Risk of dementia after initiation of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in adults aged 40-69 years with type 2 diabetes: population based cohort study

Anna Shin,[1] Bo Kyung Koo,[2] Jun Young Lee,[3] Eun Ha Kang[4]

[1]Medical Research Collaborating Centre, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

[2]Division of Endocrinology, Department of Internal Medicine, Seoul National University College of Medicine, SMG-SNU Boramae Medical Centre, Seoul, Korea

[3]Department of Psychiatrics, Seoul National University College of Medicine, SMG-SNU Boramae Medical Centre, Seoul, Korea

[4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Correspondence to: E H Kang
kangeh@snubh.org
(ORCID 0000-0001-9697-1159)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2024;386:e079475
http://dx.doi.org/10.1136/bmj-2024-079475

Accepted: 04 July 2024

ABSTRACT

OBJECTIVE

To compare the risk of dementia associated with sodium-glucose cotransporter-2 (SGLT-2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors in adults aged 40-69 years with type 2 diabetes.

DESIGN

Population based cohort study.

SETTING

Korean National Health Insurance Service data, 2013-21.

PARTICIPANTS

110 885 propensity score matched pairs of adults with type 2 diabetes aged 40-69 years who were initiators of either an SGLT-2 inhibitor or a DPP-4 inhibitor.

MAIN OUTCOME MEASURES

The primary outcome was new onset dementia. Secondary outcomes were dementia requiring drug treatment and individual types of dementia, including Alzheimer's disease and vascular dementia. Control outcomes were genital infections (positive), and osteoarthritis related clinical encounters and cataract surgery (negative). Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox models. Follow-up time stratified analyses (>2 years and ≤2 years) and subgroup analyses by age, sex, concomitant use of metformin, and baseline cardiovascular risk were performed.

RESULTS

110 885 propensity score matched pairs of initiators of an SGLT-2 inhibitor or a DPP-4 inhibitor were followed-up for a mean 670 (standard deviation 650) days, generating 1172 people with newly diagnosed dementia: incidence rate 0.22 per 100 person years in initiators of SGLT-2 inhibitors and 0.35 per 100 person years in initiators of DPP-4 inhibitors, with hazard ratios of 0.65 (95% CI 0.58 to 0.73) for dementia, 0.54 (0.46 to 0.63) for dementia requiring drugs, 0.61 (0.53 to 0.69) for Alzheimer's disease, and 0.48 (0.33 to 0.70) for vascular dementia. The hazard ratios for the control outcomes were 2.67 (2.57 to 2.77) for genital infections, 0.97 (0.95 to 0.98) for osteoarthritis related encounters, and 0.92 (0.89 to 0.96) for cataract surgery. When calibrated for residual confounding measured by cataract surgery, the hazard ratio for dementia was 0.70 (0.62 to 0.80). The association was greater for more than two years of treatment (hazard ratio of dementia 0.57, 95% CI 0.46 to 0.70) than for two years or less (0.52, 0.41 to 0.66) and persisted across subgroups.

CONCLUSION

SGLT-2 inhibitors might prevent dementia, providing greater benefits with longer treatment. As this study was observational and therefore prone to residual confounding and informative censoring, the effect size could have been overestimated. Randomised controlled trials are needed to confirm these findings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Despite increasing numbers of people with dementia globally, current options for disease modifying treatments are limited

Type 2 diabetes substantially predisposes people to Alzheimer's disease and vascular dementia through multiple pathways

A previous study suggested a decreased risk of dementia associated with sodium-glucose cotransporter-2 (SGLT-2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors among people with type 2 diabetes aged >66 years

WHAT THIS STUDY ADDS

This large population based cohort study among people with type 2 diabetes aged 40-69 years found a 35% lower risk of dementia associated with use of SGLT-2 inhibitors compared with DPP-4 inhibitors

This finding persisted regardless of dementia type and across subgroups of diverse population characteristics such as age, sex, concomitant use of metformin, and baseline cardiovascular risk

The treatment effect of SGLT-2 inhibitors compared with DPP-4 inhibitors increased with time

Introduction

Dementia concerns damage to the brain parenchyma, resulting in a permanent degradation of higher cortical functions, mood, and even behaviour.[1] According to a World Health Organization (WHO) report in 2021, the number of people with dementia globally is expected to reach 78 million by 2030.[2] Despite the severe consequences of dementia, the success rate of the development for dementia drugs has been markedly low in the past two decades, leaving only extremely limited options for disease modifying treatment.[3] Evidence has, however, emerged to support the importance of modifiable risk factors for dementia, including diabetes.[4] According to a pooled analysis, type 2 diabetes is associated with a 60% greater risk of dementia,[5] predisposing such people to both Alzheimer's disease and vascular dementia.[6] The mechanisms linking type 2 diabetes and dementia are multifactorial, involving insulin resistance, hypoglycaemic episodes, and vascular compromise.[7] In line with this, meta-analyses on observational studies

have shown that certain antiglycaemic drugs may have neuroprotective effects in people with diabetes.[8-10]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a newer class of antiglycaemic drugs that inhibit reabsorption of glucose in the proximal tubule. Key randomised controlled trials have shown significant cardiorenal protection from use of SGLT-2 inhibitors beyond glucose lowering effects.[11] SGLT-2 inhibitors are now considered one of the drug repurposing candidates for disease modifying treatment of dementia.[12] Recent evidence suggests neuroprotective effects of SGLT-2 inhibitors based on penetration of the drug through the blood-brain barrier, SGLT-2 expression in brain tissue, and direct inhibition of acetylcholinesterase, as well as indirect cardiometabolic benefits.[13]

Previous observational studies have suggested better preservation of cognitive function among people with type 2 diabetes treated with SGLT-2 inhibitors than other treatments, including dipeptidyl peptidase-4 (DPP-4) inhibitors,[14-17] another newer class of antiglycaemic drugs found to have no effect on cognitive performance in recent randomised controlled trials compared with sulfonylurea and placebo.[18 19] The methodological approaches of these observational studies were often limited, however, and did not meet the active comparator new user design, leaving concerns about confounding or bias.[15 16] A recent well designed study on residents in Ontario, Canada compared new users of SGLT-2 inhibitors with new users of DPP-4 inhibitors and found that the former were associated with a 20-34% reduced risk of dementia among people older than 66 years.[14] The effects on younger populations and specific types of dementia (eg, Alzheimer's disease, vascular dementia) were not, however, examined. Moreover, it is unclear whether different patient characteristics such as concomitant treatment or comorbidity status would modify such drug effects. We therefore compared the risk of dementia among adults with diabetes younger than 70 years who initiated an SGLT-2 inhibitor or DPP-4 inhibitor using the nationally representative Korea National Health Insurance Service database.

Methods

Data source

We conducted a cohort study using data from the Korea National Health Insurance Service database during 2013-21. This database covers the entire population of Korea and provides longitudinal patient data, including personal characteristics, ICD-10 (international classification of diseases, 10th revision) diagnosis codes, procedures, prescription and dispensing records (drug names, prescription and dispensing dates, days' supply, dose, and route of administration), and type of healthcare utilisation (outpatient, inpatient, or emergency department).[20]

Study design and population

We emulated a target trial for the outcomes of interest (see supplemental table S1 for the framework of the target trial emulation) using a propensity score matched active comparator new user cohort study design (see supplemental figure S1 for the detailed study design).

Adults aged 40-69 years with an ICD-10 code for type 2 diabetes who had initiated an SGLT-2 inhibitor or DPP-4 inhibitor were eligible for inclusion in the study (see supplemental figure S2 for the participant selection process and supplemental table S2 for ICD-10 codes used in this selection process). To implement a new user active comparator design, we only included initiators of the two competitive study drugs, an SGLT-2 inhibitor and a DPP-4 inhibitor, who had not been dispensed either drug for at least 365 days (the baseline period) before the first dispensing date of the study drug (the index date). To be included, individuals were required to be free of any dementia and related drugs ever before the index date. We also excluded those with ICD-10 diagnosis codes for type 1 diabetes mellitus, HIV, or end stage renal disease (or dialysis service) during the baseline period, and those who concomitantly used glucagon-like peptide-1 receptor agonists or thiazolidinedione on the index date.

Outcome measurement

Our primary outcome was incident dementia based on ICD-10 diagnosis codes in a primary position recorded on inpatient or outpatient claims (see supplemental table S3 for ICD-10 codes used to define outcomes).[21] To improve specificity of outcome ascertainment, we examined dementia defined by the diagnosis codes along with dispensing of dementia drugs (donepezil, rivastigmine, galantamine, or memantine) as a secondary outcome. In Korea, dementia drugs are reimbursed by the Rare and Intractable Diseases programme, where beneficiaries should qualify for a diagnosis certificate of dementia based on brain imaging and cognitive function testing. Other secondary outcomes were individual types of dementia (eg, Alzheimer's disease, vascular dementia) in a primary position.

Control outcomes

To assess reproducibility of established relations and unmeasured systematic bias, we also compared the risk of positive and negative control outcomes between the two treatment groups (see supplemental table S3). Given the higher risk of genital infections associated with SGLT-2 inhibitors compared with DPP-4 inhibitors in randomised controlled trials, we examined genital infections as a positive control outcome.[22] We also examined osteoarthritis related encounters and cataract surgery as negative control outcomes. A null association with treatment is expected for appropriate negative control outcomes, which share unmeasured confounders with the outcome and are unaffected by treatment.[23] As with dementia, osteoarthritis and cataract are degenerative diseases of older people. Therefore, osteoarthritis related encounters and cataract surgery would share with dementia unmeasured confounders such as frailty, lifestyle, and healthcare system usage patterns associated with

ageing, and cataract surgery would also share smoking and alcohol consumption.[24 25] Osteoarthritis related encounters would be expected for symptomatic or advanced osteoarthritis. Thus we considered such encounters to be minimally affected by the study drugs despite mild weight reduction effect of SGLT-2 inhibitors.[11] Also, two meta-analyses reported a null association between the development of cataract and treatment with SGLT-2 inhibitors.[26 27] Using a deviation from the null association between a negative control outcome and treatment, we estimated corrected hazard ratios and corresponding 95% confidence intervals (CIs) adjusting for residual confounding.[23 28]

Covariates

We identified covariates related to diabetes severity and risk of dementia for the 365 day pre-index baseline period (see supplemental table S2 for ICD-10 codes used to ascertain covariates). The covariates included personal characteristics, sociodemographic factors, complications from diabetes (retinopathy, nephropathy, neuropathy, and diabetic foot), classes and number of antiglycaemic drugs, risk factors for dementia (ie, cardiometabolic risk factors, hearing loss, head trauma, fracture history, mood or mental disorders, and anticholinergic drugs), other comorbidities and related drugs, Charlson-Deyo comorbidity index,[29] and healthcare service use patterns such as hospital admissions, emergency department visits, and outpatient clinic visits.

Statistical analysis

We used propensity score matching to account for confounding. The propensity score was estimated for each comparison using a multivariable logistic regression model that included >110 baseline covariates (see supplemental table S4 for the full list). Nearest neighbour matching for SGLT-2 inhibitor versus DPP-4 inhibitor was done in a ratio of 1:1, with a caliper of 0.025 on the propensity score scale. Balance between covariates after propensity score matching was considered to have been achieved when the absolute standardised difference was <0.1 between the two treatment groups.[30] Propensity score matched incidence rates of primary and secondary outcomes were calculated per 100 person years.

We primarily used Cox proportional hazard models to estimate the hazard ratios and corresponding 95% CIs. Owing to the discrete difference in mortality between the two treatments,[11] we also presented hazard ratios (95% CIs) from Fine-Gray models, adjusting for competing risk of death.[31] The proportional hazard assumption was tested by adding the interaction term between treatment and follow-up time in the model. When the interaction was statistically significant, we performed a follow-up time stratified analysis to examine the time varying treatment effect. We sorted propensity score matched study participants into two groups according to their follow-up times (≤2 years or >2 years), then estimated a matched set stratified hazard ratio (95% CI) within the two groups.

In our primary as treated analysis, patients were followed from the day after the index date up to the first occurrence of the censoring events (outcome event, disenrollment, death, end of database (31 December 2021), or treatment change through discontinuation, switching, or adding). Drug discontinuation was defined as no dispensing within 90 days from the expected refill date. The expected refill date was calculated by adding days' supply to the last dispensing date of the study drug. Participants who discontinued the study drug were followed up until the last expected refill date plus a 30 day grace period. Although switching between different SGLT-2 inhibitors or between different DPP-4 inhibitors was not a censoring event, adding or switching to other classes of antiglycaemic treatments resulted in immediate censoring. We performed an intention-to-treat analysis as our secondary analysis, where participants were followed up until censoring events except for treatment change to deal with concerns of informative censoring.

Sensitivity analyses—Firstly, to avoid reverse causation from delayed diagnosis of dementia, we started follow-up after 365 days from the index date in both as treated and intention-to-treat analyses (up to three years and the whole follow-up). Secondly, we applied a grace period of 180 or 365 days for the censoring by treatment change to capture delayed diagnoses made after the change of treatment. Thirdly, to eliminate the effect of hypoglycaemic episodes during treatment, analyses were done excluding those who concurrently used drugs with hypoglycaemia potential (insulin, sulfonylurea, or glinides) on the index date. Fourthly, we adjusted for the duration of diabetes mellitus for those who had an ascertainable type 2 diabetes diagnosis date, defined as the first date of an ICD-10 code for type 2 diabetes diagnosis in the primary position free of such codes for at least 365 days before the diagnosis date. Lastly, we utilised the entirety of new users of SGLT-2 inhibitors and DPP-4 inhibitors using propensity score based fine stratification and weighting to achieve greater generalisability.[32]

Subgroup analyses—Prespecified propensity score matched subgroup analyses were done based on participants' age (≥60 years and <60 years), sex, concurrent metformin use, and baseline cardiovascular risk. The estimation of propensity score and matching were done separately for individual subgroups. The subgroup with high cardiovascular risk was defined as men aged ≥50 years and women aged ≥55 years who had at least one diagnosis of angina, myocardial infarction, stroke, or peripheral vascular disease during the one year pre-index period.[20] We tested interaction terms between the treatment and individual stratifying factors.

Patient and public involvement

This study analysed secondary data without patient involvement. Patients were not invited to be involved in the study design, development of outcomes, interpretation of

the results, or drafting of the manuscript. The primary barrier against patient and public involvement was use of an administrative database, which requires a specific study design and pharmacoepidemiological method to ensure internal validity, leaving minimal potential for the patient and public to be engaged.

Results

Baseline patient characteristics

Supplemental figure S2 shows the selection process of the study cohort. We identified 112 663 new users of SGLT-2 inhibitors and 847 999 new users of DPP-4 inhibitors who were free of known dementia and did not use either of the study drugs at baseline. Before propensity score matching, most baseline covariates, including diabetes complications and number of antiglycaemic drugs, were overall relatively well balanced, reflecting the effectiveness of the active comparator new user design (table 1, also see supplemental table S4 for the distribution of the full list of covariates between the two groups). Some covariates showed imbalance, with standardised differences >0.1, particularly cardiovascular comorbidities, which were more prevalent among initiators of SGLT-2 inhibitors than among initiators of DPP-4 inhibitors (16.8% *v* 10.6% for angina pectoris, 3.1% *v* 1.6% for myocardial infarction, 7.8% *v* 4.2% for heart failure, 66.6% *v* 59.8% for hypertension, 78.8% *v* 70.9% for hyperlipidaemia). After propensity score matching in a 1:1 ratio, 110 885 pairs of initiators of SGLT-2 inhibitors and DPP-4 inhibitors were included in the analysis (mean age 61.9 years, 55.7% men) (table 1, also see supplemental table S4). All propensity score matched baseline covariates, including psychiatric disorders, cardiovascular diseases, other comorbidities, use of drugs with anticholinergic activity, and use of other drugs, were well balanced (standardised differences <0.1). The study participants' mean comorbidity score was 2.4 (standard deviation (SD) 1.8). Cardiometabolic factors were highly common, with 66.5% of participants having hypertension and 78.6% having hyperlipidaemia. Established cardiovascular diseases were observed in 16.7% of participants with angina, 6.4% with stroke, and 3.1% with myocardial infarction. The most common oral antiglycaemic agents used during the baseline period were biguanide (52.2%), followed by sulfonylurea (27.8%) and thiazolidinedione (8.2%). The most common index SGLT-2 inhibitor was dapagliflozin (58.6%), followed by empagliflozin (35.4%), and the most common index DPP-4 inhibitors were gemigliptin (22.7%), linagliptin (22.4%), and sitagliptin (20.4%) (see supplemental table S5).

Table 1 | Select baseline characteristics of propensity score matched cohort. Values are number (percentage) unless stated otherwise

	Before propensity score matching			After propensity score matching		
Characteristics	SGLT-2 inhibitors (n=112 663)	DPP-4 inhibitors (n=847 999)	Standardised difference	SGLT-2 inhibitors (n=110 885)	DPP-4 inhibitors (n=110 885)	Standardised difference
Mean (SD) age (years)	61.9 (4.4)	61.8 (4.8)	0.01	61.9 (4.4)	61.9 (4.5)	0.003
Men	62 898 (55.8)	499 388 (58.9)	0.06	61 795 (55.7)	61 743 (55.7)	<0.001
Income level						
Basic beneficiary (lowest)	4388 (3.9)	34 087 (4.0)	0.03	4300 (3.9)	4273 (3.9)	<0.001
First quarter	23 359 (20.7)	176 243 (20.8)		22 996 (20.7)	23 039 (20.8)	
Second quarter	22 792 (20.2)	172 908 (20.4)		22 433 (20.2)	22 532 (20.3)	
Third quarter	28 210 (25.0)	217 185 (25.6)		27 769 (25.0)	27 794 (25.1)	
Fourth quarter (highest)	33 914 (30.1)	247 576 (29.2)		33 387 (30.1)	33 247 (30.0)	
Mental disorders						
Mood disorders	10 958 (9.7)	80 921 (9.5)	0.006	10 724 (9.7)	10 695 (9.7)	<0.001
Anxiety	18 002 (16.0)	137 331 (16.2)	0.006	17 689 (16.0)	17 821 (16.1)	0.003
Psychosis	1002 (0.9)	8042 (1.0)	0.006	984 (0.9)	929 (0.8)	0.005
Delirium	76 (0.1)	718 (0.1)	0.006	70 (0.1)	90 (0.1)	0.007
Diabetes complications						
Retinopathy	14 532 (12.9)	96 818 (11.4)	0.05	14 055 (12.7)	14 119 (12.7)	0.002
Nephropathy	11 278 (10.0)	67 629 (8.0)	0.07	10 955 (9.9)	11 014 (9.9)	0.002
Neuropathy	18 066 (16.0)	120 285 (14.2)	0.05	17 458 (15.7)	17 628 (15.9)	0.004
Diabetic foot	9279 (8.2)	62 632 (7.4)	0.03	9020 (8.1)	9099 (8.2)	0.003
Diabetes drugs at baseline						
Insulin	12 023 (10.7)	74 690 (8.8)	0.06	11 514 (10.4)	11 568 (10.4)	0.002
Biguanide	58 895 (52.3)	454 358 (53.6)	0.03	57 756 (52.1)	57 848 (52.2)	<0.001
GLP-1 receptor agonist	1025 (0.9)	526 (0.1)	0.12	543 (0.5)	430 (0.4)	0.02
Sulfonylurea	31 751 (28.2)	274 851 (32.4)	0.09	30 828 (27.8)	30 826 (27.8)	<0.001
Glinides	627 (0.6)	5608 (0.7)	0.01	611 (0.6)	617 (0.6)	<0.001
Thiazolidinedione	9453 (8.4)	42 050 (5.0)	0.14	8852 (8.0)	9157 (8.3)	0.01
α glucosidase	3333 (3.0)	36 734 (4.3)	0.07	3262 (2.9)	3278 (3.0)	<0.001
No of oral hypoglycaemic drugs						
0	40 997 (36.4)	291 346 (34.4)	0.07	40 711 (36.7)	39 694 (35.8)	0.06
1-2	65 745 (58.4)	518 360 (61.1)		64 795 (58.4)	66 024 (59.5)	
>3	5921 (5.3)	38 293 (4.5)		5379 (4.9)	5167 (4.7)	

(*Continued*)

doi: 10.1136/bmj-2024-079475 | *BMJ* 2024;386:e079475 | the bmj

Table 1 | Continued

Characteristics	Before propensity score matching			After propensity score matching		
	SGLT-2 inhibitors (n=112 663)	DPP-4 inhibitors (n=847 999)	Standardised difference	SGLT-2 inhibitors (n=110 885)	DPP-4 inhibitors (n=110 885)	Standardised difference
Diabetes drug at index date						
Insulin	8342 (7.4)	67 830 (8.0)	0.02	8252 (7.4)	8324 (7.5)	0.009
Biguanide	86 176 (76.5)	699 675 (82.5)	0.15	84 786 (76.5)	85 784 (77.4)	0.04
Sulfonylurea	21 814 (19.4)	188 026 (22.2)	0.07	21 213 (19.1)	21 228 (19.1)	0.001
Glinides	46 (0.04)	743 (0.09)	0.02	41 (0.04)	51 (0.05)	0.003
α glucosidase	223 (0.2)	3352 (0.4)	0.04	212 (0.2)	212 (0.2)	0.002
Cardiovascular comorbidities						
Angina pectoris	18 871 (16.8)	90 128 (10.6)	0.18	18 411 (16.6)	18 641 (16.8)	0.006
Atrial fibrillation	3333 (3.0)	14 494 (1.7)	0.08	3240 (2.9)	3226 (2.9)	<0.001
Myocardial infarction	3520 (3.1)	13 105 (1.6)	0.11	3367 (3.0)	3476 (3.1)	0.006
Stroke	7279 (6.5)	54 043 (6.4)	0.004	7102 (6.4)	7013 (6.3)	0.003
Heart failure	8750 (7.8)	35 184 (4.2)	0.15	8502 (7.7)	8602 (7.8)	0.003
Hypertension	75 060 (66.6)	506 937 (59.8)	0.14	73 791 (66.6)	73 772 (66.5)	<0.001
Peripheral vascular disease	21 340 (18.9)	139 170 (16.4)	0.07	20 937 (18.9)	21 168 (19.1)	0.005
Other comorbidities						
Chronic kidney disease	6533 (5.8)	39 253 (4.6)	0.05	6295 (5.7)	6391 (5.8)	0.004
Hyperlipidaemia	88 815 (78.8)	601 149 (70.9)	0.18	87 337 (78.8)	87 046 (78.5)	0.006
Liver disease	55 461 (49.2)	399 075 (47.1)	0.04	54 598 (49.2)	54 747 (49.4)	0.003
COPD	22 650 (20.1)	172 494 (20.3)	0.006	22 240 (20.1)	22 370 (20.2)	0.003
Asthma	14 301 (12.7)	104 767 (12.4)	0.01	14 075 (12.7)	14 053 (12.7)	<0.001
Alcohol use and related disorders	5050 (4.5)	43 333 (5.1)	0.03	4955 (4.5)	4920 (4.4)	0.002
Thyroid disease	29 297 (26.0)	185 147 (21.8)	0.10	28 775 (26.0)	29 123 (26.3)	0.007
Osteoporosis	12 476 (11.1)	91 003 (10.7)	0.01	12 250 (11.1)	12 260 (11.1)	<0.001
Head injury	4458 (4.0)	36 819 (4.3)	0.02	4375 (4.0)	4361 (3.9)	<0.001
Fracture	6618 (5.9)	50 369 (5.9)	0.003	6482 (5.9)	6616 (6.0)	0.005
Malignancy	10 645 (9.5)	81 035 (9.6)	0.004	10 408 (9.4)	10 389 (9.4)	<0.001
Mean (SD) comorbidity score	2.4 (1.8)	2.3 (1.8)	0.049	2.4 (1.8)	2.4 (1.8)	0.002
Drugs						
Antidepressant	10 850 (9.6)	77 414 (9.1)	0.02	10 624 (9.6)	10 600 (9.6)	<0.001
SSRI	3799 (3.4)	25 426 (3.0)	0.02	3732 (3.4)	3747 (3.4)	<0.001
SNRI	2684 (2.4)	16 914 (2.0)	0.03	2610 (2.4)	2584 (2.3)	0.002
TCA	2493 (2.2)	18 408 (2.2)	0.003	2449 (2.2)	2474 (2.2)	0.002
Antipsychotics	2510 (2.2)	20 452 (2.4)	0.01	2455 (2.2)	2474 (2.2)	0.001
Antihistamines	58 077 (51.6)	465 964 (55.0)	0.07	57 121 (51.5)	57 193 (51.6)	0.001
Antimuscarinics	5049 (4.5)	38 869 (4.6)	0.005	4963 (4.5)	4919 (4.4)	0.002
ACE inhibitor/ARB	61 529 (54.6)	395 973 (46.7)	0.16	60 463 (54.5)	60 447 (54.5)	<0.001
Beta blockers	24 512 (21.8)	146 874 (17.3)	0.11	23 964 (21.6)	24 173 (21.8)	0.005
Calcium channel blocker	46 093 (40.9)	314 582 (37.1)	0.08	45 353 (40.9)	45 228 (40.8)	0.002
Any diuretics	24 776 (22.0)	181 722 (21.4)	0.01	24 336 (22.0)	24 224 (21.9)	0.002
Loop diuretics	6028 (5.4)	38 925 (4.6)	0.04	5849 (5.3)	5901 (5.3)	0.002
Nitrate	9771 (8.7)	43 556 (5.1)	0.14	9479 (8.6)	9611 (8.7)	0.004
Anticoagulants	5817 (5.2)	30 882 (3.6)	0.07	5622 (5.1)	5684 (5.1)	0.003
Antiplatelets	30 971 (27.5)	208 915 (24.6)	0.07	30 279 (27.3)	30 478 (27.5)	0.004
Antiarrhythmics	9008 (8.0)	64 959 (7.7)	0.01	8816 (8.0)	8848 (8.0)	0.001
Statins	68 896 (61.2)	420 741 (49.6)	0.23	67 648 (61.0)	67 463 (60.8)	0.003
Other lipid lowering agents	20 232 (18.0)	106 156 (12.5)	0.15	19 825 (17.9)	19 834 (17.9)	<0.001
Proton pump inhibitor	41 141 (36.5)	282 569 (33.3)	0.07	40 423 (36.5)	40 427 (36.5)	<0.001
H_2 blocker	48 036 (42.6)	400 431 (47.2)	0.09	47 227 (42.6)	47 452 (42.8)	0.004
NSAIDs	55 580 (49.3)	434 615 (51.3)	0.04	54 646 (49.3)	54 757 (49.4)	0.002
Opioids	11 453 (10.2)	117 077 (13.8)	0.08	11 221 (10.1)	11 275 (10.2)	0.002
Steroid	55 918 (49.6)	421 853 (49.8)	0.002	54 999 (49.6)	55 108 (49.7)	0.002
Healthcare utilisation						
Hospital admission	23 997 (21.3)	180 150 (21.2)	0.001	23 435 (21.1)	23 784 (21.5)	0.008
Emergency room visits	12 190 (10.8)	99 619 (11.8)	0.03	11 940 (10.8)	11 932 (10.8)	<0.001
Mean (SD) No of outpatient clinic visits	22.3 (20.2)	22.8 (21.0)	0.03	22.2 (20.0)	22.2 (19.5)	<0.001
Investigations						
Electrocardiography	45 726 (40.6)	310 585 (36.6)	0.08	44 842 (40.4)	45 087 (40.7)	0.005
HbA_{1c}	39 084 (34.7)	425 012 (50.1)	0.32	38 541 (34.8)	38 634 (34.8)	0.002
Lipid/cholesterol	36 461 (32.4)	395 790 (46.7)	0.30	35 959 (32.4)	36 018 (32.5)	0.001
Serum creatinine	35 603 (31.6)	389 077 (45.9)	0.30	35 101 (31.7)	35 184 (31.7)	0.002

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; COPD=chronic obstructive pulmonary disease; HbA_{1c}=glycated haemoglobin; NSAID=non-steroidal anti-inflammatory drug; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

Comparative risk of dementia between initiators of SGLT-2 inhibitors and DPP-4 inhibitors

The mean follow-up time of patients was 670 (SD 650) days, with 612 (SD 613) days for initiators of SGLT-2 inhibitors and 728 (SD 679) days for initiators of DPP-4 inhibitors (see supplemental table S6 for distribution of censoring events). A total of 1172 participants with newly diagnosed dementia were identified, with incidence rates per 100 person years of 0.22 for initiators of SGLT-2 inhibitors and 0.35 for initiators of DPP-4 inhibitors. The corresponding hazard ratio was 0.65 (95% CI 0.58 to 0.73; table 2). The lowered risk of dementia associated with use of SGLT-2 inhibitors compared with DPP-4 inhibitors was similarly observed for secondary outcomes: hazard ratio 0.54 (0.46 to 0.63) for dementia requiring drugs, 0.61 (0.53 to 0.69) for Alzheimer's disease, and 0.48 (0.33 to 0.70) for vascular dementia. The results were consistent with those of intention-to-treat analyses: 0.65 (0.60 to 0.71) for dementia, 0.60 (0.54 to 0.67) for dementia requiring drugs, 0.63 (0.57 to 0.69) for Alzheimer's disease, and 0.62 (0.49 to 0.79) for vascular dementia. Estimates for the Fine-Gray models were also similar. We found a 2.67-fold risk (95% CI 2.57-fold to 2.77-fold) of genital infections associated with SGLT-2 inhibitors versus DPP-4 inhibitors. The hazard ratios for association between treatment and negative control outcomes were 0.97 (95% CI 0.95 to 0.98) for osteoarthritis related encounters and 0.92 (0.89 to 0.96) for cataract surgery. When corrected using the association between treatment and cataract surgery, the hazard ratios for dementia increased by about 7.7% (see supplemental table S7), to 0.70 (0.62 to 0.80).

Follow-up time stratified analysis

A significant interaction (P<0.05) was observed between treatment and follow-up time for all outcomes except vascular dementia in the as treated analysis. The Kaplan-Meier curve diverged more in the later follow-up period for these outcomes (fig 1), indicating that the effect would be greater with longer treatment. According to the follow-up time stratified analyses (46 767 propensity score matched pairs treated for two or less years, 16 827 pairs treated for more than two years; see supplemental table S8 for the distribution of baseline covariates for individual stratified groups), the magnitude of association modestly increased with more than two years of treatment compared with two years or less for these outcomes (see supplemental table S9): hazard ratio for more than two years versus two years or less of treatment was 0.52 (95% CI 0.41 to 0.66) *v* 0.57 (0.46 to 0.70) for dementia, 0.41 (0.29 to 0.57) *v* 0.45 (0.33 to 0.61) for dementia requiring drugs, and 0.48 (0.37 to 0.63) *v* 0.53 (0.41 to 0.68) for Alzheimer's disease.

Sensitivity analyses

The results were highly consistent even after accounting for the 365 day lag time from the index date (table 3), with hazard ratios in as treated analyses of 0.57 (0.48 to 0.68) for dementia, 0.48 (0.38 to 0.61) for dementia requiring drugs, 0.55 (0.45 to 0.67) for Alzheimer's disease, and 0.46 (0.26 to 0.80) for vascular dementia. In the intention-to-treat analyses with lag time applied, the hazard ratios were 0.80 (0.75 to 0.86) for dementia, 0.84 (0.77 to 0.91) for dementia requiring drugs, 0.80 (0.74 to 0.86) for Alzheimer's disease, and 0.80 (0.66 to 0.98) for vascular dementia.

Table 2 | Comparative risk of dementia between initiators of SGLT-2 inhibitors and DPP-4 inhibitors in main propensity score matched cohort

	SGLT-2 inhibitors (n=110 885)			DPP-4 inhibitors (n=110 885) (ref)			Hazard ratio (95% CI)	
	Events	Person years	Incidence rate per 100 person years (95% CI)	Events	Person years	Incidence rate per 100 person years (95% CI)	Cox model	Fine-Gray model
As treated analysis								
Dementia	408	185 879	0.22 (0.20 to 0.24)	764	221 254	0.35 (0.32 to 0.37)	0.65 (0.58 to 0.73)	0.65 (0.57 to 0.73)
Dementia requiring drugs	220	186 117	0.12 (0.10 to 0.13)	471	221 729	0.21 (0.19 to 0.23)	0.54 (0.46 to 0.63)	0.57 (0.49 to 0.67)
Alzheimer's disease	315	186 006	0.17 (0.15 to 0.19)	615	221 517	0.28 (0.26 to 0.30)	0.61 (0.53 to 0.69)	0.63 (0.55 to 0.72)
Vascular dementia	37	186 363	0.02 (0.01 to 0.03)	84	222 271	0.04 (0.03 to 0.05)	0.48 (0.33 to 0.70)	0.53 (0.36 to 0.77)
Genital infection	8371	171 248	4.89 (4.78 to 4.99)	3987	213 795	1.87 (1.81 to 1.92)	2.67 (2.57 to 2.77)	2.45 (2.36 to 2.54)
Osteoarthritis related encounters	24 661	143 880	17.14 (16.93 to 17.35)	28 007	165 739	16.90 (16.70 to 17.10)	0.97 (0.95 to 0.98)	0.97 (0.95 to 0.99)
Cataract surgery	5026	178 672	2.81 (2.74 to 2.89)	6385	211 021	3.03 (2.95 to 3.10)	0.92 (0.89 to 0.96)	0.93 (0.90 to 0.97)
Death	583	186 412	0.31 (0.29 to 0.34)	1268	222 419	0.57 (0.54 to 0.60)	0.50 (0.45 to 0.55)	
Intention-to-treat analysis								
Dementia	609	235 191	0.26 (0.24 to 0.28)	1207	293 352	0.41 (0.39 to 0.44)	0.65 (0.60 to 0.71)	0.65 (0.59 to 0.72)
Dementia requiring drugs	370	235 593	0.16 (0.14 to 0.17)	792	294 215	0.27 (0.25 to 0.29)	0.60 (0.54 to 0.67)	0.61 (0.54 to 0.69)
Alzheimer's disease	485	235 428	0.21 (0.19 to 0.22)	992	293 830	0.34 (0.32 to 0.36)	0.63 (0.57 to 0.69)	0.64 (0.57 to 0.71)
Vascular dementia	67	236 030	0.03 (0.02 to 0.04)	138	295 266	0.05 (0.04 to 0.06)	0.62 (0.49 to 0.79)	0.61 (0.45 to 0.82)
Genital infection	9340	217 114	4.30 (4.22 to 4.39)	5028	283 409	1.77 (1.73 to 1.82)	2.37 (2.30 to 2.45)	2.24 (2.17 to 2.32)
Osteoarthritis related encounters	28 994	179 435	16.16 (15.97 to 16.34)	33 712	216 447	15.58 (15.41 to 15.74)	0.97 (0.96 to 0.98)	0.98 (0.97 to 1.00)
Cataract surgery	6281	225 600	2.78 (2.72 to 2.85)	8262	279 271	2.96 (2.90 to 3.02)	0.94 (0.91 to 0.96)	0.95 (0.92 to 0.98)
Death	1077	236 159	0.46 (0.43 to 0.48)	2579	295 594	0.87 (0.84 to 0.91)	0.52 (0.49 to 0.56)	

CI=confidence interval; DPP-4=dipeptidyl peptidase-4; SGLT-2=sodium-glucose cotransporter-2.

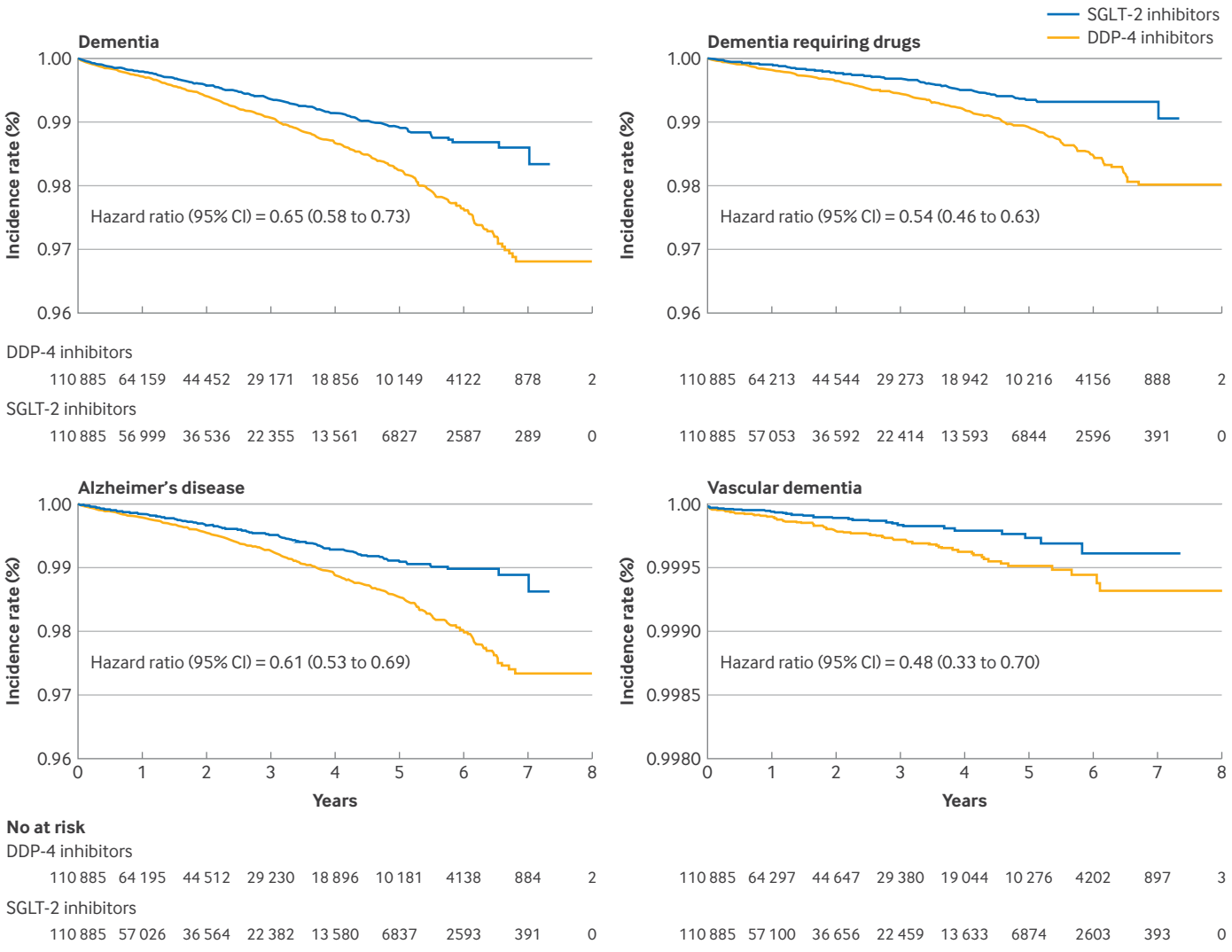

Fig 1 | Kaplan-Meier curves for dementia-free survival comparing propensity score matched initiators of SGLT-2 inhibitors with initiators of DPP-4 inhibitors. CI=confidence interval; DPP-4=dipeptidyl peptidase-4; SGLT-2=sodium-glucose cotransporter-2

For as treated analyses with longer grace periods after treatment change, a slightly increased incidence rate of dementia was noted in both treatment groups but to a greater degree among initiators of SGLT-2 inhibitors, with a hazard ratio of 0.72 (0.65 to 0.80) for dementia for a grace period of 180 days and 0.76 (0.69 to 0.83) for a grace period of 365 days (see supplemental table S10). Decreased incidence rates of genital infections were also noted among initiators of SGLT-2 inhibitors.

The results were consistent regardless of concurrent use of a drug with hypoglycaemic potential (see supplemental tables S11 and S12), with a hazard ratio of 0.69 (0.60 to 0.80) for dementia. The duration of type 2 diabetes was identified for 45 088 propensity score matched pairs (1008 *v* 925 days for initiators of SGLT-2 inhibitors and DPP-4 inhibitors, respectively, with a standardised difference of 0.10). Consistent results were observed after adjusting for duration of type 2 diabetes (see supplemental tables S13 and S14), with a hazard ratio of 0.60 (0.50 to 0.72) for dementia. We also observed similar results in propensity score based fine stratification weighted analyses (see supplemental tables S15 and S16), with a hazard ratio of 0.68 (0.62 to 0.75) for dementia.

Subgroup analysis

Supplemental table S17 presents the baseline characteristics of the subgroups. The lower risk associated with SGLT-2 inhibitors was overall consistent across subgroups stratified by age, sex, concurrent metformin use, and baseline cardiovascular risk (fig 2, also see supplemental table S18). However, statistical significance was not achieved for the subgroups with relatively small outcome numbers (eg, those aged <60 years). We did not find any interaction between the treatment and individual stratifying factors.

Table 3 | Lag time analyses on comparative risk of dementia in main propensity score matched cohort, with follow-up starting after 365 days from index date

		SGLT-2 inhibitors			DPP-4 inhibitors (ref)			Hazard ratio (95% CI)	
	No of propensity score matched pairs	Events	Person years	Incidence rate per 100 person years (95% CI)	Events	Person years	Incidence rate per 100 person years (95% CI)	Cox model	Fine-Gray model
As treated analysis									
Dementia	34 048	159	69 466	0.23 (0.19 to 0.26)	293	77 010	0.38 (0.34 to 0.42)	0.57 (0.48 to 0.68)	0.61 (0.50 to 0.74)
Dementia requiring drugs	34 113	89	69 665	0.13 (0.10 to 0.15)	191	77 305	0.25 (0.21 to 0.28)	0.48 (0.38 to 0.61)	0.53 (0.41 to 0.68)
Alzheimer's disease	34 085	129	69 569	0.19 (0.15 to 0.22)	246	77 198	0.32 (0.28 to 0.36)	0.55 (0.45 to 0.67)	0.59 (0.48 to 0.73)
Vascular dementia	34 180	13	69 882	0.02 (0.01 to 0.03)	33	77 634	0.04 (0.03 to 0.06)	0.46 (0.26 to 0.80)	0.44 (0.23 to 0.84)
Genital infection	31 048	1634	60 245	2.71 (2.58 to 2.84)	995	68 083	1.46 (1.37 to 1.55)	1.92 (1.79 to 2.06)	1.81 (1.68 to 1.96)
Osteoarthritis related encounters	21 991	3900	37 979	10.3 (10.0 to 10.6)	4437	41 468	10.7 (10.4 to 11.0)	0.95 (0.91 to 0.99)	0.96 (0.92 to 1.00)
Cataract surgery	32 061	1823	63 009	2.89 (2.76 to 3.03)	2253	69 216	3.26 (3.12 to 3.39)	0.93 (0.88 to 0.98)	0.92 (0.85 to 0.96)
Intention-to-treat analysis to 3 years*									
Dementia	77 396	607	172 767	0.35 (0.32 to 0.38)	770	173 238	0.44 (0.41 to 0.48)	0.77 (0.71 to 0.84)	0.79 (0.71 to 0.88)
Dementia requiring drugs	77 526	412	173 307	0.24 (0.22 to 0.26)	502	173 885	0.29 (0.26 to 0.31)	0.81 (0.73 to 0.89)	0.83 (0.73 to 0.94)
Alzheimer's disease	77 477	493	173 110	0.29 (0.26 to 0.31)	635	173 639	0.37 (0.34 to 0.39)	0.76 (0.69 to 0.83)	0.78 (0.69 to 0.88)
Vascular dementia	77 674	77	174 010	0.04 (0.03 to 0.05)	96	174 664	0.06 (0.04 to 0.07)	0.83 (0.67 to 1.03)	0.81 (0.60 to 1.09)
Genital infection	71 479	3735	153 363	2.44 (2.36 to 2.51)	2635	156 056	1.69 (1.62 to 1.75)	1.43 (1.37 to 1.48)	1.44 (1.37 to 1.52)
Osteoarthritis related encounters	53 768	10 843	103 926	10.4 (10.2 to 10.6)	10 678	104 666	10.2 (10.0 to 10.4)	1.03 (1.01 to 1.05)	1.03 (1.00 to 1.05)
Cataract surgery	73 730	4965	159 061	3.12 (3.04 to 3.21)	5038	159 482	3.16 (3.07 to 3.25)	0.98 (0.95 to 1.01)	0.99 (0.95 to 1.03)
Intention-to-treat analysis to maximum follow-up*									
Dementia	77 396	908	227 961	0.40 (0.37 to 0.42)	1134	230 043	0.49 (0.46 to 0.52)	0.80 (0.75 to 0.86)	0.82 (0.75 to 0.89)
Dementia requiring drugs	77 526	632	228 852	0.28 (0.26 to 0.30)	768	231 156	0.33 (0.31 to 0.36)	0.84 (0.77 to 0.91)	0.84 (0.76 to 0.93)
Alzheimer's disease	77 477	755	228 538	0.33 (0.31 to 0.35)	949	230 711	0.41 (0.39 to 0.44)	0.80 (0.74 to 0.86)	0.81 (0.74 to 0.89)
Vascular dementia	77 674	97	230 144	0.04 (0.03 to 0.05)	128	232 555	0.06 (0.05 to 0.07)	0.80 (0.66 to 0.98)	0.76 (0.59 to 0.99)
Genital infection	71 479	4336	199 630	2.17 (2.11 to 2.24)	3192	205 272	1.56 (1.50 to 1.61)	1.38 (1.34 to 1.43)	1.39 (1.33 to 1.46)
Osteoarthritis related encounters	53 768	12 965	130 000	9.97 (9.80 to 10.15)	12 747	131 984	9.66 (9.49 to 9.83)	1.03 (1.01 to 1.05)	1.03 (1.01 to 1.06)
Cataract surgery	73 730	6678	206 281	3.24 (3.16 to 3.32)	6810	207 999	3.27 (3.20 to 3.35)	1.00 (0.97 to 1.02)	0.99 (0.96 to 1.03)

CI=confidence interval; DPP-4=dipeptidyl peptidase-4; SGLT-2=sodium glucose co-transporter 2.
*One year lag time applied in intention-to-treat analysis showed attenuated association. Because patients remained in the index treatment group even if they discontinued or switched from their index treatment, misclassification of drug use is least for the initial follow-up period. Therefore, starting follow-up one year after the index date will result in greater misclassification of drug use and drive the effect estimate towards null in the intention-to-treat analysis.

Discussion

This large population based cohort study among adults aged 40-69 years with type 2 diabetes found a 35% reduced risk of dementia associated with use of SGLT-2 inhibitors compared with DPP-4 inhibitors. This finding persisted regardless of dementia type and across subgroups of populations with diverse characteristics. Highly consistent results over a range of secondary and sensitivity analyses supported the robustness of our study findings. Our findings also suggest that the treatment effect of SGLT-2 inhibitors escalated with time.

Relevance of study design to internal validity

An active comparator new user design is a powerful pharmacoepidemiological approach that effectively copes with both measured and unmeasured confounding in observational studies.[33] One of the key advantages of this approach would be that similar disease (type 2 diabetes in our example) severity and related comorbidity profile can be expected between the two treatment groups because the participants in both groups are at the beginning of a similar stage of a given treatment. International guidelines had equally recommended SGLT-2 inhibitors and DPP-4 inhibitors as second line treatment until December 2018 [34] when the revised guideline preferentially recommended use of SGLT-2 inhibitors in the presence of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.[35] This approach also ensures that selection bias associated with depletion of susceptible people (to inefficacy or intolerance, or both) is avoided, allowing all individuals initiating the study drug to contribute to the follow-up from the start of the treatment. In this context, our study design offered greater internal validity than in previous studies.[15 16]

Interpretation of results and comparison with other studies

We observed a known association between a positive control outcome and treatment.[22] The association for osteoarthritis related encounters was close to null (hazard ratio 0.97, 95% CI 0.95 to 0.98), which achieved statistical significance owing to excess power from a highly frequent outcome. A slight deviation (0.92, 0.89 to 0.96) from the null association was observed for cataract surgery. A bias measure (7.7% increased hazard ratio) based on this deviation indicated that the association between treatment and dementia was largely unexplained solely by residual confounding.

In preclinical studies, SGLT-2 inhibitors have shown direct neuroprotective effects through multiple pathways.[13 36-38] These drugs exhibited anticholinergic

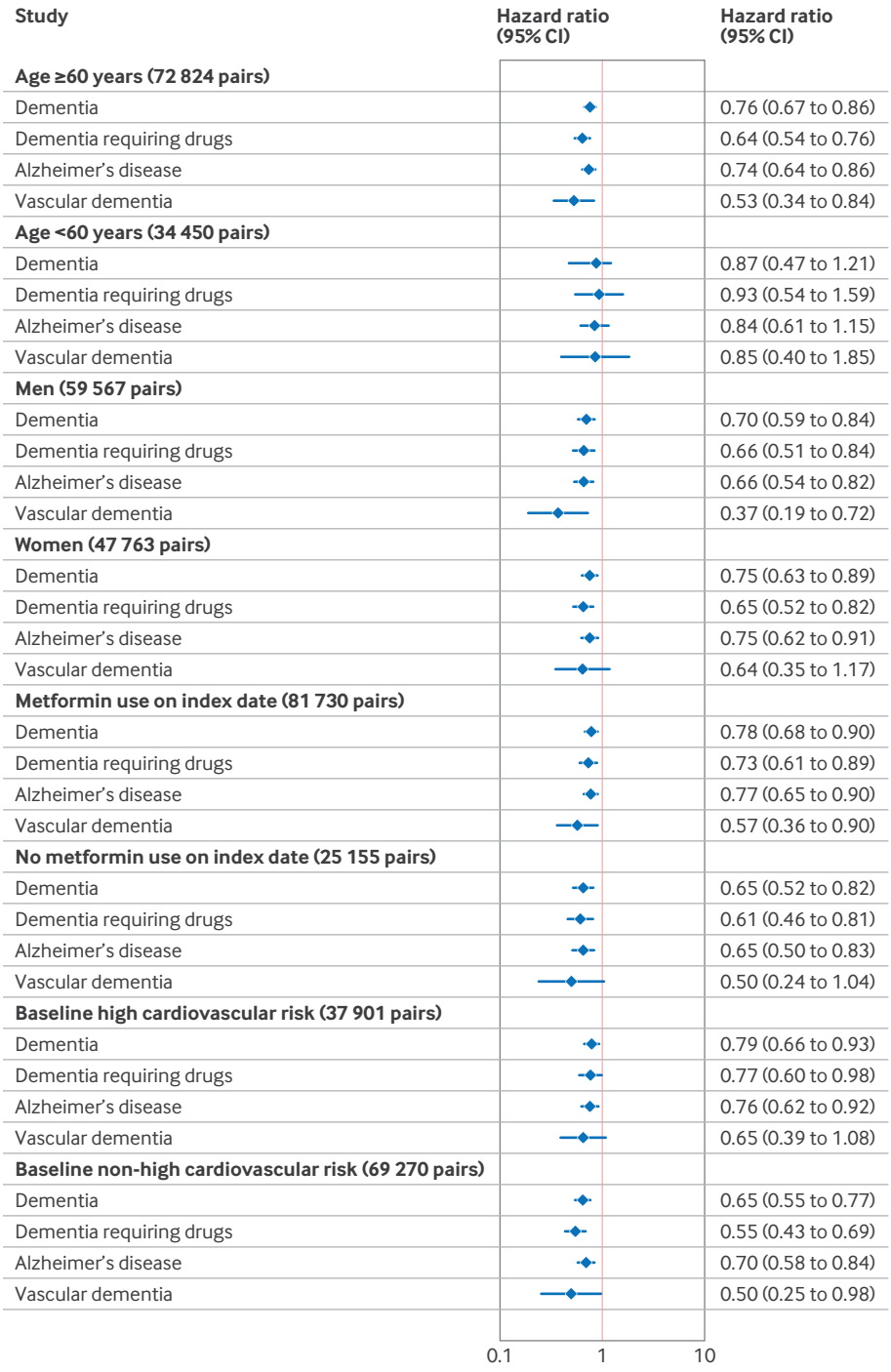

Fig 2 | Comparative risk of dementia between initiators of sodium-glucose cotransporter-2 inhibitors and initiators of dipeptidyl peptidase-4 inhibitors in individual propensity score matched subgroups (as treated analysis). CI=confidence interval

activity,[13] prevented ultrastructural changes of neurovascular units associated with cognitive decline in mice with diabetes,[36] and ameliorated amyloid β deposition and tau phosphorylation in the brain tissue of mice with Alzheimer's disease and type 2 diabetes.[37] Diurnal catabolism induced by SGLT-2 inhibitors restored autophagy by downregulating the mTOR (mechanistic target of rapamycin) pathway, which is chronically activated in Alzheimer's disease.[38] Based on these preclinical findings, SGLT-2 inhibitors may delay the progression of dementia in people with type 2 diabetes both for Alzheimer's disease and for vascular dementia, independent of the cardiorenal benefits exerted by SGLT-2 inhibitors.

A considerable effect estimate found within a relatively short period (≤2 years) of follow-up needs

attention. Dementia develops through a continuum of accumulated molecular and structural changes.[7] Heterogeneous states of disease progression yet to reach definitive dementia are likely to exist among people with type 2 diabetes at baseline or even after applying a one year lag time. This is likely true since mild cognitive impairment, a transitional state between normal ageing and dementia,[7] is prevalent among 12-18% and 23% of people aged ≥60 years in the US and Korea, respectively, with 10-15% of the annual conversion to dementia.[39 40] Notably, mild cognitive impairment is 1.4~2.0 times more prevalent among people with type 2 diabetes with accelerated progression.[41-44] Because the time span between mild cognitive impairment and dementia has already been shortened, and progression is particularly rapid among people with type 2 diabetes, early risk reduction against dementia could be seen in the presence of effective treatment (see supplementary figure S3 for a schematic explanation). This scenario also complies with the finding that the cognitive benefits of SGLT-2 inhibitor use versus non-use were better noted for those with mild cognitive impairment than with normal cognitive function at baseline.[17] Moreover, the visible action of SGLT-2 inhibitors versus DPP-4 inhibitors was rapid, based on the time elapsed until the first statistically significant result as early as day 5 for the benefits on death and worsening heart failure.[45]

A recent prospective cohort study found that use of SGLT-2 inhibitors for more than three years improved cognitive function scores compared with non-use.[46] Although this finding suggests that longer treatment might generate more benefits, the study was subject to confounding by indication and immortal time bias owing to the comparison between users (eg, prevalent users) and non-users of SGLT-2 inhibitors.[33] Our study comparing new users of two competing drugs, SGLT-2 inhibitors and DPP-4 inhibitors, further supports favourable results for early initiation of the drug and prolonged treatment.

We observed attenuated results with lag time applied in intention-to-treat analyses and with longer grace periods. Since incidence rates of genital infections continually decreased among users of SGLT-2 inhibitors in these analyses, loss of treatment effect associated with misclassification of drug use played a role in driving the results towards null. Initiators of SGLT-2 inhibitors, however, were more frequently censored by treatment change than initiators of DPP-4 inhibitors. Because patients with risk factors for treatment change (non-adherence, inefficacy, or adverse events) can be more prone to develop dementia than patients without these risk factors, informative censoring may have overestimated the results in our as treated analysis. Nevertheless, the overall results between as treated and intention-to-treat analyses were similar (table 2), suggesting non-substantial informative censoring.

In subgroup analyses, we observed highly consistent results, but did not find an interaction between treatment and individual characteristics of the study population. Unlike the expectation that SGLT-2 inhibitors might be associated with greater benefits against the risk of vascular dementia than Alzheimer's disease, the magnitude of association was accompanied by widely overlapping 95% CIs between the two types of dementia for all analyses. Thus, it is not surprising to observe no interaction between treatment and baseline cardiovascular risk. A recent meta-analysis also reported that the pooled beneficial association between dementia and use of SGLT-2 inhibitors versus other antiglycaemic treatments was not affected by cardiovascular diseases.[10] These findings suggest that the underlying mechanisms are not limited to cardiorenal pathways, possibly involving direct neuroprotective pathways observed in preclinical studies.[13 36-38] According to previous studies on metformin monotherapy versus no treatment, metformin was not associated with incident dementia.[47 48] Based on these findings, concurrent use of metformin is unlikely to interact with SGLT-2 inhibitors in modifying the risk of dementia.

Strengths and limitations of this study

Several important strengths of this study deserve comment. Firstly, we used rigorous pharmacoepidemiological approaches, in particular we adopted an active comparator new user design and extensive propensity score matching.[33] The diagnosis codes in the primary position and applying disease specific drugs would increase the specificity of the outcome. The sensitivity analyses and control outcomes add relevant internal validity to this study. Secondly, compared with a previous study,[14] we included relatively younger people (aged 40-69 years) with type 2 diabetes, broadening the target population of benefits associated with use of SGLT-2 inhibitors. Thirdly, we used a nationally representative database, providing high generalisability. Fourthly, we performed comprehensive analyses for time varying comparisons of SGLT-2 inhibitors versus DPP-4 inhibitors, diverse subgroups, and individual types of dementia, presenting highly consistent results.

This study also has limitations. Firstly, owing to the observational nature of our study, it is inherently subject to residual or unmeasured confounding. Although we balanced many proxies of type 2 diabetes severity and comorbidities and used negative control outcomes, direct test results on serum glucose levels, renal function, severity of other comorbidities, health behaviours (eg, smoking and alcohol consumption), and duration of type 2 diabetes were not fully ascertainable from the claims data. Secondly, diagnoses of dementia are commonly delayed, rendering studies on dementia risk particularly susceptible to informative censoring, reverse causation, and outcome misclassification, which may have resulted in overestimation of our results. Thirdly, our study did not provide exact mechanisms of neuroprotection.

Conclusions

This large population based cohort study found that initiation of SGLT-2 inhibitors was associated with a 35% lower risk of dementia compared with initiation

of DPP-4 inhibitors in people with type 2 diabetes aged 40-69 years. This association was similarly observed for Alzheimer's disease and vascular dementia and was also consistent across subgroups. We observed a greater association with treatment duration longer than two years. These findings underscore the need for future randomised controlled trials.

We thank Joongyub Lee (Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea) for comments on the pharmacoepidemiological design of this study.

Contributors: EHK conceived and designed the study and drafted the manuscript. AS did the analyses. EHK and AS had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors interpreted the data, critically revised the manuscript for important intellectual content, and approved the final version. EHK is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was supported by the Korea Health Industry Development Institute (KHIDI)-AZ Diabetes Research programme (grant No 08-2022-0261). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the Korea Health Industry Development Institute (KHIDI)-AZ Diabetes Research programme; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. EHK receives grants from Celltrion and SK Chemicals to Seoul National University Bundang Hospital for unrelated studies. BKK receives grants from KHIDI to SMG-SNU Boramae Medical Centre for unrelated studies.

Ethical approval: The Institutional Review Board of the Seoul National University Bundang Hospital exempted the study protocol (X-2206-762-901) and waived written patient consent based on the fully deidentified database.

Data sharing: Patient level data are not publicly allowed according to data use agreement. Aggregate level data can be requested from the corresponding author.

Transparency: The guarantor (EHK) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The use of deidentified data preclude direct dissemination to participants, and we have no plans to involve patients in the dissemination of study results. Study findings will be disseminated by all coauthors through their own institutions. The article will be distributed within the corresponding author's institution.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 5th ed. APA, 2013.
2 World Health Organization. Fact sheets of dementia. Geneva, Switzerland: WHO; 2021. www.who.int/news-room/fact-sheets/detail/dementia.
3 Gauthier S, Albert M, Fox N, et al. Why has therapy development for dementia failed in the last two decades?*Alzheimers Dement* 2016;12:60-4. doi:10.1016/j.jalz.2015.12.003
4 Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;396:413-46. doi:10.1016/S0140-6736(20)30367-6
5 Chatterjee S, Peters SA, Woodward M, et al. Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia. *Diabetes Care* 2016;39:300-7. doi:10.2337/dc15-1588
6 Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006;5:64-74. doi:10.1016/S1474-4422(05)70284-2
7 Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol* 2018;14:591-604. doi:10.1038/s41574-018-0048-7
8 Tang H, Shao H, Shaaban CE, et al. Newer glucose-lowering drugs and risk of dementia: A systematic review and meta-analysis of observational studies. *J Am Geriatr Soc* 2023;71:2096-106. doi:10.1111/jgs.18306
9 Kuate Defo A, Bakula V, Pisaturo A, Labos C, Wing SS, Daskalopoulou SS. Diabetes, antidiabetic medications and risk of dementia: A systematic umbrella review and meta-analysis. *Diabetes Obes Metab* 2024;26:441-62. doi:10.1111/dom.15331
10 Gunawan PY, Gunawan PA, Hariyanto TI. Risk of Dementia in Patients with Diabetes Using Sodium-Glucose Transporter 2 Inhibitors (SGLT2i): A Systematic Review, Meta-Analysis, and Meta-Regression. *Diabetes Ther* 2024;15:663-75. doi:10.1007/s13300-024-01538-1
11 Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. *Lancet* 2021;398:262-76. doi:10.1016/S0140-6736(21)00536-5
12 He D, Aleksic S. Is it time to repurpose geroprotective diabetes medications for prevention of dementia?*J Am Geriatr Soc* 2023;71:2041-5. doi:10.1111/jgs.18405
13 Katsenos AP, Davri AS, Simos YV, et al. New treatment approaches for Alzheimer's disease: preclinical studies and clinical trials centered on antidiabetic drugs. *Expert Opin Investig Drugs* 2022;31:105-23. doi:10.1080/13543784.2022.2022122
14 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;46:297-304. doi:10.2337/dc22-1705
15 Mui JV, Zhou J, Lee S, et al. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors vs. Dipeptidyl Peptidase-4 (DPP4) Inhibitors for New-Onset Dementia: A Propensity Score-Matched Population-Based Study With Competing Risk Analysis. *Front Cardiovasc Med* 2021;8:747620. doi:10.3389/fcvm.2021.747620
16 Siao WZ, Lin TK, Huang JY, Tsai CF, Jong GP. The association between sodium-glucose cotransporter 2 inhibitors and incident dementia: A nationwide population-based longitudinal cohort study. *Diab Vasc Dis Res* 2022;19:14791641221098168. doi:10.1177/14791641221098168
17 Youn YJ, Kim S, Jeong HJ, Ah YM, Yu YM. Sodium-glucose cotransporter-2 inhibitors and their potential role in dementia onset and cognitive function in patients with diabetes mellitus: a systematic review and meta-analysis. *Front Neuroendocrinol* 2024;73:101131. doi:10.1016/j.yfrne.2024.101131
18 Biessels GJ, Verhagen C, Janssen J, et al. Effects of linagliptin vs glimepiride on cognitive performance in type 2 diabetes: results of the randomised double-blind, active-controlled CAROLINA-COGNITION study. *Diabetologia* 2021;64:1235-45. doi:10.1007/s00125-021-05393-8
19 Biessels GJ, Verhagen C, Janssen J, et al, CARMELINA Investigators. Effect of Linagliptin on Cognitive Performance in Patients With Type 2 Diabetes and Cardiorenal Comorbidities: The CARMELINA Randomized Trial. *Diabetes Care* 2019;42:1930-8. doi:10.2337/dc19-0783
20 Kang EH, Park EH, Shin A, Song JS, Kim SC. Cardiovascular risk associated with allopurinol vs. benzbromarone in patients with gout. *Eur Heart J* 2021;42:4578-88. doi:10.1093/eurheartj/ehab619
21 Taylor DHJr, Østbye T, Langa KM, Weir D, Plassman BL. The accuracy of Medicare claims as an epidemiological tool: the case of dementia revisited. *J Alzheimers Dis* 2009;17:807-15. doi:10.3233/JAD-2009-1099
22 Liu J, Li L, Li S, et al. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. *Sci Rep* 2017;7:2824. doi:10.1038/s41598-017-02733-w
23 Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010;21:383-8. doi:10.1097/EDE.0b013e3181d61eeb
24 Lindblad BE, Håkansson N, Wolk A. Smoking cessation and the risk of cataract: a prospective cohort study of cataract extraction among men. *JAMA Ophthalmol* 2014;132:253-7. doi:10.1001/jamaophthalmol.2013.6669
25 Lindblad BE, Håkansson N, Philipson B, Wolk A. Alcohol consumption and risk of cataract extraction: a prospective cohort study of women. *Ophthalmology* 2007;114:680-5. doi:10.1016/j.ophtha.2006.07.046
26 Zhou B, Shi Y, Fu R, et al. Relationship Between SGLT-2i and Ocular Diseases in Patients With Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. *Front Endocrinol (Lausanne)* 2022;13:907340. doi:10.3389/fendo.2022.907340

27 Ma Y, Lin C, Cai X, et al. The association between the use of sodium glucose cotransporter 2 inhibitor and the risk of diabetic retinopathy and other eye disorders: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2022;15:877-86. doi:10.1080/17512433.2022.2102973
28 Richardson DB, Laurier D, Schubauer-Berigan MK, Tchetgen Tchetgen E, Cole SR. Assessment and indirect adjustment for confounding by smoking in cohort studies using relative hazards models. *Am J Epidemiol* 2014;180:933-40. doi:10.1093/aje/kwu211
29 Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004;57:1288-94. doi:10.1016/j.jclinepi.2004.03.012
30 Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. *Commun Stat Simul Comput* 2009;38:1228-34. doi:10.1080/03610910902859574.
31 Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* 2016;133:601-9. doi:10.1161/CIRCULATIONAHA.115.017719
32 Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. *Epidemiology* 2017;28:249-57. doi:10.1097/EDE.0000000000000595
33 Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol* 2015;11:437-41. doi:10.1038/nrrheum.2015.30
34 Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38:140-9. doi:10.2337/dc14-2441
35 Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669-701. doi:10.2337/dci18-0033
36 Hayden MR, Grant DG, Aroor AR, DeMarco VG. Empagliflozin Ameliorates Type 2 Diabetes-Induced Ultrastructural Remodeling of the Neurovascular Unit and Neuroglia in the Female *db/db* Mouse. *Brain Sci* 2019;9:57. doi:10.3390/brainsci9030057
37 Hierro-Bujalance C, Infante-Garcia C, Del Marco A, et al. Empagliflozin reduces vascular damage and cognitive impairment in a mixed murine model of Alzheimer's disease and type 2 diabetes. *Alzheimers Res Ther* 2020;12:40. doi:10.1186/s13195-020-00607-4
38 Esterline RL, Vaag A, Oscarsson J, Vora J. MECHANISMS IN ENDOCRINOLOGY: SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?*Eur J Endocrinol* 2018;178:R113-25. doi:10.1530/EJE-17-0832
39 2022 Alzheimer's disease facts and figures. *Alzheimers Dement* 2022;18:700-89.
40 Shin JH. Dementia Epidemiology Fact Sheet 2022. *Ann Rehabil Med* 2022;46:53-9. doi:10.5535/arm.22027
41 Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. *Arch Neurol* 2007;64:570-5. doi:10.1001/archneur.64.4.570
42 Winkler A, Dlugaj M, Weimar C, et al. Association of diabetes mellitus and mild cognitive impairment in middle-aged men and women. *J Alzheimers Dis* 2014;42:1269-77. doi:10.3233/JAD-140696
43 Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. *Diabetologia* 2005;48:2460-9. doi:10.1007/s00125-005-0023-4
44 Dove A, Shang Y, Xu W, et al. The impact of diabetes on cognitive impairment and its progression to dementia. *Alzheimers Dement* 2021;17:1769-78. doi:10.1002/alz.12482
45 Fu EL, Patorno E, Everett BM, et al. Sodium-glucose cotransporter 2 inhibitors vs. sitagliptin in heart failure and type 2 diabetes: an observational cohort study. *Eur Heart J* 2023;44:2216-30. doi:10.1093/eurheartj/ehad273
46 Low S, Goh KS, Ng TP, et al. Association Between Use of Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors and Cognitive Function in a Longitudinal Study of Patients with Type 2 Diabetes. *J Alzheimers Dis* 2022;87:635-42. doi:10.3233/JAD-215678
47 Wu CY, Wang C, Saskin R, et al. No association between metformin initiation and incident dementia in older adults newly diagnosed with diabetes. *J Intern Med* 2024;295:68-78. doi:10.1111/joim.13723
48 Salas J, Morley JE, Scherrer JF, et al. Risk of incident dementia following metformin initiation compared with noninitiation or delay of antidiabetic medication therapy. *Pharmacoepidemiol Drug Saf* 2020;29:623-34. doi:10.1002/pds.5014

Supplementary information: Additional figures S1-S3 and tables S1-S18