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Original article

Sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase IV inhibitors and risk of dementia among patients with type 2 diabetes and comorbid mental disorders: A population-based cohort study

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ABSTRACT

Aim: To evaluate whether the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors which have shown potential neuroprotective effects, is associated with lower risk of dementia in patients with type 2 diabetes (T2D) and comorbid mental disorders, who are considerably more susceptible to dementia.

Methods: Using the nationwide healthcare data of South Korea between 2010 and 2022, we conducted a retrospective cohort study among patients with T2D and comorbid mental disorders initiating SGLT2 inhibitors versus active comparator (Dipeptidyl Peptidase IV (DPP4) inhibitors). Hazard ratios (HRs) and rate differences (RDs) per 1000 person-years of incident dementia were estimated after weighting by propensity score fine stratification method.

Results: Over a 4.8-year median follow-up, SGLT2 inhibitors were associated with a 12 % lower risk of dementia compared with DPP4 inhibitors (11.31 vs. 12.86 events per 1000 person years; HR 0.88, 95 % CI 0.84 to 0.92; RD -1.55, -2.13 to -0.97). The results were consistent when stratified by age, sex, individual component, severe mental disorders, presence of insulin, history of cardiovascular disease, or history of hypertension.

Conclusions: SGLT2 inhibitors versus DPP4 inhibitors were associated with a lower risk of incident dementia in patients with T2D and comorbid mental disorders. Further randomized controlled trials are required to confirm our findings.

Introduction

Mental disorders encompass a wide range of conditions that affect cognition, emotion, and behavior, represent a substantial global health challenge [1]. It is estimated that half of individuals worldwide will experience one or more mental disorders across their lifespan [2]. The sustained high prevalence of these conditions is concerning because beyond their immediate impact on mental well-being, mental disorders are also associated with increased mortality and the risk of other health outcomes, such as dementia. Mental disorders cause an up to six-fold increase in susceptibility to dementia [3], a debilitating disease that severely impairs functioning and quality of life, and whose economic burden exceeds that of heart disease and cancer [4]. Furthermore, mental disorders also present a complex bidirectional association with type 2 diabetes (T2D), which results in a high prevalence ranging from 8 % to 40 % of coexisting mental disorders and T2D [5,6]. An even more alarming finding is that the association between mental disorders and dementia is compounded in coexistent T2D. Research has shown that the co-occurrence of mental disorders and T2D remarkably increases the risk of developing dementia compared to either disorder alone [7].

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Therefore, there is an urgent need to explore therapeutic approaches to mitigate the risk of dementia in this high-risk population.

Over the past few years, the neuroprotective effects of novel classes of glucose-lowering medications such as sodium–glucose cotransporter-2 inhibitors (SGLT2 inhibitors) have been reported [8,9]. Preclinical studies using murine models of T2D have shown that SGLT2 inhibitors reduce oxidative stress and neuroinflammation, and improved neuronal plasticity and the mitochondrial brain pathway [10,11]. SGLT2 inhibitors have also been shown to reduce the brain extra-cellular and intra-cellular accumulation of amyloid beta and neurofibrillary tangles, which are primary pathological characteristics of dementia [12,13]. Furthermore, SGLT2 inhibitors are associated with a 20 % lower risk of dementia in T2D patients compared with other antidiabetic medications (i.e., dipeptidyl peptidase IV (DPP-4) inhibitors) or placebo (14;). However, to the best of our knowledge, no study has explicitly examined the relationship between the use of SGLT2 inhibitors and the risk of dementia in patients with T2D and mental disorders. Thus, whether the neuroprotective effects associated with these drugs persist in patients with T2D and mental disorders who are considerably more susceptible to dementia remains uncertain.

To address this critical knowledge gap, we conducted a nationwide retrospective cohort study to comprehensively compare the risk of dementia among patients with T2D and comorbid mental disorders who were treated with SGLT2 inhibitors versus those treated with DPP-4 inhibitors.

Research design and methods

Data source

We performed a retrospective cohort study using the National Health Insurance Service-National Health Insurance Database (NHIS-NHID) from 2010 to 2022. This database encompasses around 50 million individuals, representing approximately 98 % of the entire South Korea's population [15]. The database collects data from a variety of sources, including healthcare providers, hospitals, clinics, and pharmacies, and information from insurance reimbursement process (in which healthcare providers submit claims for the services they have provided to insured individuals). The database includes de-identified individual-level demographic details such as age, sex, income level, and medical history including records of diagnoses, prescriptions, and procedures through inpatient, outpatient, and emergency department visits. Diagnoses are documented using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10) codes. Procedures are identified through unique codes developed by the NHIS. Medication prescriptions are recorded using NHIS-specific codes and aligned with the World Health Organization-Anatomical, Therapeutic, and Chemical Codes to ensure precision and consistency. Additionally, to gather information on mortality, we linked data from the NHIS-NHID to Statistics Korea [16], which included details on the date and cause of death (classified using the ICD-10 codes). This study was approved by the Institutional Review Board of Sungkyunkwan University (SKKU 2023–10–023), and the requirement for informed consent was waived.

Study population and exposure

We constructed an active comparator, new user cohort: SGLT2 inhibitors vs. DPP-4 inhibitors cohort, which consisted of patients diagnosed with T2D prescribed SGLT2 inhibitors (dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin) or DPP-4 inhibitors (linagliptin, alogliptin, anagliptin, evogliptin, gemigliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin) between September 1, 2014 (the first day of reimbursement of SGLT2 inhibitors in South Korea) and December 31, 2020. The index date was defined as the first date of prescription of the SGLT2 inhibitors or DPP-4 inhibitors during the study period. We selected DPP-4 inhibitors as active comparators since DPP-4 inhibitors are commonly prescribed second-line glucose-lowering medications in patients with similar stage of disease and have been previously shown to have no effects on cognitive function [17,18]. To avoid exposure misclassification, patients prescribed both SGLT2 inhibitors and DPP-4 inhibitors on the index date were excluded. In both cohorts, we excluded patients aged<40 on the index date. Furthermore, patients who were diagnosed with end-stage renal disease or underwent dialysis within a year before the index date were excluded because SGLT2 inhibitors were contraindicated in those patients. To identify new users of study drugs, we excluded patients who were prescribed SGLT2 inhibitors or DPP-4 inhibitors within a year before the index date. To identify dementia-free patients, we excluded patients diagnosed with dementia at any time before the index date (at least a 3-year look-back window).

Furthermore, we required patients with mental disorders, which were identified through the at least one inpatient or two outpatient visits before the index date [19,20] including non-affective psychotic disorders, affective psychotic disorders, alcohol or drug misuse, mood disorders, anxiety and stress related disorders, eating disorders, and personality disorders. Finally, we applied a 1-year lag time to minimize the concern of disease latency and mitigate reverse causality, and patients who were censored (occurrence of outcome or death) within one year from the index date were excluded.

Detailed definitions of the inclusion and exclusion criteria are provided in **Supplementary Table 2.** The study flowchart is shown in **Supplementary Fig. 1**.

Study outcomes and follow-up

The primary outcome was the incidence of new-onset dementia, which was defined using a previously validated algorithm with a positive predictive value of 94.7 % [21]. Dementia cases were identified based on the presence of specific diagnostic codes in combination with the prescription of dementia management medications (rivastigmine, galantamine, memantine, and donepezil). We followed patients by applying the intention-to-treat approach, in which patients were followed from one year after the index date until the earliest occurrence of dementia, death, or the study end date (December 31, 2022). The specific definitions of the study outcomes are shown in **Supplementary Table 2.**

Potential confounders

A wide range of potential confounders were evaluated. Age, sex, income level, and the calendar year of the initial study drug prescription were included. We considered variables of proxies for diabetes severity, including prescriptions for any other antidiabetic prescription, the number of diabetic medication types used, and the level of antidiabetic treatment, all measured within 1 year before the index date. We defined the level of antidiabetic treatment according to type and number of distinct antidiabetic drug classes and categorized it into 3 levels: level 1, patients not prescribed an antidiabetic drug or treated with only one non-insulin antidiabetic drug; level 2, patients treated with ≥2 different classes of non-insulin antidiabetic drugs; level 3, patients treated with ≥1 insulin either alone or in combination with other antidiabetic drugs. We also included proxies for the severity of mental disorders, such as the event of each type of mental disorder recorded before the index date, the number of psychiatric prescriptions, type of psychiatric medication prescribed in the year before the index date (including antidepressants, antipsychotics, anxiolytics, hypnotics and sedatives, and psychostimulants), and the number of hospitalizations for mental disorders recorded within the year before the index date. Furthermore, we considered a wide range of comorbidities before the index date, including diabetes-related complications (nephropathy, neuropathy, retinopathy, myocardial infarction, ischemic stroke, hemorrhagic stroke, and peripheral artery disease) and other common comorbidities (other ischemic heart

disease, hypertension, heart failure, atrial fibrillation, other cerebrovascular diseases, coronary revascularization, chronic liver disease, chronic kidney disease, chronic pulmonary disease, dyslipidemia, seizure, Parkinson's disease, rheumatic disease, and cancer) (**Supplementary Table 4**). We included drugs (beta-blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II antagonists, calcium channel blockers, diuretics, lipid lowering drugs, nitrates, anticoagulants, antiplatelets, corticosteroids, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs)) used within a year before the index date. As markers of overall health status, we included Charlson comorbidity score (CCI) category and number of hospitalizations and emergency room visits in the year prior to the index date (as categorical variables).

Statistical analyses

We adjusted for potential confounders using propensity score fine stratification. Using a multivariable logistic regression model conditional on the selected covariates listed above, we calculated the propensity score for each patient, which was defined as the predicted probability of receiving the SGLT2 inhibitors versus the active comparator (DPP-4 inhibitors). After trimming the observations in the non-overlapping regions of the propensity score distribution, patients receiving the study drugs were divided into 50 equal-sized strata based on the propensity score distribution. In each stratum, patients receiving SGLT2 inhibitors were assigned a weight of one; patients receiving DPP-4 inhibitors were re-weighted according to the proportion of exposed numbers in the corresponding stratum. By this, we aimed to estimate the average treatment effect in the treated [22].

We provided the mean for continuous variables and the numbers and frequencies for categorical variables before and after propensity score weighting. Absolute standardized differences (aSD) were calculated to assess the balance of covariates, with a value <0.1 indicating a good balance between treatment groups [23]. We tabulated the number of events, incidence rates and rate differences (RDs) per 1000 person-years with 95 % CIs for dementia. In each cohort, Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95 % CIs for dementia. We also generated Kaplan-Meier curves to show cumulative incidence of dementia over time, and log-rank tests were used to compare the two treatment groups. All statistical analyses were performed using the SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA). A two-sided P value <0.05 indicated statistical significance.

Secondary analyses

We conducted several subgroup analyses. First, we assessed the potential effect modification by age (40–64 and $\geq$65 years) and sex. Second, we assessed whether there was varied effect of individual components within each study drug class, which was limited to those with a sufficient sample size. Third, we conducted a subgroup analysis stratified by severity of mental disorders. Non-affective or affective disorders with psychotic features, which are likely to be characterized by cognitive impairment and social isolation, and lead to non-seeking treatment, poor treatment adherence and poor prognosis, were defined as severe mental disorders [19,20]. Fourth, we assessed whether there was a varied effect based on the presence of insulin, with the use of insulin possibly indicating a more advanced diabetes severity. Finally, we assessed whether the association varied according to a history of cardiovascular disease (CVD) and hypertension, both of which are risk factors for dementia [24]. CVD was defined as a composite outcome of myocardial infarction, ischemic stroke, peripheral artery disease, other ischemic heart diseases, and coronary revascularization. We reperformed the propensity score estimation and weighting within each subgroup. We employed the Wald test for homogeneity to determine whether there was an effect modification between subgroups, with a two-sided P value <0.05 as an indication of heterogeneity.

Sensitivity analyses

We conducted four sensitivity analyses to assess the robustness of our findings. First, to mitigate the risk of potential exposure misclassification, we performed an as-treated analysis that considered the instances of medication discontinuation and switching. Uninterrupted usage was defined as the occurrence of a subsequent prescription within the supply period of the preceding prescription, augmented by an additional 90-day extension period. Following this method, the follow-up period for the treatment groups were from one year after the index date until the earliest of these events: diagnosis of dementia, death, one year after discontinuation or switching, or the end of the study period. Second, we conducted a competing risk analysis using Fine and Gray's proportional sub-hazards model, considering death as a competing risk. Third, to improve the validity of mental disorders, we used a stricter definition by identifying patients with mental disorders as those who had both predefined diagnoses and at least one prescription for psychiatric medications. Fourth, we introduced a two-year lag time to further mitigate any potential bias arising from disease latency.

Results

42 874 patients initiating SGLT2 inhibitors and 385 045 patients initiating DPP-4 inhibitors were included (**Supplementary Fig. 1**). Patients were followed for a median duration of 4.8 years (interquartile range, 3.2 to 6.5 years), including the 1-year lag period. In the SGLT2 inhibitors group, there were 1667 incident dementia events during 147 426 person-years of follow-up, generating a crude incidence rate of 11.31 (95 % CI, 10.77 to 11.86) per 1000 person years. There were 34 520 incident dementia events during 1 489 691 person-years of follow-up in the DPP-4 inhibitors group, generating a crude incidence rate of 23.17 (95 % CI, 22.93 to 23.42) per 1000 person years.

Before propensity score weighting, patients initiating SGLT2 inhibitors were younger, more likely to be female, less likely to be prescribed insulin, had lower prevalence of diabetes-related complications, and had a higher number of emergency room visits than those initiating DPP-4 inhibitors (**Supplementary Table 5**). After propensity score weighting, all covariates were well balanced between the treatment groups (Table 1). The most common ingredients prescribed on the index date were dapagliflozin (n = 24 970, 58.2 %) in the SGLT2 inhibitors group, and linagliptin (n = 93 533, 24.2 %) in the DPP-4 inhibitors group (**Supplementary Table 6**).

Overall, SGLT2 inhibitors were associated with a 12 % lower risk of incident dementia compared with DPP-4 inhibitors (11.31 vs. 12.86 events per 1000 person years; HR 0.88, 95 % CI 0.84 to 0.92; RD −1.55, −2.13 to −0.97) (Table 2). The cumulative incidence curves comparing SGLT2 inhibitors with DPP-4 inhibitors showed consistent results and diverged approximately two years after treatment initiation (Fig. 1).

The results of the subgroup analyses are shown in Fig. 2 **and Supplementary Table 6.** SGLT2 inhibitors versus DPP-4 inhibitors were associated with a larger benefit in patients<65 years (HR 0.78, 95 % CI 0.68 to 0.88). We found no effect modification for sex, or individual components such as dapagliflozin and empagliflozin, severity of mental disorders, presence of insulin, history of CVD, or history of hypertension. The findings remained consistent in several sensitivity analyses (**Supplementary Tables 7–10**).

Discussion

In this nationwide population-based cohort study, compared with DPP-4 inhibitors, the initiation of SGLT2 inhibitors was associated with a 12 % lower risk of incident dementia in patients with T2D and comorbid mental disorders. These results remained robust in all predefined subgroup and sensitivity analyses.

Table 1
Baseline characteristics of patients receiving comparing SGLT2 inhibitors with DPP-4 inhibitors before and after propensity score fine stratification.

Characteristics	Before weighting			After weighting		
	SGLT2 inhibitors (n = 42 874)	DPP-4 inhibitors (n = 385 045)	aSD	SGLT2 inhibitors (n = 42 873)	DPP-4 inhibitors (n = 384 757)	aSD
Mean age (SD)	59.8 (10.5)	64.7 (11.0)	0.454	59.8 (10.5)	59.8 (10.6)	0.000
Age group, n (%)						
40–64	29 010 (67.7)	188 060 (48.8)	0.389	29 009 (67.7)	260 434 (67.7)	0.001
65–74	9695 (22.6)	114 093 (29.6)	0.160	9695 (22.6)	86 365 (22.4)	0.004
≥75	4169 (9.7)	82 892 (21.5)	0.329	4169 (9.7)	37 958 (9.9)	0.005
Sex, n (%)						
Male	17 728 (41.3)	168 794 (43.8)	0.050	17 728 (41.4)	159 384 (41.4)	0.002
Female	25 146 (58.7)	216 251 (56.2)	0.050	25 145 (58.6)	225 373 (58.6)	0.002
Income level, n (%)						
Low	13 936 (32.5)	123 793 (32.2)	0.008	13 936 (32.5)	125 346 (32.6)	0.002
Medium	13 239 (30.9)	114 929 (29.8)	0.022	13 238 (30.9)	118 849 (30.9)	0.000
High	15 699 (36.6)	146 323 (38.0)	0.029	15 699 (36.6)	140 563 (36.5)	0.002
Calendar year, n (%)						
2013	NA	NA	NA	NA	NA	NA
2014	1136 (2.6)	17 647 (4.6)	0.104	1136 (2.6)	10 279 (2.7)	0.001
2015	3976 (9.3)	71 664 (18.6)	0.272	3976 (9.3)	35 933 (9.3)	0.002
2016	5520 (12.9)	68 588 (17.8)	0.137	5520 (12.9)	49 256 (12.8)	0.002
2017	6726 (15.7)	60 275 (15.7)	0.001	6726 (15.7)	60 101 (15.6)	0.002
2018	6719 (15.7)	57 209 (14.9)	0.023	6719 (15.7)	60 047 (15.6)	0.002
2019	9183 (21.4)	55 147 (14.3)	0.186	9183 (21.4)	82 590 (21.5)	0.001
2020	9614 (22.4)	54 515 (14.2)	0.215	9613 (22.4)	86 550 (22.5)	0.002
Type of antidiabetics use, n (%)						
Metformin (Glucophage)	25 359 (59.1)	245 409 (63.7)	0.094	25 358 (59.1)	227 353 (59.1)	0.001
Sulfonylureas	11 301 (26.4)	133 440 (34.7)	0.181	11 301 (26.4)	101 689 (26.4)	0.002
Thiazolidinedione	3310 (7.7)	23 545 (6.1)	0.063	3310 (7.7)	29 803 (7.7)	0.001
Meglitinides	263 (0.6)	3857 (1.0)	0.043	263 (0.6)	2375 (0.6)	0
a-Glucosidase inhibitors	1423 (3.3)	18 943 (4.9)	0.081	1423 (3.3)	12 831 (3.3)	0.001
GLP-1RAs	196 (0.5)	375 (0.1)	0.068	195 (0.5)	1410 (0.4)	0.014
Insulin	4966 (11.6)	54 034 (14.0)	0.073	4966 (11.6)	44 399 (11.5)	0.001
Level of antidiabetic treatment, n (%)						
Level 1	28 284 (66.0)	227 494 (59.1)	0.143	28 284 (66.0)	253 940 (66.0)	0
Level 2	9624 (22.4)	103 517 (26.9)	0.103	9623 (22.4)	86 571 (22.5)	0.001
Level 3	4966 (11.6)	54 034 (14.0)	0.073	4966 (11.6)	44 247 (11.5)	0.001
No. of diabetic medications used, n (%)						
0–1	29 155 (68.0)	236 152 (61.3)	0.140	29 155 (68)	261 688 (68)	0
2–3	13 222 (30.8)	143 196 (37.2)	0.134	13 221 (30.8)	118 635 (30.8)	0
≥4	497 (1.2)	5697 (1.5)	0.028	497 (1.2)	4435 (1.2)	0.001
Mental disorders, n (%)						
Non-affective psychotic disorders	2486 (5.8)	20 217 (5.3)	0.024	2486 (5.8)	22 419 (5.8)	0.001
Affective psychotic disorders	3304 (7.7)	23 849 (6.2)	0.060	3304 (7.7)	29 730 (7.7)	0.001
Alcohol or drug misuse	2816 (6.6)	29 195 (7.6)	0.040	2816 (6.6)	25 182 (6.5)	0.001
Mood disorders	23 258 (54.2)	198 487 (51.5)	0.054	23 257 (54.2)	208 687 (54.2)	0
Anxiety and stress related disorders	34 795 (81.2)	312 201 (81.1)	0.002	34 794 (81.2)	312 411 (81.2)	0.001
Eating disorders	241 (0.6)	1835 (0.5)	0.012	241 (0.6)	2146 (0.6)	0.001
Personality disorders	322 (0.8)	2539 (0.7)	0.011	322 (0.8)	2902 (0.8)	0
Severity of mental disorders						
Number of psychiatric prescriptions, n (%)						
0	9620 (22.4)	74 882 (19.4)	0.074	9620 (22.4)	86 180 (22.4)	0.001
1–5	14 825 (34.6)	127 299 (33.1)	0.032	14 824 (34.6)	132 868 (34.5)	0.001
6–10	5848 (13.6)	58 646 (15.2)	0.045	5848 (13.6)	52 571 (13.7)	0.001
≥11	12 581 (29.3)	124 218 (32.3)	0.063	12 581 (29.3)	113 137 (29.4)	0.001
Number of hospitalizations for mental disorders, n (%)						
0	42 050 (98.1)	374 875 (97.4)	0.048	42 049 (98.1)	377 356 (98.1)	0
≥1	824 (1.9)	10 170 (2.6)	0.048	824 (1.9)	7401 (1.9)	0
Type of psychiatric medications, n (%)						
Antidepressants	15 101 (35.2)	137 167 (35.6)	0.008	15 100 (35.2)	135 670 (35.3)	0.001
Antipsychotics	14 969 (34.9)	142 221 (36.9)	0.042	14 969 (34.9)	134 394 (34.9)	0
Anxiolytics	23 510 (54.8)	230 156 (59.8)	0.100	23 509 (54.8)	211 186 (54.9)	0.001
Hypnotics and sedatives	12 514 (29.2)	116 857 (30.3)	0.025	12 513 (29.2)	112 445 (29.2)	0.001
Psychostimulants	5673 (13.2)	58 580 (15.2)	0.057	5673 (13.2)	50 946 (13.2)	0
CCI, n (%)						
0	18 802 (43.9)	157 817 (41.0)	0.058	18 802 (43.9)	168 735 (43.9)	0
1	12 570 (29.3)	122 137 (31.7)	0.052	12 569 (29.3)	112 800 (29.3)	0
2	6281 (14.6)	52 597 (13.7)	0.028	6281 (14.7)	56 340 (14.6)	0
≥3	5221 (12.2)	52 494 (13.6)	0.043	5221 (12.2)	46 882 (12.2)	0
Other comorbidities, n (%)						
Diabetic nephropathy	3247 (7.6)	32 732 (8.5)	0.034	3247 (7.6)	28 944 (7.5)	0.002
Diabetic neuropathy	6702 (15.6)	74 786 (19.4)	0.100	6702 (15.6)	60 256 (15.7)	0.001
Diabetic retinopathy	1240 (2.9)	12 862 (3.3)	0.026	1240 (2.9)	11 067 (2.9)	0.001
Myocardial infarction	1213 (2.8)	8369 (2.2)	0.042	1213 (2.8)	10 719 (2.8)	0.003
Ischemic stroke	3868 (9.0)	45 361 (11.8)	0.090	3868 (9.0)	34 801 (9.0)	0.001
Hemorrhagic stroke	454 (1.1)	5031 (1.3)	0.023	454 (1.1)	4065 (1.1)	0

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Before weighting			After weighting		
	SGLT2 inhibitors (n = 42 874)	DPP-4 inhibitors (n = 385 045)	aSD	SGLT2 inhibitors (n = 42 873)	DPP-4 inhibitors (n = 384 757)	aSD
Peripheral artery disease	11 722 (27.3)	110 512 (28.7)	0.030	11 722 (27.3)	105 289 (27.4)	0.001
Other ischemic heart disease	11 405 (26.6)	95 651 (24.8)	0.040	11 404 (26.6)	102 363 (26.6)	0
Hypertension	29 684 (69.2)	271 961 (70.6)	0.030	29 683 (69.2)	266 495 (69.3)	0.001
Heart failure	2839 (6.6)	25 073 (6.5)	0.004	2838 (6.6)	25 384 (6.6)	0.001
Atrial fibrillation	1460 (3.4)	12 685 (3.3)	0.006	1460 (3.4)	13 013 (3.4)	0.001
Other cerebrovascular disease	8010 (18.7)	81 961 (21.3)	0.065	8010 (18.7)	71 943 (18.7)	0
Coronary revascularization	1352 (3.2)	7967 (2.1)	0.068	1352 (3.2)	11 987 (3.1)	0.002
Chronic liver disease	23 577 (55.0)	192 311 (49.9)	0.101	23 577 (55.0)	211 504 (55.0)	0
Chronic kidney disease	815 (1.9)	12 869 (3.3)	0.09	815 (1.9)	7382 (1.9)	0.001
Chronic pulmonary disease	21 609 (50.4)	195 059 (50.7)	0.005	21 608 (50.4)	193 954 (50.4)	0
Dyslipidemia	32 898 (76.7)	276 271 (71.8)	0.114	32 897 (76.7)	294 957 (76.7)	0.002
Seizure	2198 (5.1)	20 111 (5.2)	0.004	2198 (5.1)	19 743 (5.1)	0
Rheumatic disease	5439 (12.7)	48 611 (12.6)	0.002	5439 (12.7)	48 727 (12.7)	0.001
Cancer	4000 (9.3)	42 568 (11.1)	0.057	4000 (9.3)	35 829 (9.3)	0.001
Parkinson's disease	424 (1.0)	5997 (1.6)	0.051	424 (1.0)	3825 (1.0)	0.001
Concomitant drugs, n (%)						
Beta-blockers	11 100 (25.9)	92 643 (24.1)	0.042	11 099 (25.9)	99 565 (25.9)	0
ACEi/ARB	21 910 (51.1)	186 633 (48.5)	0.053	21 909 (51.1)	196 459 (51.1)	0.001
Calcium channel blockers	17 479 (40.8)	161 271 (41.9)	0.023	17 478 (40.8)	157 007 (40.8)	0.001
Diuretics	11 867 (27.7)	112 070 (29.1)	0.032	11 866 (27.7)	106 496 (27.7)	0
Lipid lowering drugs	27 094 (63.2)	223 374 (58.0)	0.106	27 094 (63.2)	242 778 (63.1)	0.002
Nitrates	3361 (7.8)	25 771 (6.7)	0.044	3361 (7.8)	30 141 (7.8)	0
Anticoagulant	970 (2.3)	8165 (2.1)	0.010	970 (2.3)	8630 (2.2)	0.001
Antiplatelets	14 116 (32.9)	138 447 (36.0)	0.064	14 116 (32.9)	126 590 (32.9)	0.001
Corticosteroids	26 270 (61.3)	235 953 (61.3)	0	26 269 (61.3)	235 897 (61.3)	0.001
Antibiotics	32 058 (74.8)	287 812 (74.7)	0.001	32 058 (74.8)	287 811 (74.8)	0.001
NSAIDs	31 467 (73.4)	285 117 (74.0)	0.015	31 466 (73.4)	282 599 (73.4)	0.001
Number of hospitalizations, n (%)						
0	31 147 (72.6)	265 717 (69.0)	0.080	31 147 (72.6)	279 700 (72.7)	0.001
1–2	9475 (22.1)	90 561 (23.5)	0.034	9474 (22.1)	84 869 (22.1)	0.001
≥3	2252 (5.3)	28 767 (7.5)	0.091	2252 (5.3)	20 189 (5.2)	0
Number of emergency room visits, n (%)						
0	36 896 (86.1)	336 780 (87.5)	0.042	36 895 (86.1)	331 154 (86.1)	0
1	5978 (13.9)	48 265 (12.5)	0.042	5978 (13.9)	53 603 (13.9)	0

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; aSD, absolute standardized difference; CCI, charlson comorbidity score; DPP-4, Dipeptidyl peptidase 4; GLP-1RAs, glucagon-like peptide-1 receptor agonists; NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; SGLT2, sodium-glucose cotransporter-2.

Table 2
Hazard ratios of dementia comparing SGLT2 inhibitors with DPP-4 inhibitors.

Population	No. of patients	Events	Person-years	Incidence Rate*[†]	Rate Difference*[†] (95 % CI)	Crude HR (95 % CI)	Weighted HR* (95 % CI)
SGLT2 inhibitors vs. DPP-4 inhibitors							
SGLT2 inhibitors	42 874	1667	147 426	11.31	−1.55 (−2.13 to −0.97)	0.49 (0.47 to 0.52)	0.88 (0.84 to 0.92)
DPP-4 inhibitors	385 045	34 520	1 489 691	12.86	Reference	Reference	Reference

Abbreviations: CI, confidence interval; DPP-4, Dipeptidyl peptidase 4; HR, hazard ratio; SGLT2, sodium-glucose cotransporter-2.
*Weighted using propensity score fine stratification.
[†] Per 1000 person-years.

To the best of our knowledge, none of the previous studies including trials and observational studies, have specifically examined the effect of SGLT2 inhibitors on cognitive impairment or the risk of dementia in patients with T2D and comorbid mental disorders, rendering it challenging to draw formal comparisons with available data. Several observational studies have assessed the risk of dementia associated with the use of SGLT2 inhibitors in patients with T2D. Wu et al. found that compared with DPP-4 inhibitors, SGLT2 inhibitors were linked to a 20 % decrease in the risk of developing dementia (HR 0.80, 0.71 to 0.89) [14]. Two previous cohort studies conducted in Taiwan and Hong Kong among patients with T2D have also reported a reduction in the risk for dementia associated with SGLT2 inhibitors compared with non-SGLT2 inhibitors and DPP4 inhibitors, respectively [25,26]. However, patients with T2D and comorbid mental disorders were not specifically investigated in those studies.

Several potential mechanisms could explain the reduced risk of incident dementia following treatment with SGLT2 inhibitors. First, SGLT2 inhibitors may exert direct neuroprotective effects. In murine models with T2D, SGLT2 inhibitors have been shown to reduce oxidative stress and neuroinflammation [27,28]. SGLT2 inhibitors prevent neuroinflammation and blood-brain barrier disorders mediated by NLRP3/IL/TNF-α/miR-501–3p/ by inhibiting the activation of NLRP3 inflammasome [29]. In a mixed murine model of dementia and T2D, SGLT2 inhibitors have been demonstrated to ameliorate the burden of major pathological features of dementia, such as amyloid beta and neurofibrillary tangles. Furthermore, studies have revealed that SGLT2 inhibitors exert an inhibitory effect on acetylcholinesterase, which is the main mechanism of action of anti-dementia [12,30]. Second, chronic hyperglycemia and insulin resistance in patients with T2D can lead to dementia through various biological pathways, such as oxidative stress, inflammation and impaired insulin signaling in the brain. SGLT2 inhibitors are known to have favorable effects on lowering glucose and improving insulin resistance [31]. Third, studies have shown that obesity increases the risk of dementia by 34 % and obesity is the top

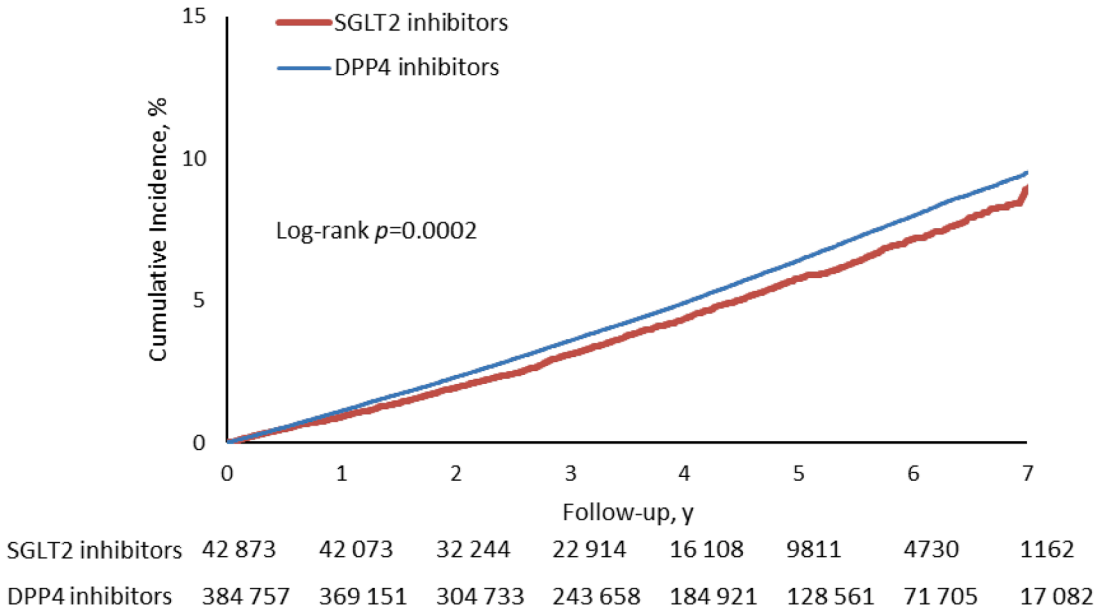

Fig. 1. Cumulative incidence curves of dementia comparing SGLT2 inhibitors with DPP-4 inhibitors. **SGLT2 inhibitors vs. DPP-4 inhibitors**.
Abbreviations: DPP-4, Dipeptidyl peptidase 4; SGLT2, sodium-glucose cotransporter-2.

Variable	SGLT2 inhibitors vs. DPP-4 inhibitors	
	HR* (95% CI)	P for homogeneity
AAge		
<65	0.78 (0.68 to 0.88)	0.021
≥65	0.92 (0.87 to 0.97)	
Sex		
Male	0.86 (0.78 to 0.94)	0.318
Female	0.91 (0.86 to 0.97)	
Individual component		
Dapagliflozin	0.91 (0.85 to 0.96)	0.230
Empagliflozin	0.85 (0.78 to 0.94)	
Severe mental disorders†		
Yes	0.76 (0.65 to 0.90)	0.069
No	0.89 (0.85 to 0.94)	
Presence of insulin		
Yes	0.89 (0.80 to 0.997)	0.860
No	0.88 (0.83 to 0.93)	
History of CVD‡		
Yes	0.89 (0.84 to 0.95)	0.676
No	0.87 (0.79 to 0.94)	
History of hypertension		
Yes	0.89 (0.84 to 0.94)	0.408
No	0.84 (0.74 to 0.95)	

Fig. 2. Hazard ratios comparing SGLT2 inhibitors with DPP-4 inhibitors in each subgroup analysis.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DPP-4, Dipeptidyl peptidase 4; HR, hazard ratio; SGLT2, sodium-glucose cotransporter-2. **Note:** *Weighted using propensity score fine stratification. †Severe mental disorders were defined as non-affective or affective disorders with psychotic features. ‡CVD was defined as the presence of myocardial infarction, ischemic stroke, peripheral artery disease, other ischemic heart diseases, or coronary revascularization.

modifiable dementia risk factor [32]. SGLT2 inhibitors might reduce the risk of dementia by virtue of their weight loss effects [33]. More research is needed to explore the mechanisms involved in SGLT2 inhibitors effects on dementia, and whether such benefits persist in patients with mental disorders without T2D.

Strengths and limitations of study

This study has several strengths. First, this is the first study to investigate the effects of SGLT2 inhibitors on the development of incident dementia in patients with T2D and comorbid mental disorders, and it provides new evidence for the role of these medications in this

vulnerable population. Second, we applied an active comparator, new user design, that allowed us to avoid biases including the depletion of susceptible and confounding by indication. Third, we defined the outcomes by employing a previously validated algorithm, which achieved a positive predictive value of 94.7 %. Thus, we believe that our research was more resilient to potential outcome misclassifications.

This study has some limitations. First, there could be residual confounding arising from unmeasured confounders like glycated hemoglobin levels, kidney function status, and duration of T2D. Nevertheless, we argue that such potential bias was reduced by ensuring a balance in the 63 baseline characteristics between the treatment groups through propensity score weighting. Second, we could not incorporate canagliflozin into our research because of a lack of insurance coverage or their unavailability in the market. Third, although we attempted to minimize potential protopathic bias and address concerns related to disease latency through the inclusion of individuals without dementia and the incorporation of a lag time, such biases remained a concern.

Conclusions

In conclusion, in this large population-based cohort study, SGLT2 inhibitors were associated with a 12 % lower risk of incident dementia in patients with T2D and comorbid mental disorders compared with DPP-4 inhibitors. Further randomized controlled trials are required to confirm our findings, and if replicated, healthcare practitioners should consider these results when selecting an optimized antidiabetic treatment strategy in this high-risk population for dementia.

Prior presentation

None to declare.

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CRediT authorship contribution statement

Bin Hong: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Hyesung Lee:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Ahhyung Choi:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Woo Jung Kim:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Young Min Cho:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Dong Keon Yon:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Ju-Young Shin:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: this study was funded by the Ministry of Food and Drug Safety, South Korea. JYS received grants from the Ministry of Food and Drug Safety, Ministry of Health and Welfare, National Research Foundation of Korea, and Government-wide R&D Fund for Infectious Disease Research and Pharmaceutical Companies, including Pfizer, LG Chemical, and Union Chimique Belge. BH was supported by China Scholarship Council (Grant no. #202,308,260,057). YMC received research grants from Daewoong Pharmaceuticals and Sanofi, and consultation fees from Hanmi and LG Chemical. The other authors report no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2024.101581.

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