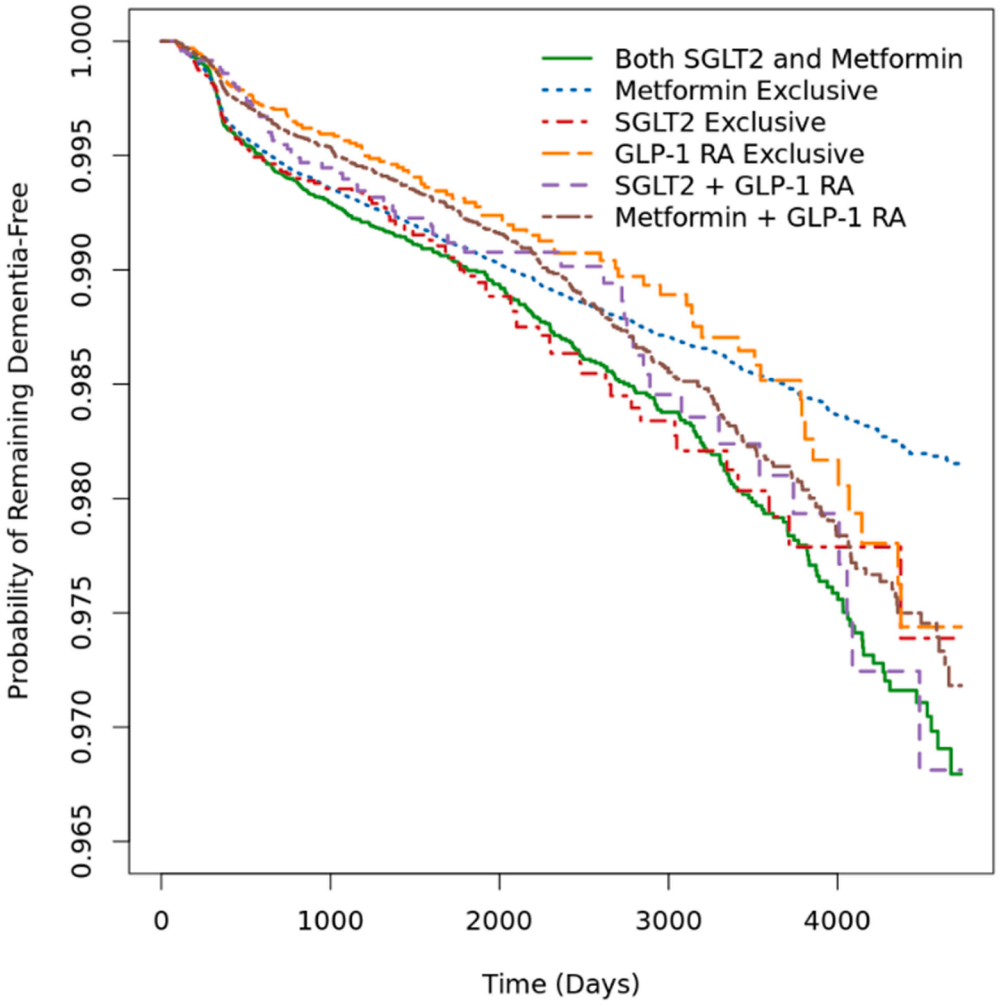

Fig. 1. Kaplan-Meier plot displaying the probability of remaining dementia-free over time (in days) across the chosen treatment groups.

adjustment and inverse-probability weighting (IPTW) accounted for measured comorbidities and background antidiabetic exposure (insulin, DPP-4 inhibitors, sulfonylureas, TZDs), residual confounding by diabetes duration, glycemic control, and clinical severity remains plausible and likely contributes to the elevated hazard in this group.

metformin (Glucophage)-only showed a modestly higher adjusted hazard relative to SGLT2-only (HR 1.24, 95 % CI 1.05–1.47), consistent with a literature that has alternately reported benefit, neutrality, and harm [11–13,16]. Several non-exclusive explanations are compatible with our data: persistence on metformin (Glucophage)-only despite deteriorating control; heterogeneous disease duration within the monotherapy group; and unmeasured confounding from metabolic, vascular, or social factors [1].

SGLT2+GLP-1 did not differ significantly from SGLT2-only in adjusted models (HR 0.85, 95 % CI 0.64–1.15) and showed a crude dementia risk of 0.86 % (62 events among 7210 patients). metformin

Table 3
Multivariable Cox model including all six groups and covariates (age, sex, comorbidities, and concomitant medications): adjusted hazard ratios for dementia.

Term (reference SGLT2-only)	Adjusted HR	95 % CI	p value
metformin (Glucophage)-only	1.24	1.05–1.47	0.011
GLP-1-only	0.94	0.74–1.20	0.614
SGLT2+metformin (Glucophage)	1.21	1.00–1.46	0.045
SGLT2+GLP-1	0.85	0.64–1.15	0.299
metformin (Glucophage)+GLP-1	1.18	0.97–1.42	0.092
Age (per year)	1.12	1.11–1.13	<0.001
Male sex (vs female)	1.02	0.90–1.15	0.729
Cardiovascular disease	1.43	1.31–1.56	<0.001
Hypertension	1.77	1.63–1.92	<0.001
Chronic kidney disease	1.70	1.57–1.85	<0.001
Obesity	0.88	0.81–0.96	0.004
Smoking	1.23	1.09–1.39	0.002
Anticholinergic/OAB meds	1.42	1.16–1.73	<0.001
Tricyclic antidepressants	1.34	1.20–1.49	<0.001
Proton-pump inhibitors	1.02	0.91–1.15	0.624
Opioids	0.66	0.60–0.73	<0.001
Benzodiazepines	1.55	1.42–1.70	<0.001
Insulin flag	1.86	1.73–1.99	<0.001
DPP-4 flag	1.25	1.14–1.36	<0.001
Sulfonylurea flag	0.86	0.79–0.94	<0.001
TZD flag	1.19	1.06–1.35	0.003

Table 4
One-versus-rest Cox models for the three single-agent exposures (effect of being in the target group vs everyone else); unweighted and IPTW-weighted estimates.

Target exposure (vs rest)	HR (unweighted)	p (unweighted)	HR (IPTW)	p (IPTW)
SGLT2 only	0.84	0.0360	0.82	0.033
metformin (Glucophage) only	1.12	0.0028	1.01	0.774
GLP-1 only	0.79	0.0050	0.98	0.027

Note: IPTW used to reduce covariate imbalance.

Table 5
Cohort assembly and background antidiabetic exposure.

Stage or metric	N or %
Starting population with complete time fields	513,722
Excluded: none of three target classes	150,388
Excluded: triple exposure	32,139
Final analytic cohort	363,334
Group counts: SGLT2-only / metformin (Glucophage)-only / GLP-1-only / SGLT2+metformin (Glucophage) / SGLT2+GLP-1 / metformin (Glucophage)+GLP-1	22,677 / 219,523 / 35,012 / 37,317 / 7210 / 41,595
Ever-exposed in analytic cohort: Insulin / DPP-4 / Sulfonylurea / TZD	31.1 % / 12.5 % / 15.8 % / 5.7 %

(Glucophage)+GLP-1 trended higher than SGLT2-only (HR 1.18, 95 % CI 0.97–1.42) with a crude incidence of 1.01 %. This pattern is internally consistent with channeling of combination therapy to more complex patients and a generally favorable signal for GLP-1 exposure.

The covariate pattern also informs interpretation. Benzodiazepine exposure, an established risk marker for cognitive decline, retained a positive association after adjustment, reinforcing the value of medication review and deprescribing when feasible. Background antidiabetic flags (especially insulin and DPP-4 inhibitor exposure) were associated with higher hazard, consistent with channeling to patients with longer or more severe diabetes and offering qualitative support for the severity-confounding explanation of combination-therapy findings [1,4].

We also observed an apparent “obesity paradox”: baseline obesity prevalence was highest in the GLP-1–only group, which nonetheless had the lowest crude dementia incidence. In the pooled model, baseline obesity was associated with a hazard ratio below unity (HR 0.88, 95 % CI 0.81–0.96). Potential explanations include selection into GLP-1 therapy for weight-forward management, unmeasured weight loss after initiation, survivorship and diagnostic biases, and central GLP-1 mechanisms [10,16]. These results should not be interpreted as evidence that baseline obesity protects against dementia; rather, they highlight the importance of modeling weight trajectories and treatment-mediated weight loss in future work.

Table 6
Follow-up duration and censoring by group.

Group	Mean follow-up (years)	Median (IQR) (years)	Min–Max (years)	Proportion censored
SGLT2-only	2.85	1.96 (2.39)	0.01–12.95	0.993
metformin (Glucophage)-only	5.81	5.34 (6.03)	0.00–12.95	0.991
GLP-1-only	2.76	1.81 (2.22)	0.03–12.95	0.996
SGLT2+metformin (Glucophage)	5.42	4.13 (3.75)	0.46–12.95	0.988
SGLT2+GLP-1	4.40	3.44 (4.14)	0.12–12.95	0.991
metformin (Glucophage)+ GLP-1	5.57	4.84 (5.62)	0.07–12.95	0.990

Methodologically, the triangulation of unadjusted and adjusted approaches supported consistent clinical conclusions. One-versus-rest analyses yielded directionally similar estimates to the pooled model. After applying stabilized IPTW with 1st–99th percentile truncation, covariate balance improved materially: across 17 measured covariates, the median absolute standardized mean difference decreased from roughly 0.12–0.18 pre-weighting to 0.02–0.05 post-weighting across the six contrasts; all covariates achieved <0.10 post-weighting, and the largest residual imbalance was <0.07. These diagnostics increase confidence that weighted estimates better reflect treatment effects in the presence of measured confounding.

Clinical implications are pragmatic. Within treated T2D, GLP-1 regimens appear cognitively safe and possibly favorable; SGLT2 monotherapy is broadly comparable to the cohort average; and metformin (Glucophage) monotherapy and SGLT2+metformin (Glucophage) identify cohorts at comparatively higher risk. Given small ARDs and certain missing confounders (e.g. HbA1c, disease duration, APOE genotype), findings should not prompt therapy changes solely to modify dementia risk. Rather, they support choices that prioritize cardiometabolic indications while recognizing that GLP-1 exposure is unlikely to worsen cognitive trajectories and may be advantageous in patients at high neurodegenerative risk, particularly when weight management and cardiovascular risk reduction are concurrent goals.

Limitations

This retrospective analysis relies on clinical records rather than confirmed adherence; cumulative dose and duration were not available. Dementia ascertainment used coded diagnoses and may miss prodromal disease or reflect variation in diagnostic intensity. We lacked hemoglobin A1c, duration of diabetes, education, socioeconomic variables, weight trajectory, and APOE genotype, precluding adjustment for useful confounders. The six-group design excluded a small triple-exposed subset. Exposure categories do not capture switching sequences. Although IPTW with truncation improved covariate balance, residual confounding is possible, especially for indications that simultaneously influence therapy choice and cognitive outcomes.

Conclusions

In older adults with T2D cared for across a large academic health

system, GLP-1 RA monotherapy exhibited the lowest crude incidence of dementia and a favorable adjusted profile, while metformin (Glucophage) monotherapy and SGLT2+metformin (Glucophage) identified cohorts with comparatively higher risk. However, absolute differences were small. Prospective studies incorporating glycemic control, exposure duration, and genetic risk are needed to determine whether observed patterns reflect causal class effects or clinical selection and to guide neuroprotective diabetes care.

Data availability

The data that support the findings of this study are derived from the University of California Health Data Warehouse (UCHDW), which consists of de-identified patient information. Due to the sensitive nature of the clinical data and the agreements under which they were obtained, the data cannot be made publicly available.

Funding

None

Ethics approval

This study is exempt from human subject protection under IRB protocol 1604,619–1 of the University of California Health System.

Patient consent statement

Not applicable.

Clinical trial registration

Not applicable.

CRediT authorship contribution statement

Gabrielle R. Nemeh: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Aubrey L. Doede:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Raphael E. Cuomo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors have nothing to declare.

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